SINGAPORE INTERNATIONAL SKIN CONFERENCE

13 - 15 March 2024

10 Years ANNIVERSARY

Speaker Abstracts

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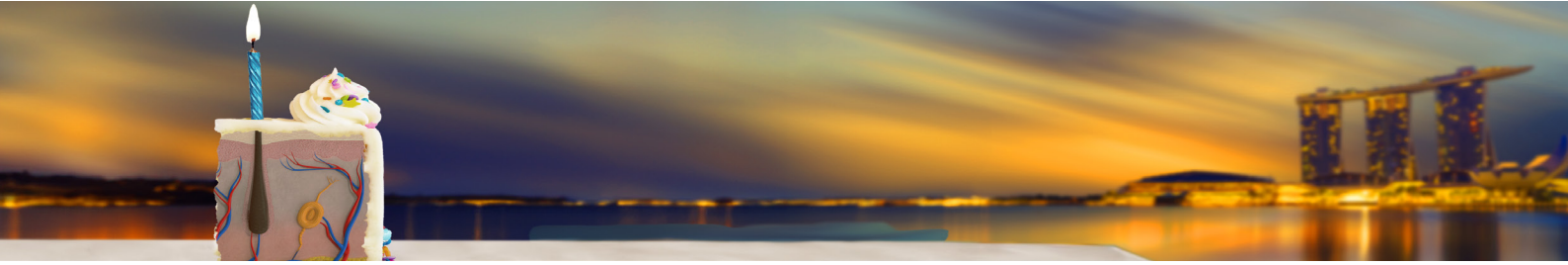
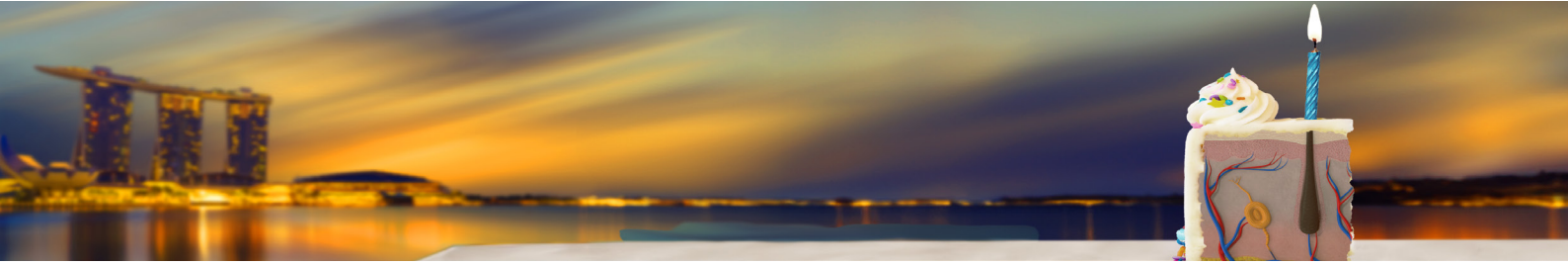


SPEAKER ABSTRACTS

Day 1

13 Mar 2024



Exploiting endothelial plasticity in understanding and modelling skin diseases

Kiarash Khosrotehrani

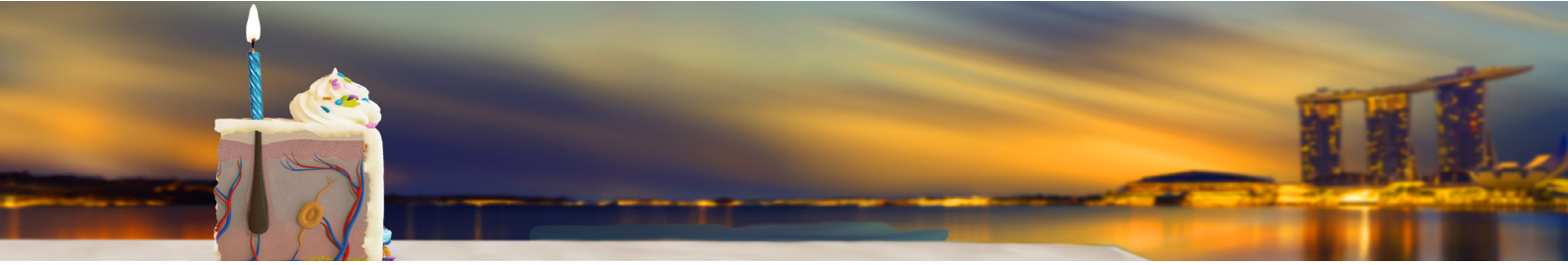
Experimental Dermatology Group, Dermatology Research Centre, Frazer Institute, Brisbane, Australia

ABSTRACT

Dermatological disease burden affects a large part of the population globally and requires significant efforts in improving our understanding and developing effective therapies. The complexity of human skin has always represented a major barrier to using adequate in vitro models and although major progress has been made in understanding the epidermal and immune components of the skin, other important fraction such as fibroblasts or the vasculature are understudied. Here we will discuss, the role of the vasculature in wounds and skin cancer, how it can be manipulated to improve outcomes and how ultimately it can be used to provide adequate in vitro study models for further research.

BIO

Prof Khosrotehrani obtained his MD in Paris, France, where he specialized in Dermatology. He is a former graduate of the Ecole Normale Supérieure and the Institut Pasteur of Paris (Université Paris VI, Pierre et Marie Curie) where he obtained a PhD in Physiology and Physiopathology. He completed his post-doctoral training in stem cell biology and clinical genetics at Tufts-New England Medical Centre in Boston, USA. He is a fellow of the Australian College of Dermatologists and the director of Dermatology at the Princess Alexandra Hospital. He is the co-director of the Australian Skin and Skin Cancer Research Centre. He is the immediate-past president of the Australasian Society for Dermatology Research, a board director of the Australasian College of Dermatologists and the Queensland Skin and Cancer Foundation. His research is fundamentally based on regenerative medicine concepts applied at basic, translational and clinical levels to melanoma, keratinocyte cancers and skin wounds.



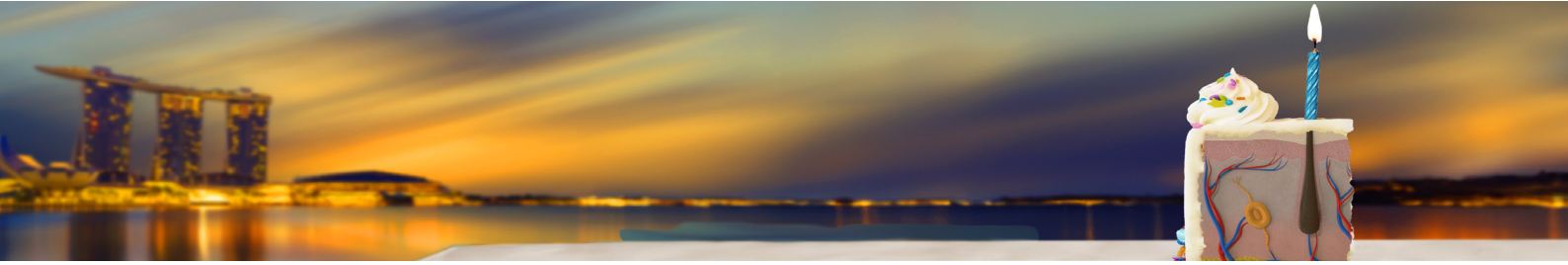
Short talk

A role for keratinocyte Arginase in skin wound healing and barrier function

Denis Szondi[1,2], Jason Wong[3], Leah Vardy[2], Sheena Cruickshank[1]

*[1]Lydia Becker Institute of Immunology and Inflammation, Manchester Academic Health Science Centre, Faculty of Biology, Medicine and Health, University of Manchester, Oxford Road, Manchester, M13 9PT, United Kingdom. [2]A*STAR Skin Research Labs, A*STAR, 8A Biomedical Grove, Singapore 138648, Singapore.[3]Blond McIndoe Laboratories, Division of Cell Matrix Biology and Regenerative Medicine, Manchester Academic Health Science Centre, School of Biological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, United Kingdom.*

Delayed cutaneous wound healing is a major clinical problem that can result in social isolation and significant morbidity. The enzyme Arginase 1 (ARG1) was shown to be markedly increased in wound healing. We have previously described a role for ARG1 in keratinocyte re-epithelialisation during wound closure, but the underlying mechanism was unknown. We aimed to determine the role of ARG1 in keratinocyte migration, differentiation and barrier formation. ARG1 expression changes were determined in 2D scratch and differentiation assays using keratinocytes treated with the ARG1 inhibitor nor-NOHA, and short hairpin RNAs. ARG1 expression was validated using immunohistochemical profiling of human skin, and by analysing spatial transcriptomics data from human wound lesions. ARG1 was strongly expressed 24h post-scratching and during late keratinocyte differentiation. Epidermal ARG1 expression was spatially highlighted in chronic lesions, further suggesting an involvement in keratinocyte migration and differentiation. ARG1 inhibition led to a significant delay in post-scratch keratinocyte migration. Furthermore, upon ARG1 inhibition, a significant expression decrease was seen in late differentiation markers Involucrin (IVL) and Filaggrin (FLG), and the levels of host defence genes Lipocalin 2 (LCN2) and Kallikrein 6 (KLK6). We find that ARG1 activity is required to produce multiple downstream metabolites, among which putrescine and urea play important roles in skin barrier function. In conclusion, our data highlights that ARG1 activity plays a major role in keratinocyte migration, differentiation, and barrier formation, which are vital for re-epithelialisation and wound closure. Manipulation of the ARG1 pathway may, therefore, have potential to be used for chronic lesion management.



Short talk

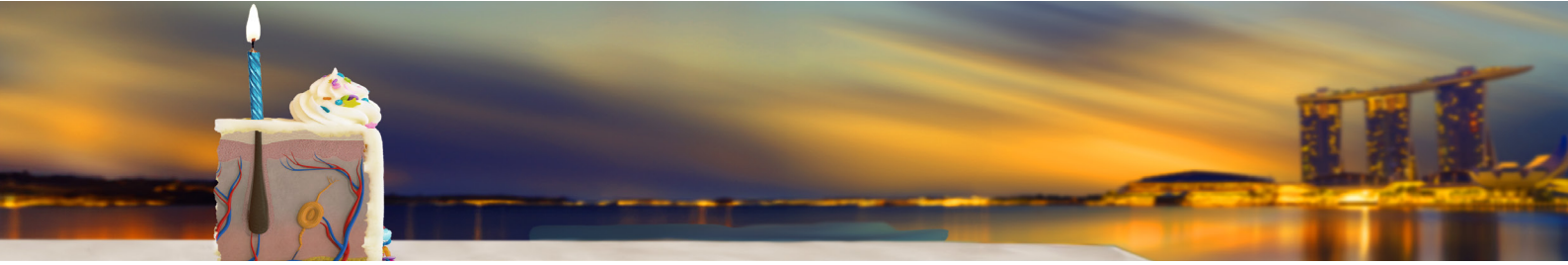
Polyamine metabolism is pivotal in the self-limiting control of wound healing

Meng Shi[1], Leigh Madden[2], Linus Oon Kah Seng[1], Hui Kheng Lim[1], Sze Han Lee[1], Dennis Kappei[3], Thiam Chye Lim[4], Kazuei Igarashi[5], Henry Yang[6], David L Becker[2], Leah A. Vardy[7]

Shi,1 Leigh Madden,2 Linus Oon Kah Seng,1 Hui Kheng Lim,1 Sze Han Lee,1 Dennis Kappei,3 Thiam Chye Lim,4 Kazuei Igarashi,5 Henry Yang,6 David L Becker,2 and Leah A. Vardy7

*[1]A*STAR Skin Research Labs and Skin Research Institute of Singapore, A*STAR, Immunos, Singapore, Singapore; [2]Lee Kong Chian School of Medicine, Nanyang Technological University, Clinical Sciences Building, 11 Mandalay Road, Singapore; Skin Research Institute Singapore, Clinical Sciences Building, 11, Mandalay Road, Singapore; [3]Cancer Science Institute of Singapore, National University of Singapore, Singapore; Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; NUS Center for Cancer Research, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [4]Division of Plastic, Reconstructive and Aesthetic Surgery, Department of Surgery, National University Hospital and National University of Singapore, Kent Ridge Wing, Singapore; [5]Graduate School of Pharmaceutical Sciences, Chiba, University, Chiba, Japan; [6]Cancer Science Institute of Singapore, National University of Singapore, Singapore; [7]A*STAR Skin Research Labs and Skin Research Institute of Singapore, A*STAR, Immunos, Singapore, Singapore; School of Biological Sciences, Nanyang Technological University, Nanyang Drive, Singapore*

With the growing global ageing population, non-healing or chronic wounds have become a heavy social and medical burden. Older adults are disproportionately affected by chronic wounds which impose substantial morbidity and mortality. Non-healing wounds are the most common cause of lower extremity amputations. However, few efficient treatments and diagnostics are available. Wound healing slows with age, but the influence of age-associated changes on wound healing are poorly understood. Understanding the basic biology underlying wound healing is of critical importance for the development of novel therapeutics and diagnostics in slow-to-heal or non-healing wounds. We identified polyamines as critical upstream regulators of wound healing in human skin. Polyamines are polycations that interact readily with negatively charged molecules and are essential for various cellular processes. Polyamine levels are reduced by up to 50% in aged skin while are maintained at high levels in cancer cells. Intracellular polyamine levels are maintained in a cell type-specific manner by tightly regulated polyamine biosynthesis and catabolism. Despite their importance, the biological and pathophysiological role of controlled polyamine metabolism on wound healing remains unknown. We find that polyamine metabolism is dynamic and transiently upregulated during healing. Inhibition of polyamine catabolism impaired keratinocyte migration during the re-epithelialization stage of healing. We show that polyamine metabolites promote cell migration through activation of urokinase-type plasminogen activator receptor mediated reorganization of actin cytoskeleton during healing. Our work suggests that polyamine metabolism is essential for efficient wound repair and that polyamine metabolites are critical signaling factors that modulate cell migration during wound healing.



Defining skin integrity: Insights from across the pigmentary spectrum

Abigail LANGTON

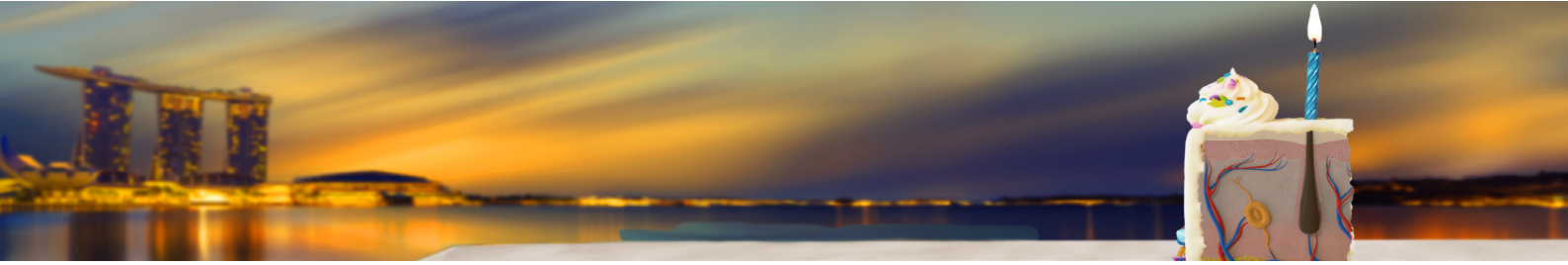
Centre for Dermatology Research, The University of Manchester & Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom

ABSTRACT

Variation in skin colour is the most obvious of human polymorphisms, yet skin's primary functions of maintaining homeostasis, defence against environmental insults and mechanical trauma, are universal. The level of melanin within our skin not only determines its colour but also significantly influences its susceptibility to sun damage. In general, the more melanin there is, the more ultraviolet radiation can be absorbed, and more protection provided. Despite the differences in melanin abundance, human studies aimed at understanding skin integrity have typically focussed on white European skin, neglecting the biology of more pigmented skin types. In recent years our fundamental knowledge of more pigmented skin has started to expand; healthy black skin has a thicker epidermis, greater interdigitation of rete ridges at the dermal-epidermal junction and a different dermal extracellular matrix composition than white skin. More recently, the defining characteristics of healthy, young skin across the entire pigmentary spectrum has been explored, revealing inherent variations in both structure and composition. In a world of rapidly advancing age, the need to maintain skin health and integrity across the life-course is universal and the future of dermatology research should address the needs of all people, setting new standards for diversity, inclusivity and equity.

BIO

Dr Abigail Langton is a Lecturer in Ethnic Skin within the Centre for Dermatology Research (CfDR), The University of Manchester. She received her PhD in cutaneous stem cell biology from The University of Manchester and joined the CfDR as a Post-Doctoral Research Associate in 2009. She has an established record of internationally recognized original research in the field of human skin health ageing, collaborating with academics at prestigious universities in the UK, USA and Asia. Abigail's current research is focused on understanding skin health and ageing across individuals of diverse skin ethnicity, setting a new standard for inclusivity in dermatology research. She uses innovative technical and clinical approaches, such as non-invasive cutometry and detailed histological analysis, to determine the functional consequences of ageing across individuals of diverse skin ethnicity. Abigail is an Executive Board member of the British Society of Investigative Dermatology and is consultant to numerous personal care companies.



Altering cell mechanics to inhibit melanoma cell migration, invasion and metastasis

Robert J. Ju[1], Kevin M. Dean[2], Reto P. Fiolka[2], David P. Sester[1], Max Nobis[3], Paul Timpson[3], Alexis J. Lomakin[4], Gaudenz Danuser[2], Sam J. Stehbens[1], Nikolas K. Haass[1]

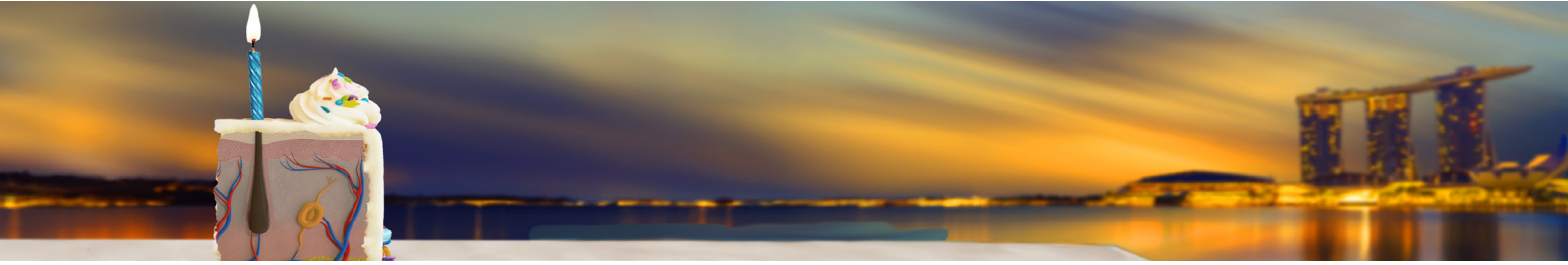
[1]University of Queensland, Australia; [2]University of Texas Southwestern Medical Centre, USA; [3]The Garvan Institute of Medical Research, Australia; 4Medical University of Vienna, Austria

ABSTRACT

Cells migrating through complex 3D environments experience considerable physical challenges including tensile stress and compression. To move, cells need to resist these forces whilst also squeezing the large nucleus through confined spaces. This requires highly coordinated cortical contractility. Microtubules can both resist compressive forces and sequester key actomyosin regulators to ensure appropriate activation of contractile forces. Yet, how these two roles are integrated to achieve nuclear transmigration in 3D is largely unknown. Here, we demonstrate that compression triggers reinforcement of a dedicated microtubule structure at the rear of the nucleus by the mechanoresponsive recruitment of CLASPs (cytoplasmic linker-associated proteins) which dynamically strengthens and repairs the lattice. These reinforced microtubules form the mechanostat: an adaptive feedback mechanism that allows the cell to both withstand compressive force and spatiotemporally organise contractility signalling pathways. The microtubule mechanostat facilitates nuclear positioning and coordinates force production to enable the cell to pass through constrictions. Disruption of the mechanostat imbalances cortical contractility, stalling migration and ultimately resulting in catastrophic cell rupture. Our findings reveal a new role for microtubules as cellular sensors which detect and respond to compressive forces, enabling movement and ensuring survival in mechanically demanding environments.

BIO

Prof Nikolas Haass is a clinician scientist and academic leader with research in melanoma cell biology and experimental melanoma therapy. He received my degree in medicine from the University of Heidelberg, Germany (1990-1998). He graduated summa cum laude with a PhD in Cell Biology from the University of Heidelberg (1993-1999) and trained in clinical dermatology at the University of Hamburg, Germany (1999-2003). In 2003 he moved to Philadelphia, PA, to work as a post-doctoral fellow in Meenhard Herlyn's lab at The Wistar Institute (2003-2007). From there he was recruited as an associate faculty member to the Centenary Institute/University of Sydney (2007-2013). In 2013 he commenced a position as Associate Professor for Cutaneous Oncology at University of Queensland Diamantina Institute (now Frazer Institute) and was promoted to full Professor in April 2016.



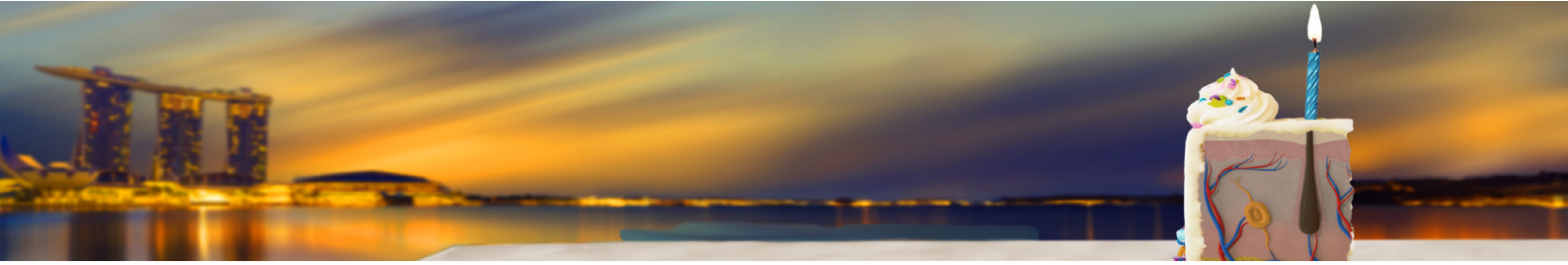
Short talk

Delineating the chain of events that trigger cellular senescence in the premature aging syndrome Hutchinson-Gilford progeria

Mattheus Xing Rong Foo, Peh Fern Ong, and Oliver Dreesen

*Cell Aging, A*STAR Skin Research Labs, Skin Research Institute of Singapore, A*STAR, Singapore, Singapore*

Hutchinson-Gilford Progeria (HGPS) is a premature aging syndrome caused by aberrant splicing of LMNA that results in a truncated and permanently farnesylated form of lamin A, called progerin. HGPS patients exhibit characteristics of aging, including alopecia, impaired growth, lipodystrophy, altered pigmentation, bone defects, and die in their mid-teens as a result of cardiovascular complications. Our goal is to elucidate the molecular mechanism that accelerates aging in progeria and understand its relevance to normal aging. On a cellular level, progerin expression causes nuclear abnormalities, perturbed nucleo-cytoplasmic transport, heterochromatin loss, DNA damage, impaired proliferation and premature senescence. Some of these defects can be prevented by ectopic expression of telomerase, or by modulating telomeric DNA damage response. What remains unclear is how these different phenotypes are temporally and mechanistically linked, and whether they are a cause, or a consequence of cellular senescence. To address these questions, we used a doxycycline-inducible expression system to introduce different lamin A mutants into human primary and telomerase-immortalized fibroblasts. This system, in conjunction with single-cell immunofluorescence microscopy, enabled us to delineate the temporal chain of events that occurs upon progerin expression across the cell cycle, and ultimately culminates in premature senescence. As perturbations of the nuclear lamina are known to occur during chronological aging, these results provide evidence for a mechanistic link between the nuclear envelope, chromatin structure and telomeres that is disrupted in progeria and possibly normal human aging.



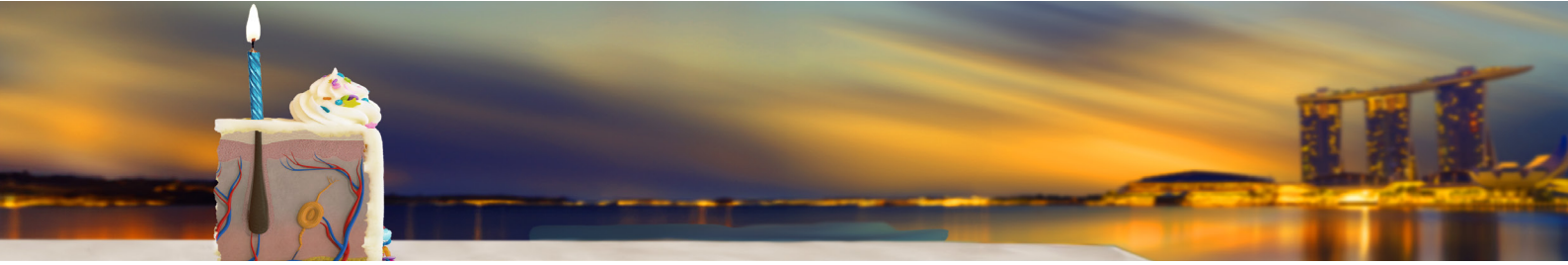
Short talk

Identification of novel targets regulating air pollution induced hyperpigmentation

Rachel Phua[1,2], Nikolaos Pantelireis[2], Carlos Clavel[1,2]

*[1]Hair Pigmentation and Development Group, A*STAR Skin Research Labs (A*SRL), Agency for Science, Technology and Research (A*STAR), Singapore; [2]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore*

Over 99 % of the world population live in areas exceeding set air quality guidelines, and air pollution is more so of a threat to our health. While recent studies explore the link between air pollution and pigmentation disorders, the exact molecular mechanisms responsible for this alteration remain largely unclear. Within the scope of particulate matter, a major air pollutant, lies polycyclic aromatic hydrocarbons (PAH). We have recently shown that an exposure to PAHs lead to an eventual increase in abnormal pigmentation in vitro and in vivo. To further elucidate the mechanisms behind this phenomenon, bulk-RNA sequencing was carried out on isolated melanocytes, post co-culture. Our initial studies have notably indicated a significant increase in melanin production, transfer and total melanin content when exposed to PAH. From our downstream transcriptome analysis, we have also pinpointed to several genes which have been differentially expressed, most significantly being CYP1A1. This prompted us to look deeper into the AhR signaling pathway. Through further analysis and subsequent confirmation through knockdown assays, we are further verifying novel downstream targets which may play a pivotal role in the regulation of skin pigmentation and senescence. Our findings potentially highlight a new approach in novel therapeutics for the treatment of hyperpigmentation disorders linked to air pollution.



Polyamines: Novel regulators of human epidermal pigmentation

Aishwarya Sridharan[1], Zhi Wei Lim[1], Nagavidya Subramaniam[1], Xenia Kodji[1], Koh Yun Suen[1], Meng Shi[1], Takeshi Uemura[3], Kazuei Igarashi[3], Nguan Soon Tan[4], Steven Thng Tien Guan[3], Leah A. Vardy[1]

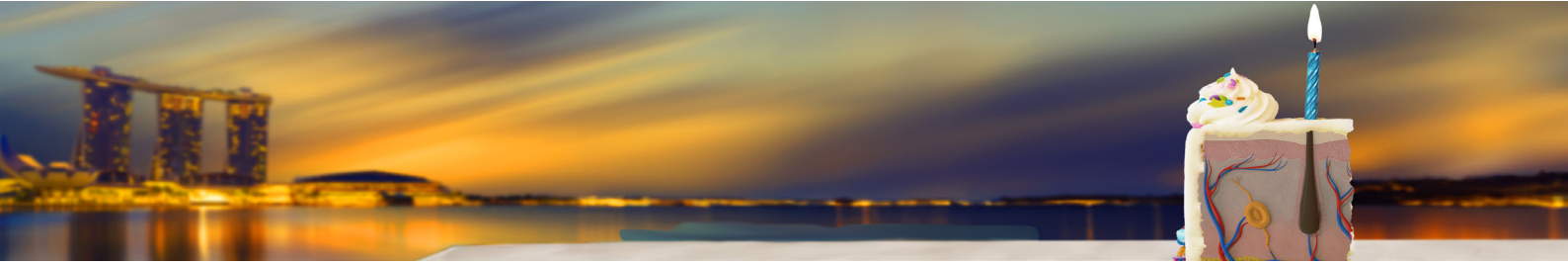
*[1]A*STAR Skin Research Labs, A*STAR, Singapore; [2]Graduate School of Pharmaceutical Sciences, Chiba University, Japan; [3]National Skin Center, NHG, Singapore; [4]Lee Kong Chian School of Medicine, Nanyang Technological University Singapore*

ABSTRACT

In this study we sought to understand the role of polyamines in modulating pigmentation in the epidermis. The three polyamines, putrescine, spermidine and spermine, are ubiquitously expressed cations that play essential roles in many cellular events. Changes in their levels can influence many cellular processes. Here, we demonstrate that polyamines are important drivers of epidermal pigmentation. Laser capture microscopy from melasma lesional compared to non-lesional skin coupled to genome wide analysis showed that ODC1, the rate limiting enzyme for polyamine biosynthesis, is increased in lesional compared to non-lesional melanocytes. To confirm a role for polyamines in promoting pigmentation we show that the polyamine putrescine can promote Tyrosinase activity and melanogenesis in human ex-vivo skin and in human melanocytes. We further show that putrescine drives an increase in polyamine catabolism through SAT1 and SMOX resulting in increased intracellular H202. Addition of a polyamine catabolism inhibitor prevents putrescine indued pigmentation indicating. We further show that addition of other polyamine modulators can inhibit or promote melanogenesis in human pigmentation models. In conclusion, our data suggest that changes in polyamine levels within the skin can drive increased melanin synthesis in the melanocyte leading to increased pigmentation.

BIO

Leah Vardy is a Research Director at the A*STAR Skin Research Labs. Leah did her Ph.D at the Imperial Cancer Research Fund in London followed by post-doctoral work at the Whitehead Institute in Cambridge, in the US. In 2007 she joined A*STAR and now works in the A*STAR Skin Research Labs where her lab focuses on understanding how the behavior of cells within human skin is controlled and how this is affected in the context of aging and disease. Her recent work has uncovered new roles for a family of metabolites called polyamines in controlling cellular behavior during pigmentation, aging and tissue repair. Research in the Vardy lab is focused on understanding the biology behind skin pathologies with the goal of developing new treatments and diagnostics for clinical application.



Animal models for Psoriasis

Nicole Ward

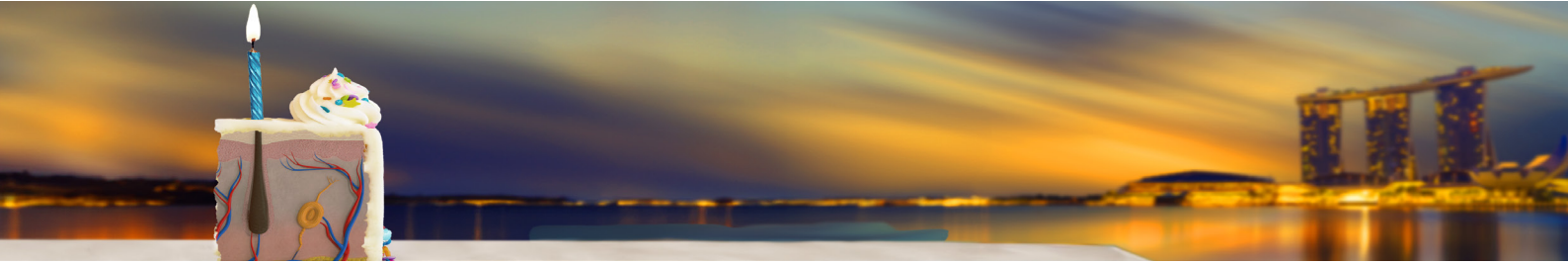
Department of Dermatology, Vanderbilt University Medical Center, Nashville, USA

ABSTRACT

The use of preclinical animal models of psoriasis has significantly increased over the last three decades, with each model having unique strengths and limitations. Some models translate better to human disease, and many have provided unique insight into psoriasis disease pathogenesis. I will discuss the strengths and weaknesses of different genetic mouse models, xenograft approaches, and elicited methods using cytokine injections into, and topical imiquimod onto mice. I will present three unique models engineered in my research lab and demonstrate how they can be used to translate new information to the clinic, and how clinical information can lead to the development of new mouse models of psoriasis.

BIO

Dr. Nicole Ward is a Professor and Vice-Chair for Basic Research in the Department of Dermatology at Vanderbilt University Medical Center in Nashville. Her research focuses on understanding psoriatic disease pathogenesis and psoriasis co-morbidities and her lab specializes in generating and studying unique mouse models of skin inflammation.



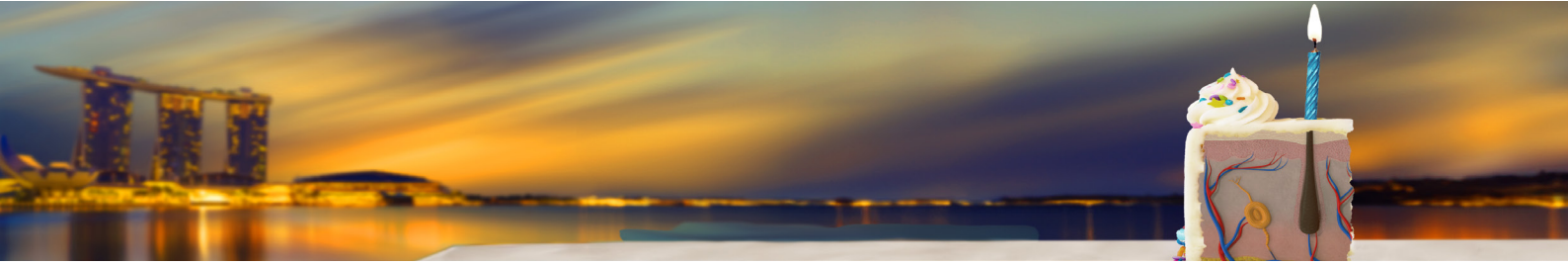
Short talk

The spatial proteome of Psoriasis

Line B.P. Møller[1,2], Bjørn Kromann[1], Sonja Kabatnik[2], Johanne Hatorp Hjortlund[1], Julie B.K. Sølberg[1], Michael Bzorek[3], Lone Skov[1], Matthias Mann[2,5], Marianne Bengtson Løvendorf[1,4] and Beatrice Dyring-Andersen[1,2,4]

[1]Department of Dermatology and Allergy, Copenhagen University Hospital - Herlev and Gentofte Hospital, Hellerup, Denmark; [2]Novo Nordisk Foundation (NNF) Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark; [3]Department of Pathology, Copenhagen University Hospital, Zealand University Hospital, Roskilde, Denmark; [4]The Leo Foundation Skin Immunology Research Center, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark; [5]Department of Proteomics and Signal Transduction, Max Planck Institute of Biochemistry, Martinsried, Germany

Analyzing the proteome of psoriasis provides the opportunity to characterize it at a deeper level, potentially leading to a broader understanding of the pathology of the disease. In this study, we used laser-capture microscopy to microdissect skin layers from both lesional and non-lesional psoriatic skin of eight patients with plaque psoriasis, and eight healthy donors. The proteomes of the samples were analyzed by mass spectrometry using data-independent acquisition. Furthermore, we cultured primary fibroblasts from lesional psoriatic skin and compared their proteomes to fibroblasts from healthy human skin. In total, we identified 6834 proteins from the microdissected skin layers (outer epidermis, inner epidermis, dermis and subcutis). The most notable differences were found in the inner epidermis when comparing lesional and non-lesional psoriatic skin (1651 differentially expressed proteins (DEPs), FDR<0.05), with high expression of alarmins, S100 proteins, and the IL-36 pathway. Additionally, our comparison of fibroblasts from psoriatic and healthy skin identified 3300 DEPs (FDR<0.05) including proteins involved in regulation of the cell cycle, TGF-beta production, and cell migration. These findings suggest dermal fibroblasts may potentiate inflammatory responses by recruiting immune cells. In conclusion, our study underscores the potential of proteomic analysis and laser-capture microdissection to deepen our understanding of psoriasis pathology.



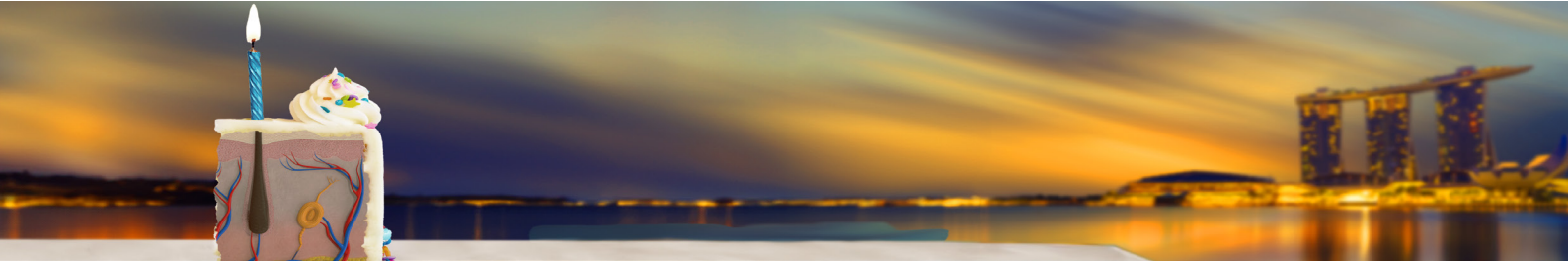
Short talk

Beyond the surface: IL-17, miR-101, EZH2 - A psoriatic Tale

Gowtham Subramanian[1], Shan Quah[1], Jonathan Tan[1] and Prabha Sampath[1,2,3]

*[1]A*STAR Skin Research Labs (A*SRL), Agency for Science Technology and Research (A*STAR), Singapore; [2]The Program in Cancer and Stem Cell Biology (CSCB), Duke-NUS Medical School, Singapore; [3]Genome Institute of Singapore, Agency for Science, Technology and Research, 60 Biopolis Street, Genome, Singapore 138672, Singapore*

Psoriasis, a chronic inflammatory skin condition characterized by accelerated keratinocyte proliferation, is influenced by epigenetic factors such as EZH2 and H3K27me3. Recognizing the intricate connection between epigenetic pathways and non-coding RNA regulation, particularly microRNAs (miRNAs), we explored their involvement in psoriasis pathogenesis. Through miRNA microarrays, we identified 68 differentially expressed miRNAs in psoriatic lesions, including miR-101, a known regulator of EZH2. Notably, miR-101, abundant in healthy epidermis, was absent in lesions, inversely correlating with EZH2 expression. Further investigations revealed IL-17 as an upstream regulator of miR-101, demonstrating its downregulation by IL-17 treatment, relieving repression on EZH2. These findings not only elucidate a molecular pathway where IL-17 induces epidermal hyperplasia but also spotlight miR-101 as a potential target for anti-psoriatic drug discovery. Overall, this study provides crucial insights into the intersection of pro-inflammatory cytokines, miRNA regulation, and epigenetic mechanisms, paving the way for targeted therapeutic interventions in psoriasis.



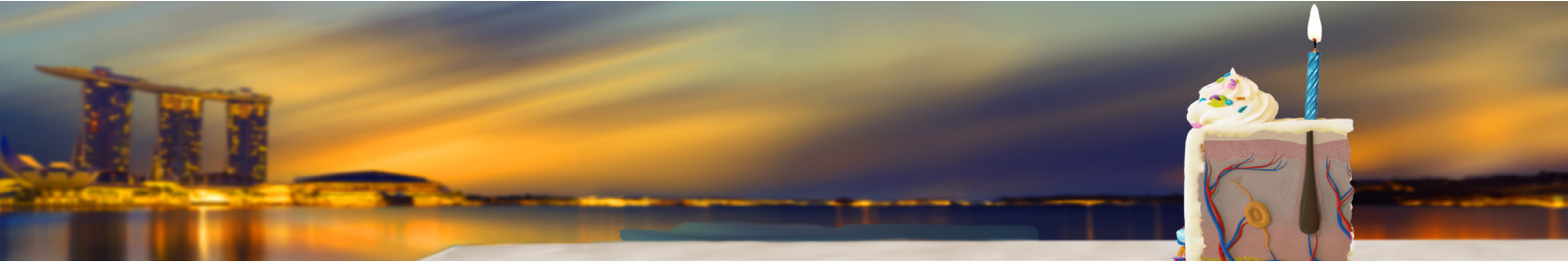
Short talk

Epidermis-derived lactate promotes sterile inflammation and psoriatic skin disease by inducing metabolic rewiring in macrophages

Uttkarsh Ayyangar[1,2], Aneesh Karkhanis3, Heather Tay[3], Aliya Farissa Binte Afandi[3], Oindrila Bhattacharjee[1], Lee Sze Han[3], James Chan[3,4], Srikala Raghavan[1,4]

*[1]Centre for Inflammation and Tissue Homeostasis, Institute for Stem Cell Science and Regenerative Medicine, Bangalore, India; [2]School for Chemical and Biotechnology, Sastra University, Thanjavur, India; [3]Singapore Institute of Food and Biotechnology Innovation, Agency for Science Technology and Research, Singapore; [4]A*Star Skin Research Labs, Agency for Science, Technology and Research Singapore.*

Macrophages are the primary responders to the inflammatory cues within the skin. Interestingly, in vitro and in vivo studies in the skin have suggested that these innate immune cells augment specific intrinsic metabolic programs to regulate their effector functions. However, how cell extrinsic metabolic factors support macrophage metabolism during skin inflammation is not well understood. In this study, we have used epidermal integrin □1 KO embryonic skin to elucidate metabolic crosstalk between macrophage and epidermis in the sterile inflammatory condition in the skin. Using transcriptomic and metabolomic approaches, we show that epidermis and macrophages primarily depend on glycolysis and TCA cycle, respectively, during sterile inflammation that drives their effector functions. An early ROS-HIF1 axis primarily regulates the glycolytic reprogramming within the epidermal compartment. Furthermore, we demonstrate that during sterile inflammation, the glycolytic end product, lactate, is generated and released by the epidermal compartment which is utilized by dermal macrophages to drive their TCA cycle. Consistently, inhibition of lactate-mediated crosstalk between epidermis and macrophages leads to a remarkable reduction in pro-remodeling fate acquisition in the dermal macrophages. Furthermore, our results suggested the existence of similar lactate-mediated crosstalk between epidermal and dermal compartments in psoriatic skin disease. Notably, inhibition of lactate transport in the imiquimod-induced mice model of psoriasis leads to a remarkable reduction in the psoriatic burden. This study provides evidence for a metabolic crosstalk between the epidermis and macrophages in conditions of inflammation within the skin.



The ZAKalpha-NLRP1 axis in skin inflammation

Muhammad Jasrie Firdaus[1], Anna Constance Vind[2], Franklin Zhong Lei[1]

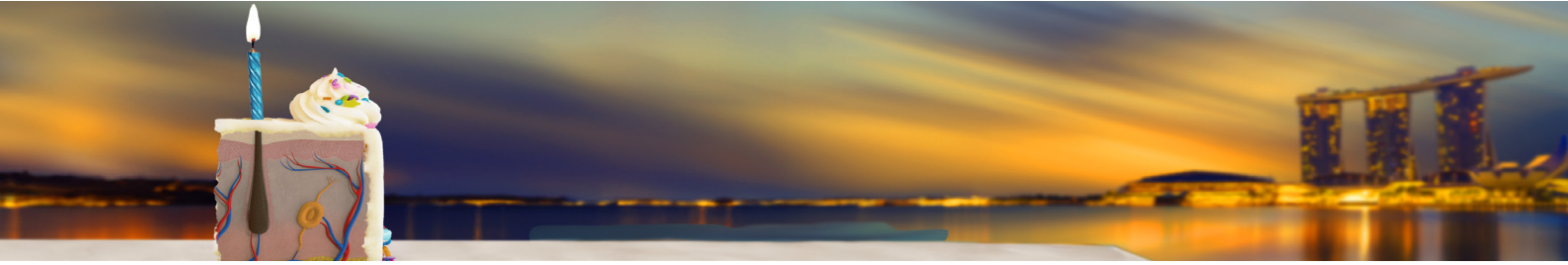
[1]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore; [2]Center for Gene Expression, Institute of Cellular and Molecular Medicine, University of Copenhagen, Copenhagen, Denmark

ABSTRACT

The skin is arguably the most important barrier organ that protects the human body against the external environment. Thus, the human skin is endowed with an elaborate defense mechanism against noxious chemicals and invasive pathogens. Here we describe our recent work on a stress response/innate immune pathway that senses perturbations in protein synthesis in skin keratinocytes. Biochemical and genetic analysis of this pathway reveals druggable targets that could be of interest for therapeutic development to treat inflammatory skin diseases.

BIO

Professor Franklin Zhong was awarded the Nanyang Assistant Professor and joined the faculty at the Lee Kong Chian School of Medicine in 2018. He completed his postdoctoral training at the Agency for Science, Technology and Research (A*STAR) in Singapore in the area of innate immunity and pathogen sensing. Asst Prof Zhong holds a PhD in Cancer Biology from Stanford University and a Bachelor's in Natural Sciences from the University of Cambridge, UK. Asst Prof Zhong's research focuses on the inner workings of the human innate immune system in barrier tissues, such as the skin, that protects body's internal organs from microbial infection. His latest work has led to the identification of new immune sensing pathways that regulate inflammation and cancer immune-surveillance, which could serve therapeutic targets in the treatment of infectious and auto-immune diseases.



KEYNOTE LECTURE

Discovery, diagnosis and doing something different for people with inherited skin diseases

John A. McGrath

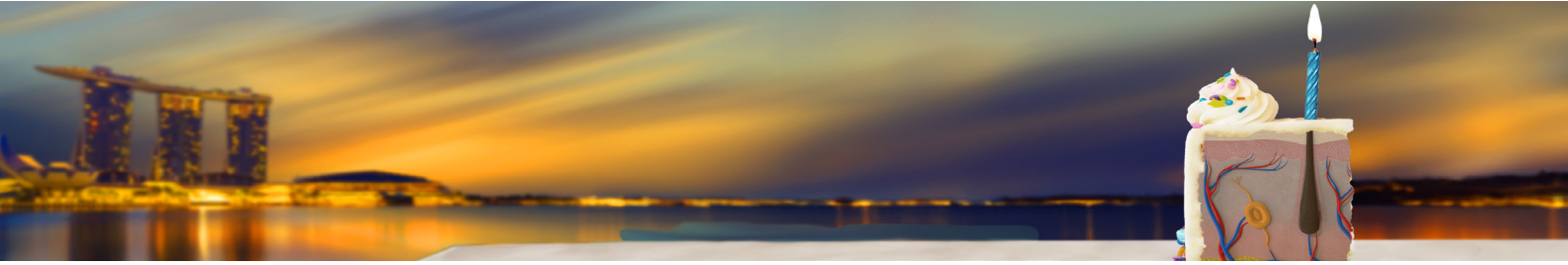
St John's Institute of Dermatology, King's College London, London, U.K.

ABSTRACT

Massive progress has been made over the last 35 years in discovering the genetic basis of inherited skin diseases. These molecular data have provided fascinating new insights into skin biology and disease pathobiology as well as helping improve genetic counselling and patient management. The advent of next generation sequencing has boosted mainstream molecular diagnostics for patients with widespread adoption of targeted gene panel screening for various genodermatoses. Major benefits for patients with inherited skin diseases, however, have been somewhat limited. Although delivery of exciting gene and cell-based therapies to a minority of patients has occurred, access to such breakthrough therapies is somewhat restricted. Moreover, although multi-omic studies have helped characterize mechanisms of disease and offered complementary approaches to treatment through alleviation of symptoms or drug repurposing, being able to change the lives of patients with rare skin diseases in any substantial way still has a long way to go. This presentation will reflect on a personal genodermatosis journey of more than 3 decades of gene hunting and discovery, of early phase clinical trials, of international collaboration, of unmet need in patients, and of an ongoing hope for being able to do something different for patients with inherited skin diseases.

BIO

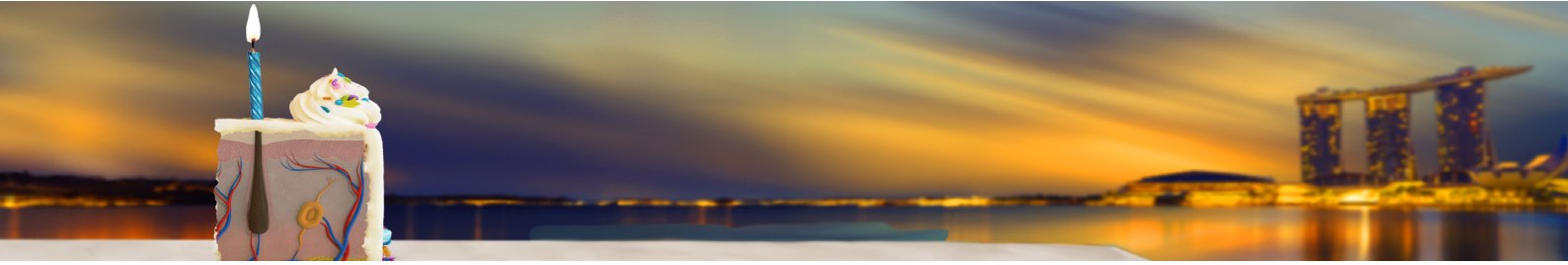
John McGrath is the academic head of St John's Institute of Dermatology in London where he also runs the Genetic Skin Disease Group. He holds the Mary Dunhill Chair in Cutaneous Medicine at King's College London and is Honorary Consultant Dermatologist to the Guy's and St Thomas' National Health Service Foundation Trust. He is also currently a Yu-Shan Fellow at the National Cheng Kung University in Tainan, Taiwan. His expertise is in genodermatoses, discovering genes and testing experimental therapies to improve patient care. He has held several leadership positions within European dermatology including serving as President for the European Society for Dermatological Research and the European Dermatology Forum. He has published >550 articles and will become editor-in-chief of the British Journal of Dermatology from July 2024.



SPEAKER ABSTRACTS

Day 2

14 Mar 2024



Spatial regulation of extracellular matrix turnover rates guides macro-scale organ shape in mouse skin

Hironobu Fujiwara

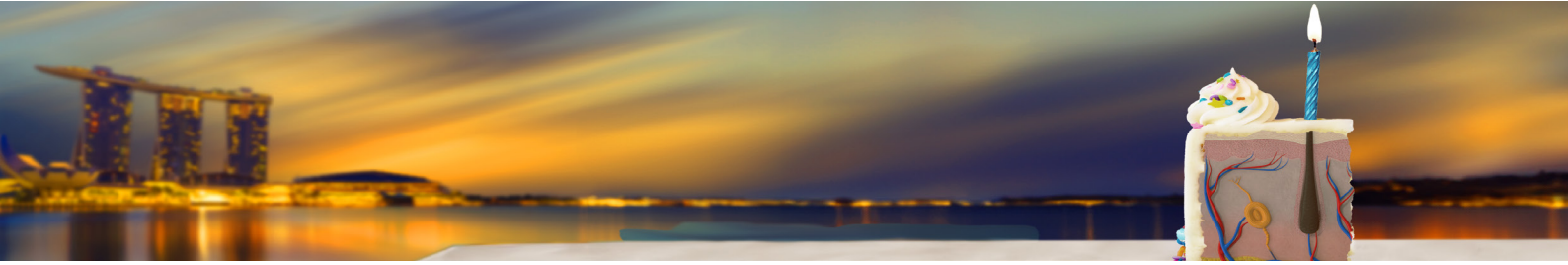
RIKEN Center for Biosystems Dynamics Research (BDR), Kobe, Japan

ABSTRACT

Multicellular organisms are intricate composites of cells and extracellular matrices (ECMs). An ECM is a complex polymer network of proteins that provides cells with diverse biochemical and biomechanical cues/memories with geometrical information. One major type of ECM is the basement membrane (BM), which is a thin, dense, sheet-like ECM that surrounds most tissues in metazoans. The BM has long been considered a static support structure, but recent studies in Drosophila and C. elegans suggest that it is far more dynamic than previously thought at molecular and tissue levels. In this talk, using a developing mouse hair follicle as a model, I will introduce our recently established long-term live imaging method of fluorescently-labelled BM proteins. This approach allows for the quantitative measurement of the BM's homeostatic turnover and its geometrical changes. I will discuss how spatially distinct BM turnover rates, from hour-to-day time scales, guide the directional expansion of the BM, cell displacement, division orientation of epithelial progenitors and macro-scale organ shape.

BIO

Hironobu Fujiwara completed his PhD study on the biochemical characterization of basement membrane proteins under the guidance of Dr. Kiyotoshi Sekiguchi at Osaka University. He undertook his post-doctoral research in the same laboratory, with a particular focus on the role of basement membrane in mouse embryonid body development. In 2007, he joined Dr. Fiona Watt's laboratory in Cambridge, where he discovered that the basement membrane of hair follicle stem cells functions as a muscle cell niche. In 2012, he became a principal investigator at the RIKEN Center for Developmental Biology (CDB), which was reorganized into the RIKEN Center for Biosystems Dynamics Research (BDR) in 2018. His current research interest lies in understanding how stem cells and their microenvironment guide skin development and regeneration.



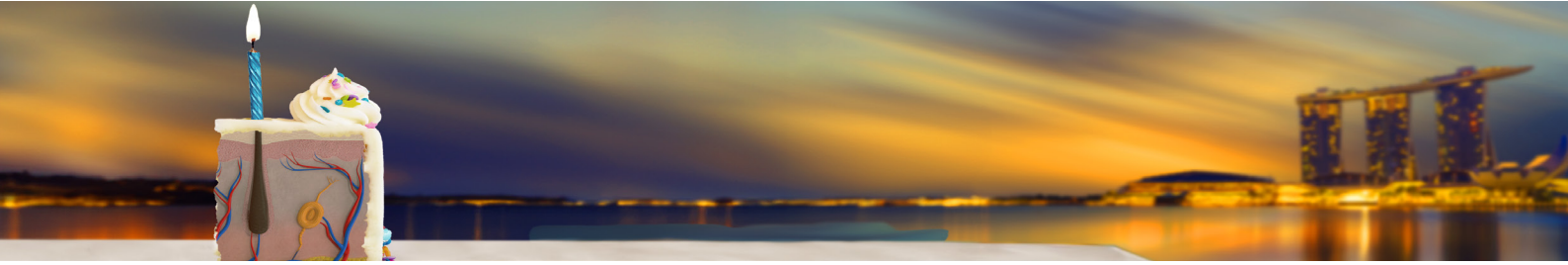
Short talk

Developing ‘diseased’ 3D *in vitro* human skin wound models to study the effect of therapeutics for chronic wounds

Priscilla L.K. Lim[1], Mandy Tan[1], Aishah Alimat[2], Joycelyn Lee[2], Alicia Yap[2], Declan Lunny[2], Cheong Ee Cherk[3], Joseph Lo4, Carine Bonnard[1,2]

*[1]Model Development, A*STAR Skin Research Labs (A*SRL), Agency for Science, Technology and Research (A*STAR), Republic of Singapore; [2]Asian Skin Biobank, Skin Research Institute of Singapore (SRIS), A*STAR, Republic of Singapore; [3]Plastic, Reconstructive and Aesthetic Surgery, Tan Tock Seng Hospital (TTSH), Republic of Singapore; [4]Vascular Surgery, Woodlands Health (WH), Republic of Singapore*

To assess the effect of new therapeutics on wound repair and explore their underlying mechanisms, simplified 2D and 3D in vitro skin wound models are used. To simulate the pathophysiology of chronic wounds, animal models are well-recognized alternatives. However, none of the current models can fully recapitulate chronic wounds in humans, leading to failure of many clinical trials. We therefore aim to develop ‘diseased’ human skin models that mimic chronic wound context to validate our findings on acute wounds and establish an efficient platform to test new therapeutics for hard-to-heal wounds and investigate their mode of action. We are optimizing a well-established de-epidermized dermis-human skin equivalent (DED-HSE) wound model to recapitulate chronic wound environment following three main approaches: 1) incorporate ‘unhealthy’ skin cells and/or acellular dermis derived from patients with recalcitrant wounds, 2) modulate tissue culture systems by incorporating external ‘stress’ factors, and 3) validate our in vitro model by assessing their response to therapeutics. In collaboration with local surgeons, waste surgical skin tissues are collected from individuals undertaking plastic surgery and patients who undergo lower limb major amputations to prepare ‘healthy’ and ‘diseased’ DED-HSEs. Preliminary results showed great variability of wound re-epithelialization across different donors’ DEDs although the same control keratinocytes were used. Wound closure was significantly slower in ‘unhealthy’ DEDs compared to control, suggesting that the extra cellular matrix composition plays a central role in the re-epithelialization process. Upon validation, this platform will be used to assess new therapeutics and investigate their mode of action.



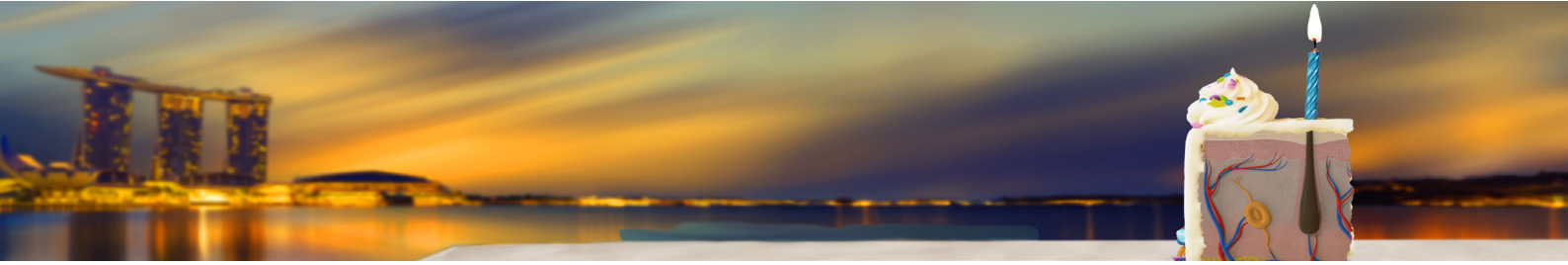
Short talk

TGF-β1 secretion via keratinocytes-derived extracellular vesicles drives fibroblast induced tissue contraction

Khek-Chian Tham[1], Thankiah Sudhaharan[2], Keng-Hwee Chiam[3], Soon Yew John Lim[2], Seong Soo Lim[1], Graham D. Wright[2], Carine Bonnard[1], John E.A. Common[1]

*[1]A*STAR Skin Research Labs (A*SRL), Agency for Science, Technology and Research (A*STAR), Singapore; [2]A*STAR Microscopy Platform (AMP), Research Support Centre (RSC), Agency for Science, Technology and Research (A*STAR), Singapore; [3]Bioinformatics Institute (BII), Agency for Science, Technology and Research (A*STAR), Singapore*

Tissue contraction and remodelling are important processes for wound healing and homeostasis. We investigated molecular and cellular events that regulate skin contraction using our 3D reconstructed full-thickness skin models. Significant contraction of the collagen-matrix was observed only when fibroblasts and keratinocytes were co-cultured, suggesting that paracrine signalling may drive contraction. Disrupting the actomyosin network using Y-27632 (ROCK inhibitor) or Blebbistatin (Myosin inhibitor) could independently prevent contraction. RNAseq, RNAscope and pathway analysis revealed TGF- β1 activation in 'contracted' 3D skin models compared to Y-27632-treated models, with upregulation of several extracellular matrix genes, such as COL1A2, COL6A1, FN1, DCN, MMP1, MMP3, and MMP9. Multiphoton microscopy confirmed increased collagen density around fibroblasts in contracted collagen-matrix versus Y-27632-treated model. Targeted inhibition of the TGF- β1 signaling pathway with LY364947, or with TGF- β1 neutralizing antibodies, could rescue the contraction. Through microscopy imaging, we observed that (1) TGF-β 1 co-localized with extracellular vesicles (EV) below the basal keratinocytes in contracted cultures, (2) Y-27632 prevented EV secretion, and (3) Calpeptin, an EV inhibitor, reduced collagen-matrix contraction. Collectively, our data show that the ROCK signalling pathway promotes EV formation and release by basal keratinocytes. TGF- β1secreted by EV subsequently activates expression of target genes that drive ECM remodelling and tissue contraction. We therefore propose that 3D reconstructed skin model is a suitable in vitro tool for studying wound healing and skin fibrosis.



Uncovering the role of resident skin macrophages in development and disease

Srikala Raghavan, Uttkarsh Ayyangar and Ryan Lim

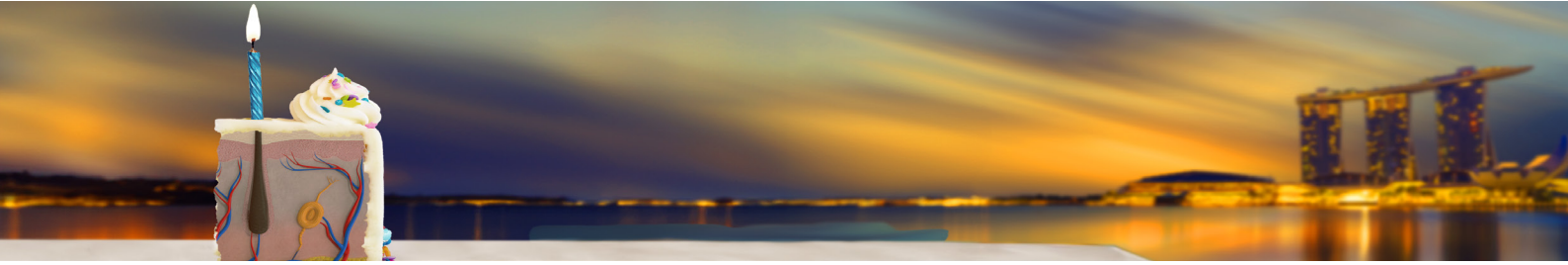
*A*STAR Skin Research Labs*

ABSTRACT

Tissue-resident macrophages are recruited to the embryonic skin from both the yolk sac and the fetal liver at around E12.5, concomitant with the onset of skin development. Work in our lab has focused on understanding the role of these embryonic skin resident macrophages in development and disease. Depleting macrophages using blocking antibodies and genetic models results in remarkable developmental delays characterized by defects in hair follicle growth and epithelial homeostasis. On the other hand, using a mouse model for sterile inflammation, we show that embryonic skin resident macrophages acquire an increased pro-remodeling state that results in exacerbated disruption of skin-ECM homeostasis. Notably, these state changes in the macrophages are associated with dynamic cytokine and metabolic crosstalk between the epidermis and macrophages. Using genetic KOs, NGS, small molecule, and metabolic pathway inhibitors, I will discuss our efforts to uncover the epithelial-immune crosstalk that underpins the roles of these innate immune cells.

BIO

Dr. Srikala Raghavan obtained her Ph.D from the University of Cambridge and did her post-doctoral training with Prof. Elaine Fuchs at the University of Chicago and later at The Rockefeller University. In 2005, Dr. Raghavan established her lab at Columbia University NY, at the College of Dental Medicine and Dept of Dermatology. In 2012, she was recruited to inStem Bangalore to establish the Centre for Inflammation and Tissue Homeostasis where she is an Associate Professor. In January 2020, Prof. Raghavan joined A*SRL, A*STAR as a Principal Investigator. The Raghavan Lab studies stem cell homeostasis and immune regulation in the skin.



Newly identification of a CXCR6+ pathogenic skin-resident CD4+ T cell subset in a mouse model of allergic dermatitis that requires CXCL16 for its maintenance

Kenji Kabashima[1,2], Shuto Kanameishi[1], Ryota Asahina[1]

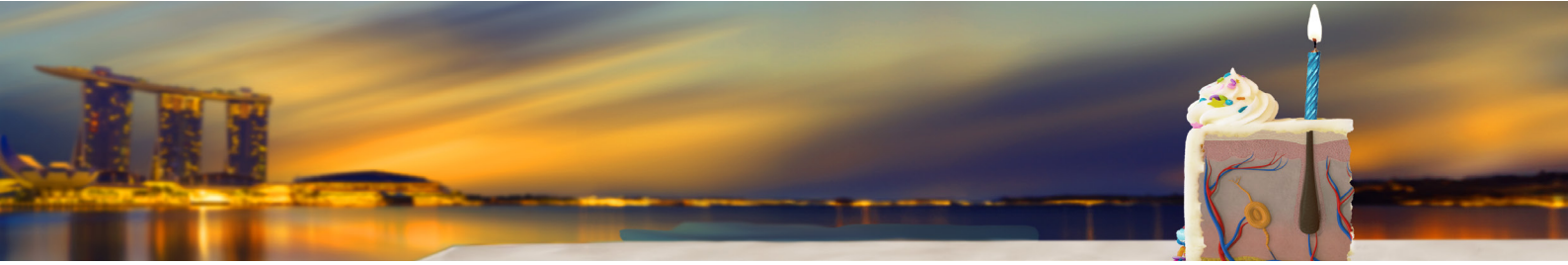
*[1]Department Dermatology, Kyoto University, Kyoto, Japan; [2]SRIS/A*SRL, Singapore*

ABSTRACT

CD4+ tissue-resident memory T (TRM) cells persist in the dermis following an allergic response and facilitate immediate inflammation upon antigen re-encounter. The mechanisms governing CD4+ TRM cell maintenance and their functional diversity, however, are not fully elucidated. In this study, we utilized a delayed-type hypersensitivity model and performed adoptive transfer of ovalbumin (OVA)-specific CD4+ T cells into T cell receptor-β deficient mice. Post sensitization with OVA emulsion and subsequent OVA challenge in the ear skin, CD4+ T cells with a CD44+CD69+ TRM phenotype were observed in the dermis on day 35, post-resolution of ear swelling. Parabiosis experiments substantiated their tissue-resident nature. Immunohistochemical analysis demonstrated clustering of CD4+ TRM cells with CD301b+ dermal dendritic cells. The significance of this interaction was investigated by selectively depleting CD301b+ cells in CD301b-diphtheria toxin receptor mice, resulting in a reduction of both CD4+ TRM cell numbers and their clusters. This depletion correspondingly diminished CXC-chemokine ligand 16 (CXCL16) expression. The receptor for CXCL16, CXC-chemokine receptor 6 (CXCR6), was predominantly expressed on CD4+ TRM cells. Inhibition of CXCL16 curtailed the proliferation of CXCR6+CD4+ TRM cells and mitigated rapid ear swelling upon antigen re-exposure. RNA sequencing revealed that upon re-challenge, CXCR6+CD4+ TRM cells generated IFN-γ and IL-13, while CXCR6-CD4+ TRM cells exhibited a Foxp3+ regulatory T cell phenotype. These findings suggest that CXCR6+CD4+ TRM cells contribute to pathogenesis in recall responses by secreting effector cytokines and that their sustenance is mediated through interactions with CD301b+ dendritic cells via CXCL16. This elucidates a potential novel therapeutic avenue for preventing recurrent chronic allergic skin disorders, such as atopic dermatitis.

BIO

Dr. Kenji Kabashima graduated from Kyoto University in 1996 and further honed his medical and dermatology skills through training at the US Naval Hospital in Yokosuka, Kyoto University Hospital, and the University of Washington Medical Center. He initiated his research on bioactive lipid mediators at Kyoto University and received his PhD there. Subsequently, he pursued his studies at UCSF and the University of Occupational and Environmental Health. Currently, Dr. Kabashima holds several prominent positions, including Professor and Chair of the Department of Dermatology at Kyoto University Graduate School of Medicine, Senior Principal Investigator at A*STAR (Singapore), and Visiting Consultant at the National Skin Centre (Singapore). He also serves as the President of the Japanese Society for Investigative Dermatology. His research focuses on understanding the underlying mechanisms of inflammatory skin diseases such as atopic dermatitis, contact dermatitis, and psoriasis, as well as exploring 3D visualization of the skin using two-photon microscopy and drug development.



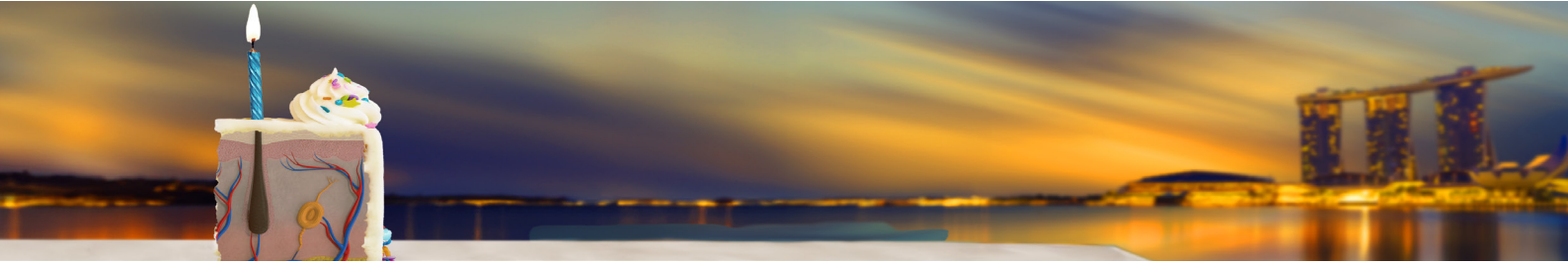
Short talk

Epidermal disruption induced by *Vulcanodinium rugosum* toxin is rescued by gene knockout of ZAKα

Stephen Wearne[1], Pritisha Rozario[2], Gee Ann Toh[2], John Common[1], Franklin Zhong[2]

*[1]A*STAR Skin Research Labs (A*SRL), Agency for Science, Technology and Research (A*STAR), Singapore; [2]Lee Kong Chian School of Medicine (LKCMedicine), Nanyang Technological University (NTU), Singapore*

The mitogen activated protein kinase, ZAKα, is involved in the innate immune response through the activation of the NLRP1 inflammasome. Previous work has established that ZAKα and NLRP1 sense and respond to bacterial toxins which specifically target ribosome elongation factors, resulting in apoptosis, such as the diphtheria toxin. The algae, *Vulcanodinium rugosum*, has been found to produce a compound called portimine A, another potent inducer of apoptosis. With algal blooms of *V. rugosum* having been associated with dermatitis in swimmers. Here, we therefore assessed ZAKα response to portimine A in skin. The compound was applied onto an in vitro 3D skin model comprised of primary keratinocytes either with or without the ZAKα knocked out via CRISPR-Cas9 gene editing. We found that exposure to portimine A resulted in excessive epidermal cell death, tissue damage and cytokine release. However, ZAKa gene knockout rescued this phenotype, reducing the induced damage, as well as significantly reducing IL-1α, IL-1β and IL18 cytokine levels. These results serve to highlight the critical role ZAKa has in the pathogenesis of this algal toxin and how manipulation of its expression could provide novel treatments to specific skin disruptions.



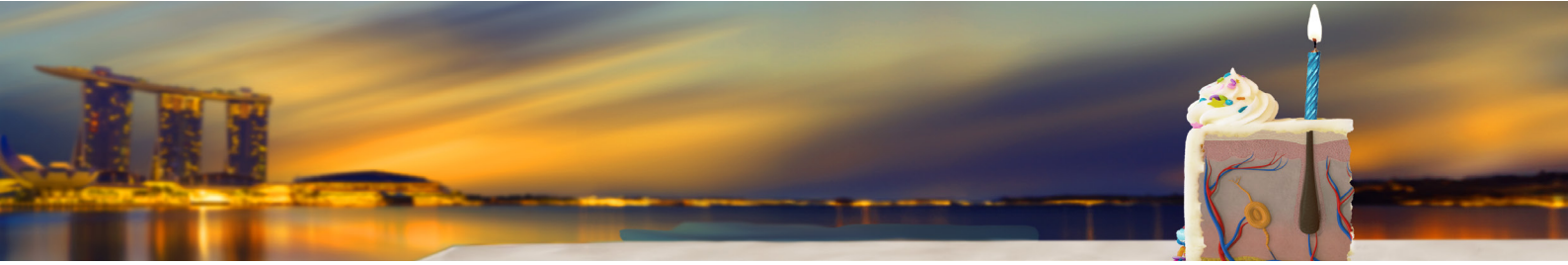
Short talk

Deciphering the immune mechanism of autoreactive B cells in Pemphigus

Baptiste Janela[1,2,3], Gerome Bohelay[4,5], Gokce Oguz[6], Vipin Narang[7], Bernett Lee[1], Adaikalavan Ramasamy[6], Anne Marie Cardine[8], Vivien Hebert[9], Florent Ginhoux[7], Evan Newell[7], Pascal Joly[9], Frederic Caux[4,5], Philippe Musette[4,5]

[1]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore; [2]Skin Research Institute of Singapore, Singapore; [3]National Skin Centre, Singapore; [4]Department of Dermatology and Referral Centre for Autoimmune Bullous Diseases, Avicenne Hospital, France; [5]Inserm UMR 1125, University Sorbonne, France; [6]Genome Institute of Singapore, Singapore; [7]Singapore Immunology Network, Singapore; [8]INSERM UMRS 976, France; [9]Inserm U1234, CHU Rouen, France

Pemphigus represents a group of severe autoimmune bullous diseases driven by the production of autoantibodies by autoreactive B cells that are mainly directed against the desmosomal 1 and 3 adhesion proteins. A better understanding of the autoreactive B cells biology will allow us to develop new therapeutic strategies targeting the specific depletion of autoreactive effector B cells while maintaining B cells immune surveillance. Our objective was to perform proteomic and transcriptomic analysis on Dsg3+ autoreactive B cells at a single cell resolution using innovative analytic tools and technologies. The characterization of the frequency and phenotype of immune B cell subsets by high dimensional analysis coupled to bulk RNA sequencing analysis have shown the presence of specific B cell subset in pemphigus patients associated with a high expression of CD83 compared to patients in remission or healthy donors. The use of “index sorting” of Dsg3+ versus Dsg3- B cell subsets coupled to single cell RNA sequencing from pemphigus patients versus healthy donors has allowed us to identify unique activated pathways and marker(s) including CD83 that are expressed mainly on these Dsg3+ B cells. Analysis of lesional skin of pemphigus patient by immunofluorescence revealed the presence of ectopic lymphocytic structures enriched with Dsg3+ CD83+ autoreactive B cells. In addition, activation of CD83 leads to anti-Dsg3 autoantibodies production in vitro. Our results allow a better understanding of the autoreactive B cells pathways involved in pemphigus.



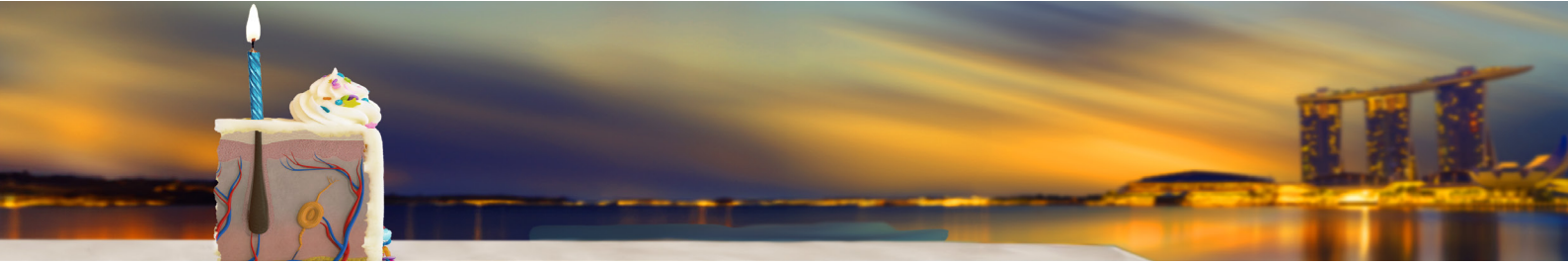
Short talk

The ribotoxic stress response drives inflammation and epidermal thickening in UV-irradiated skin *in vivo*

Anna Constance Vind[1], Zhenzhen Wu[1], Goda Snieckute[1], Toh Gee Ann[2], Malin Jessen[3], José Francisco Martinez[1], Peter Haahr[1], Thomas Levin Andersen[4], Melanie Blasius[1], Nina Loeth Maartenson[5], Mads Gyrd-Hansen[3], Franklin Zhong[2], Simon Bekker-Jensen[1]

[1]Center for Gene Expression, Department of Cellular and Molecular Medicine, University of Copenhagen, Denmark; 2Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, [3]LEO Foundation Skin Immunology Research Center, Department of Immunology and Microbiology, University of Copenhagen, Denmark; [4]Clinical Cell Biology, Department of Pathology, Odense University Hospital, Denmark; [5]Department of Pathology, Rigshospitalet, Denmark

Solar UVB light causes damage to the outermost layer of the skin. This insult induces rapid local responses such as inflammation, keratinocyte cell death and epidermal thickening. A stress response pathway that is activated by UVB light is the Ribotoxic Stress Response (RSR), which depends on the ribosome-associated MAP3K ZAK and culminates in p38 and JNK signaling. Using ZAK knockout mice, we here show that it is the RSR that is responsible for the early manifestation of UVB-induced skin inflammation and epidermal thickening in vivo. Likewise, we show ZAK mediates upregulation of multiple inflammatory transcripts in UVB-irradiated human keratinocytes. We further show that the RSR underlies both pyroptotic and apoptotic cell death responses in keratinocytes. Biochemcially, ZAK detects UVB-induced ribosomes collision via the small ribosomal protein RACK1, and consequently deletion of RACK1 abrogates these responses. In sum, our work highlights that skin cells rely on ribosomal stress signals for rapid inflammatory responses to UV exposure, and we speculate that these pathways could have broader implications for the pathogenesis of inflammatory skin diseases.



Beyond the silence: Decoding microRNA-335 dynamics in Atopic Dermatitis

Shan Quah[1], Wen Chiy Liew[1], Gowtham Subramanian[1], Ramisa F. Kabir[1], and Prabha Sampath[1,2]

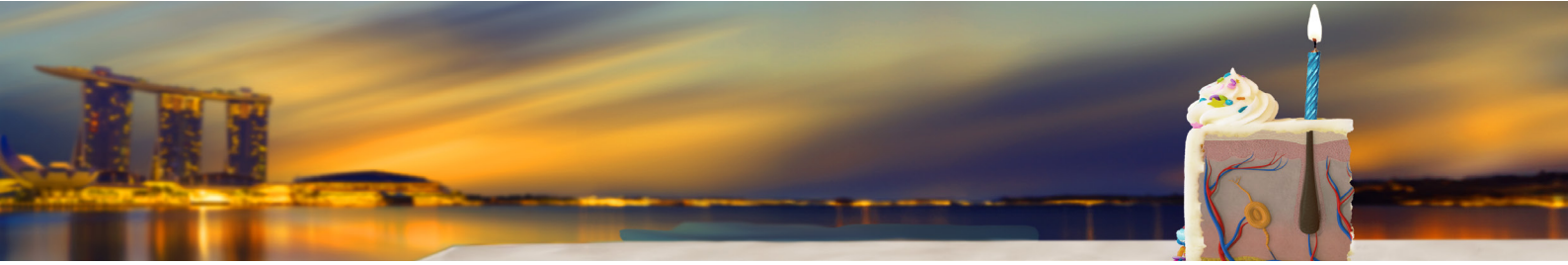
*[1]A*STAR Skin Research Labs (A*SRL), Agency for Science, Technology and Research (A*STAR), Singapore; [2]Program in Cancer and Stem Cell Biology, Duke-NUS Medical School, Singapore*

ABSTRACT

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease with severe impact on patient's quality of life, affecting one-fifth of all school children and 2-10% of adults in Singapore. Globally, AD appears to have a similar prevalence and represents a large clinical burden. Defective skin barrier and exposure to allergens are known to initiate the development of AD. We recently identified a microRNA, miR-335, as a key driver of keratinocyte differentiation and cornification, which is required for the establishment of a healthy skin barrier. In AD lesional skin, miR-335 expression is aberrantly lost and in the absence of miR-335 the target SOX6 is abnormally expressed throughout the epidermis, where it impairs skin barrier development. Further, our studies indicate a direct role of miR-335 in suppressing pro-inflammatory CASP7/TNF-a/RANTES pathway in cell-intrinsic fashion. Our objective is to restore miR-335 expression, rectify the associated dysregulated pathways, which can potentially result in the repair of barrier defect and the resolution of the allied inflammation in atopic dermatitis.

BIO

Dr. Prabha Sampath obtained her Ph.D. in Molecular Medicine in Cleveland Clinic Foundation, Ohio, United States in 2004. Working on gene regulation during inflammation, Dr. Sampath elucidated RNA and protein factors comprising major pathways in inflammation. As a postdoctoral fellow at the Center for Cardiovascular and Regenerative Medicine, University of Washington, Dr. Sampath worked on translational control mechanisms in embryonic stem cell differentiation. Dr. Sampath is the recipient of prestigious A*STAR Investigatorship award, and she joined the Institute of Medical Biology, Biopolis, Singapore to set up her own research group in May 2008. She is now a Senior Principal Investigator at ASRL, holds an adjunct position at the Duke NUS School of Medicine. Currently pursuing research on molecular mechanisms underlying dysregulated translational regulation in epithelial disorders; with an objective to integrate this information within the framework of pathophysiology her projects are focused on identification of specific targets for therapeutic intervention.



Ionic Liquids for Transdermal Drug Delivery

Samir Mitragotri

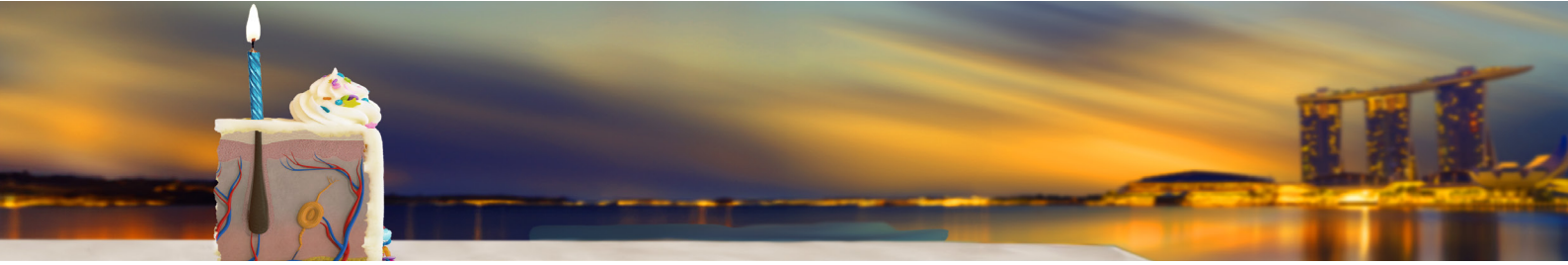
Harvard University, USA

ABSTRACT

Ionic liquids offer exciting opportunities for several therapeutic applications. Their tunable properties offer control over their design and function. Starting with biocompatible ions, we synthesized a library of ionic liquids and explored them for various drug delivery applications including transdermal drug delivery. Ionic liquids provided unique advantages including overcoming the stratum corneum barrier and delivery across the intracellular barriers within the skin. They also stabilized proteins and nucleic acids and enabled the delivery of biologics across and into skin. I will present an overview of the design features of ionic liquids and their novel applications for topical delivery.

BIO

Samir Mitragotri is the Hiller Professor of Bioengineering and Wyss Professor of Biologically Inspired Engineering at Harvard University. His research is focused on transdermal, oral, and targeted drug delivery systems. He is an elected member of the National Academy of Engineering, National Academy of Medicine and National Academy of Inventors. He is also a foreign member of Indian National Academy of Engineering. He is also an elected fellow of AAAS, CRS, BMES, AIMBE, and AAPS. He is an author of over 400 publications, an inventor on over 225 patent/patent applications, and a Clarivate Highly Cited Researcher. He received his BS in Chemical Engineering from the Institute of Chemical Technology, India and a PhD in Chemical Engineering from the Massachusetts Institute of Technology.



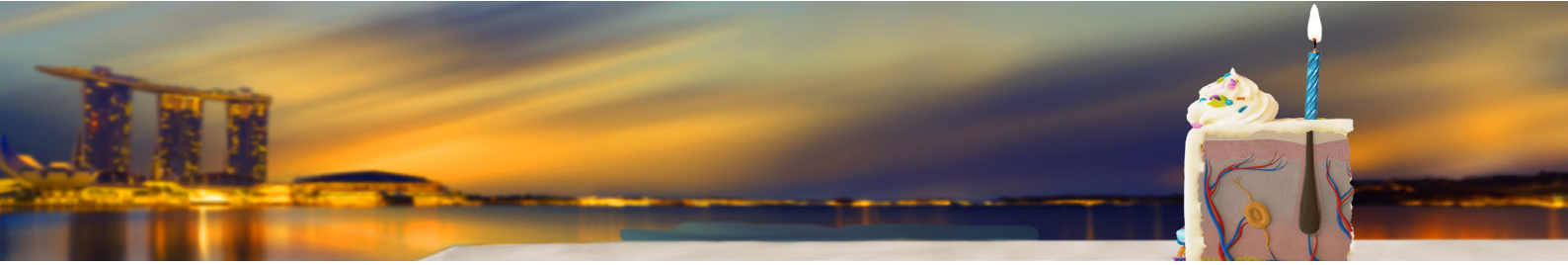
Short talk

Quantitative biochemical analysis for assessing skin inflammatory conditions using handheld confocal Raman spectroscopy

Keertana Vinod Ram[1], Dinish U. S[1], Yik Weng Yew[2,3], Renzhe Bi[1], Amalina Binte Ebrahim Attia[4], Valerie Teo Xinhui[1], Poongkulali Rajarahm[1], Hazel H. Oon[5], Steven Tien Guan Thng[2], Malini Olivo[1]

*[1]A*STAR Skin Research Labs (A*SRL), Agency for Science, Technology and Research (A*STAR), Singapore, Republic of Singapore; [2]National Skin Centre, Singapore; [3]Lee Kong Chian School of Medicine, Nanyang Technological University, Clinical Sciences Building, Singapore; [4]Biomedical Research Council (BMRC), Agency for Science, Technology and Research (A*STAR), Singapore, Singapore; [5]National Skin Centre and Skin Research Institute of Singapore (SRIS), Singapore*

Distinguishing between Atopic Dermatitis (AD) and psoriasis, the two prevalent skin inflammatory conditions that share similar symptoms, is often reliant on subjective evaluations by clinicians, introducing potential interpersonal variability. This study seeks a quantitative approach by utilizing a handheld confocal Raman spectroscopy (CRS) system to analyze skin biochemicals in 9 AD, 6 psoriasis, and 11 healthy subjects. Raman spectral measurements were conducted at 671 nm and 785 nm. Spectral unmixing was performed to deduce relative changes in skin biochemicals revealing distinct patterns. Additionally, clinical severity scores (SCORAD and PASI) were calculated, and clinical assessments included the utilization of a vapometer, moisture meter, pH meter, and erythrosine sedimentation rate for comparison with established benchmarks. Notably, AD exhibits lower water content, a finding supported by transepidermal water loss data. Specific trends in ceramide subclasses emerge: AD displays a decrease in ceramide 2 (CER 2) and ceramide 3 (CER 3) in lesional regions, while psoriasis exhibits an increase in CER 2 and a decrease in CER 3 compared to healthy skin. Cholesterol levels further contribute to differentiation, with lower concentrations in lesional AD and significantly higher concentrations in lesional psoriasis compared to healthy skin. The portable CRS system effectively identifies relative variations in water, ceramides, and cholesterol, providing an objective means of differentiation and valuable insights for the development of targeted disease-specific topical treatments.



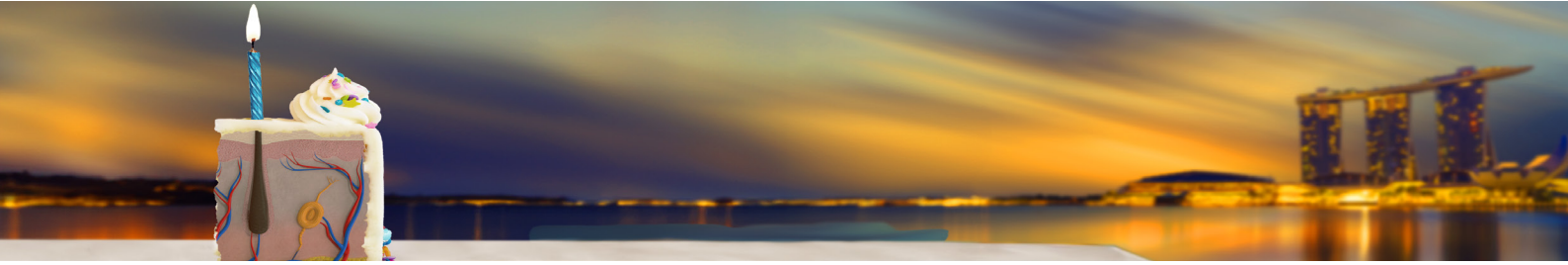
Short talk

Elucidating the role of nuclear mechanotransduction in homeostasis and fibrosis

Xianrong Wong[1], V Thamil Selvan[2], Myeongjun Jun[3], Vladimir Kozlov[1], Rafidah Abdul Mutalif[1], Qiao You Lau[1], Anandh Kumar Raju[2], Ravisankar Rajarethinam[2], Kai Ping Sem[1], Jing Wen Ng[1], Wei Liang Hong[1], Yan Chi Lam[1], Vinay Tergaonkar[2], Keng-Hwee Chiam[3], Colin L Stewart[1], Brian Burke[1] and Yin Loon Lee[1]

*[1]A*STAR Skin Research Labs, Agency for Science Technology and Research (A*STAR), Singapore; [2]Institute of Molecular and Cell Biology, Agency for Science Technology and Research (A*STAR), Singapore; [3]Bioinformatics Institute, Agency for Science Technology and Research (A*STAR), Singapore*

The transmission of mechanical forces, or mechanotransduction, in cells is important for normal development and disease progression. A major mechanotransduction hub is the nuclear envelope-localized Linker of Nucleoskeleton and Cytoskeleton (LINC) complex, which forms a link in a mechanical chain that stretches from the extracellular matrix to the cytoskeleton and the nucleus. The LINC complex is required for embryonic development, since loss of two critical LINC complex genes results in perinatal lethality. We sought to investigate the role of the LINC complex in adult homeostasis and in fibrosis, a mechanosensitive process. To do so, we generated and characterized mice where the LINC complex could be conditionally ablated in adult animals. Interestingly, the LINC complex, and by extension, nuclear mechanotransduction, appears to have a minimal role in adult homeostasis, apart from in the testes. We then investigated the role of the LINC complex in fibrosis. Using an in vitro fibroblast-myofibroblast transition assay, we found that LINC complexes are required for pro-fibrotic TGFβ signaling in dermal fibroblasts and other myofibroblast precursors. We also found that LINC complex disruption blocked durotaxis, a fibrosis-associated form of directed cell migration where cells move from soft to stiff substrates. Turning to in vivo systems, we further found that LINC complex disruption reduces fibrosis in various disease models, including in the skin. A more complete understanding of nuclear mechanotransduction in fibrosis will require further work to understand how nuclear envelope proteins regulate signal transduction from the extracellular mechanical environment.



Innovation in biophotonics technologies for objective assessment of dermatological conditions

Malini Olivo, Dinish U. S, Bi Renzhe, Ghayathri Balasundaram, Jayakumar Perumal

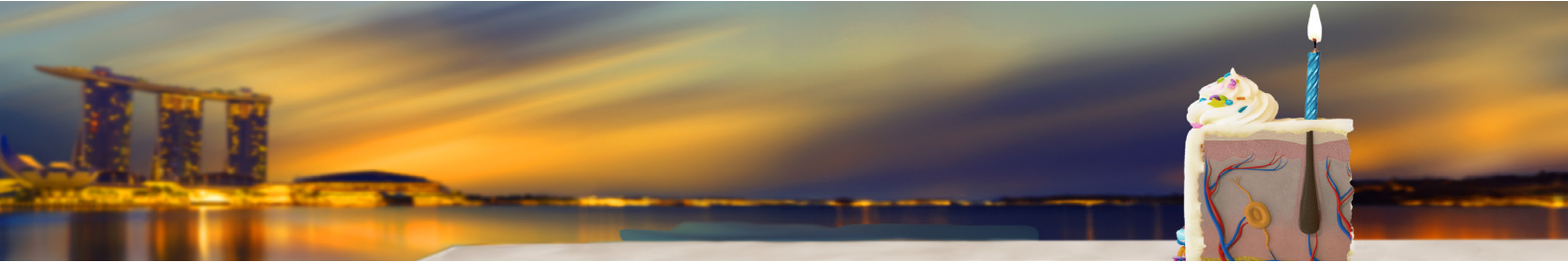
*Translational Biophotonics Lab, A*STAR Skin Research Labs (A*SRL), Agency for Science, Technology and Research (A*STAR), Singapore*

ABSTRACT

In the realm of medical diagnostics, non-invasive biophotonics techniques have emerged as powerful tools for early detection and characterization of various dermatological conditions. This talk highlights our recent advancements in these techniques tailored for enhanced diagnosis and monitoring across a spectrum of skin disorders and gynae-dermatological conditions. Firstly, photoacoustic imaging (PAI), which provides non-invasive label free and functional information in skin cancer and inflammatory conditions is presented. By leveraging on the optical absorption contrast, PAI offers deep tissue penetration and excellent spatial resolution, enabling precise delineation of tumor margins, quantitative assessment of the severity of inflammatory disorders and its treatment response. Furthermore, development of patented in-house handheld confocal Raman spectroscopy systems will be elaborated in the context of skin biochemical analysis for inflammatory skin conditions. By probing skin biochemicals, Raman spectroscopy offers valuable insights into changes associated with inflammation, facilitating early diagnosis and treatment monitoring. In addition, application of diffuse optical spectroscopy (DOS) techniques for gynae-dermatology, specifically for objective assessment of genitourinary syndrome of menopause (GSM) will be presented. By measuring tissue optical properties, DOS enabled the assessment of tissue oxygenation, lipid, and water content in the vulva skin, aiding in the diagnosis and management of GSM. Lastly, surface-enhanced Raman spectroscopy (SERS) is introduced as a novel approach for wound biomarker sensing, providing high sensitivity and specificity in detecting molecular signatures indicative of wound healing progression.

BIO

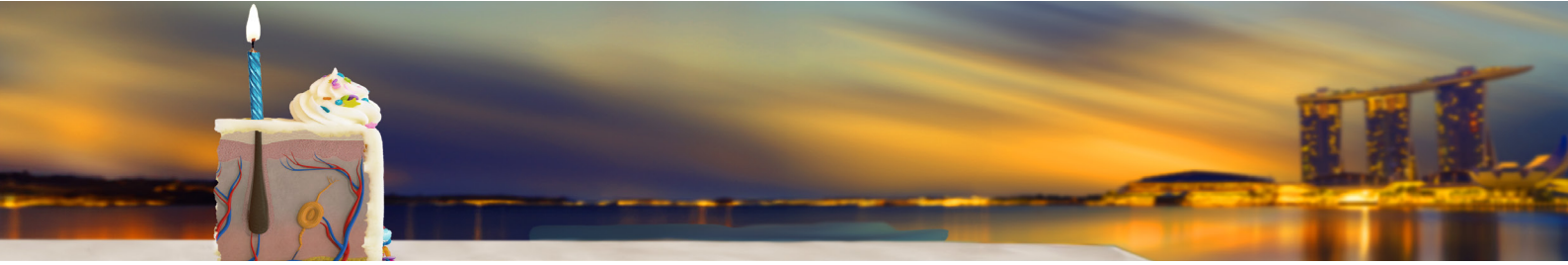
Malini Olivo is the Distinguished Principal Scientist at A*STAR Skin Research Labs (A*SRL), leading the Translational Biophotonics Laboratory. She serves as an Adjunct Professor at the Department of Obstetrics & Gynecology, NUS, Singapore. She has a PhD in Bio-Medical Physics and Malini's expertise in biophotonics has gained international recognition, earning her fellowships from prestigious organizations such as the Optical Society of America, American Institute of Biomedical Engineering and the Institute of Physics, UK. She has secured over USD 25 million in research funding, authored 500+ scientific papers and holds 50 patents for innovative technology platforms, Malini is co-founder of medtech companies highlighting her dedication In translating biophotonics research into impactful healthcare outcomes. She also sits in advisory international and local academic boards to guide and evaluate research in biophotonics.



SPEAKER ABSTRACTS

Day 3

15 Mar 2024



Dermal fat, an important deep skin layer in host defense and repair

Xiaowei Zhang[1], Lixiang Sun[1], Shuai Wu[1], Meimei Yin[1], Chao Ji[2], Maksim V. Plikus[3], Richard L. Gallo[4], Ling-juan Zhang[1]

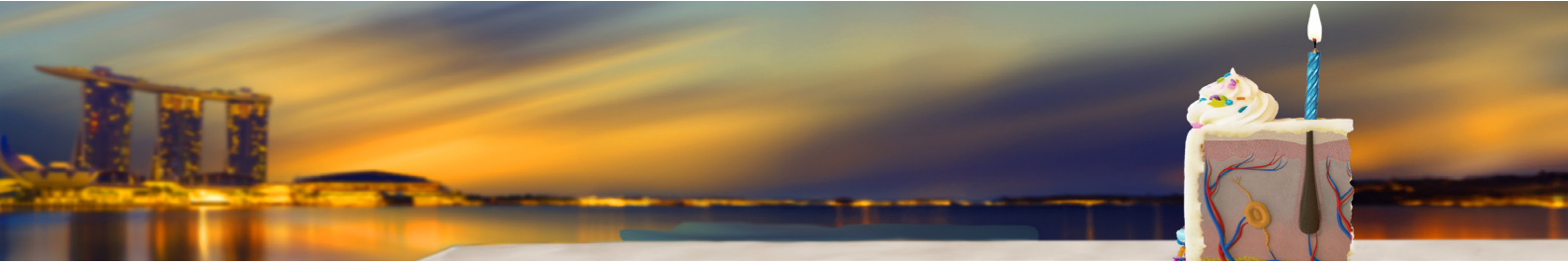
[1]State Key Laboratory of Cellular Stress Biology, School of Pharmaceutical Sciences, Xiamen University, Xiamen, China; [2]Department of Dermatology, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China; [3]Department of Developmental and Cell Biology, University of California, Irvine, USA. [4]Department of Dermatology, University of California, San Diego, USA

ABSTRACT

Dermal white adipose tissue (dWAT), also known as dermal fat, is a unique hypodermal layer consisting of adipocytes and their highly heterogeneous progenitors. We have shown that dWAT plays an essential role in skin innate immune defense against invasive Staphylococcus aureus infection by producing antimicrobial peptides, a process termed as “dermal reactive adipogenesis”. Furthermore, during aging and/or high fat diet induced obesity, activation of the TGFβ-TGFBR-SMAD2/3 pathway abolished the dermal reactive adipogenesis in response to bacterial infection, leading to increased infection risk in aged and/or obese mice. Administration of TGFBR inhibitor and/or PPARγ agonist restored the innate antimicrobial function of dermal fat in aged or obese mice. Our recent work show that reactive dermal adipogenesis is dynamically regulated by an interplay between IL1β and WNT signaling under inflammatory condition during skin development and wound regeneration. Together, our findings have revealed the previously unrecognized innate immune functions of dermal fat, and explain how dysregulation of dermal adipocyte lineage cells may lead to increased risk of bacterial infection, defective wound healing, and/or skin fibrosis.

BIO

Dr. Zhang received her Ph.D. degree in Pharmacology at Oregon State University, and had her Post-doc training then Scientist training at Dr. Richard Gallo’s lab at the department of Dermatology, University of California, San Diego. Since 2018, she has joined Xiamen University as a full time professor in the School of Pharmaceutical Sciences, the State Key Laboratory of Cellular Stress Biology. Her research focuses on exploring the innate immune function of dermal fat in skin infection, wound healing, and/or inflammatory skin diseases. She has published more than 40 papers with more than 3500 citations, and is named the world’s top 2% most-cited Scientist for the year of 2022 (by Elsevier). She serves as associated editor and/or guest editor for journals including Exp. Dermatology, Pharmaceutics, and SEMIN CELL DEV BIOL. She is also a broad member of Chinese society of Skin Immunology, and Chinese society of Investigative Dermatology.



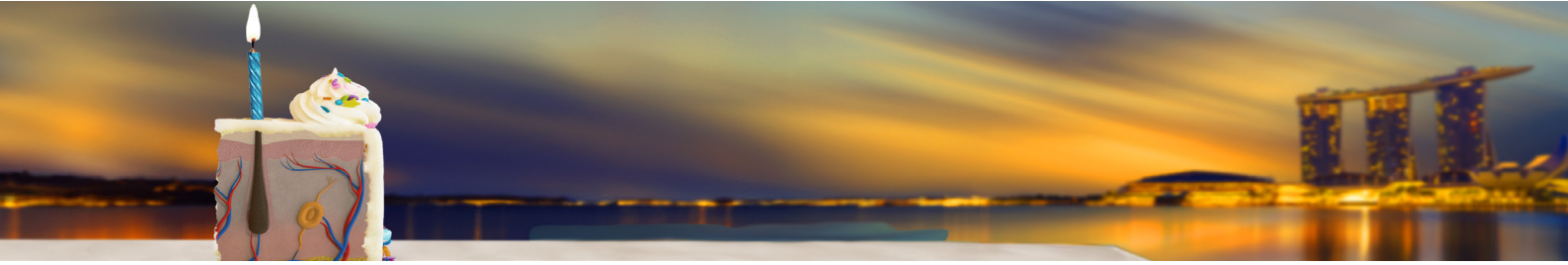
Short talk

Impact of polyketide synthase on Malassezia's PUFA metabolism and its consequence on skin-host dynamics

Shi Mun Lee, Tricia Tan, Ashely Low, Stelle Tan, Yuen-In Lam, Cheryl Leong, Martin Pagac, Thomas Dawson

*A*SRL, A*STAR, Singapore*

Malassezia, a dominant fungal commensal on human skin, is implicated in various dermatoses such as Folliculitis, Dandruff, Seborrheic Dermatitis, and Pityriasis versicolor, attributed to its overgrowth. This fungus thrives on the skin by exploiting its lipid-rich environment, owing to its lack of Fatty acid synthase (FAS), and relies on lipids like mono-, di-, triacylglycerols, and phospholipids present on human skin. To utilize these, Malassezia has evolved to enrich its genome with lipases and phospholipases to access free fatty acids (FFAs) from triacylglycerols. Experimentally, it has been demonstrated that, in the case of dandruff, Malassezia metabolizes oleic acid on the scalp, inducing desquamation, though the responsible metabolites remain unidentified, sparking interest in the roles of fatty acids and their derivatives. Drawing parallels from plant-microbe interactions, where derivatives of polyunsaturated fatty acids (PUFAs) known as oxylipins play a crucial role in resistance development in hosts, this research investigates PUFA metabolism in Malassezia, looking at skin-microbe axis. Despite lacking FAS, Malassezia spp. possess Polyketide Synthase (PKS) with potential roles in PUFA synthesis or metabolism. By knocking out the PKS gene in M. furfur CBS 14141, we observed significant changes in PUFA profiles, cytokine responses, and adhesion properties. These findings suggest that targeting Malassezia's lipid metabolism could help regulate skin inflammation and microbial overgrowth by altering its hydrophobicity. This approach aims to modulate the skin microbiome for health benefits, shifting away from the conventional strategy of eradicating microbes, thus promoting a balanced, healthy skin microbiota.



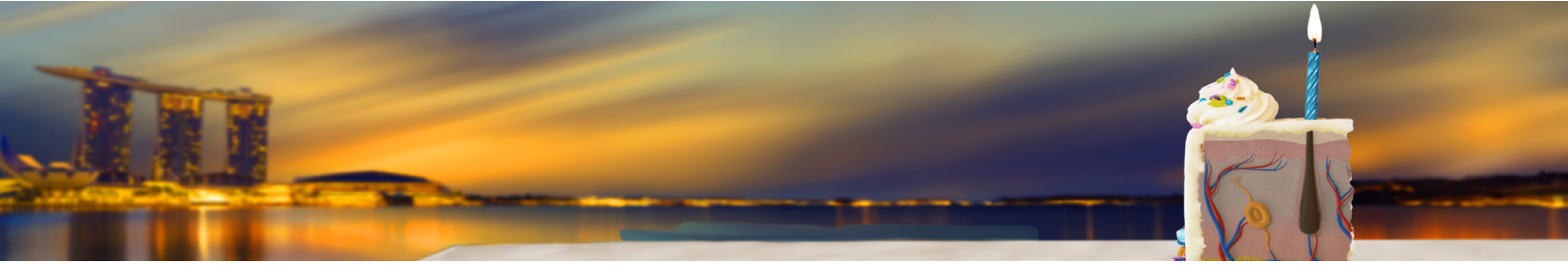
Short talk

Genetic barrier dysfunction drives skin inflammation during atopy and cutaneous pathogenic colonization

Ying Shiang Lim, Belle L.H. Yap and John E.A. Common

*A*STAR Skin Research Labs (A*SRL), Agency for Science, Technology and Research (A*STAR), Singapore, Singapore*

The skin is the first line of defense against invading pathogens and allergenic compounds in the environment, forming a mechanical innate barrier against various exposomes. As such, a dysfunctional skin barrier arising from pre-existing disorders and genetic deficiencies of crucial barrier proteins could result in a breach in this anatomical defense. Filaggrin is an epidermal barrier protein localizing in the stratum granulosum which contributes significantly to the strength of the skin barrier. Clinically, the deficiency of which has been correlated with the predisposition to ichthyosis vulgaris (IV), increasing severity to atopic dermatitis (AD) and susceptibility to several cutaneous infections. However, the mechanisms of how filaggrin-deficiency drives these skin disorders and augment the interactions with microbes remain unclear. Using a mouse model with specific deficiency for filaggrin, we first show that filaggrin-deficiency does not result in increased tissue inflammation or trans-epidermal water loss (TEWL) at baseline. However, filaggrin-deficient animals exhibit increased tissue swelling and TEWL in the ears post atopic induction with calcipotriol treatment relative to wildtype (WT) mice. Despite comparable infiltration of innate immune cells into the tissue, dermal eosinophils express higher levels of IL-1β, a proinflammatory cytokine and Siglec-F, an immunoglobulin-like lectin associated with eosinophilic activation during atopy. Moreover, we also observed that filaggrin-deficiency results in increased tissue inflammation during Staphylococcus aureus colonization, a pathobiontic bacteria commonly overrepresented in AD due to skin dysbiosis. We have thus described an animal model of skin barrier dysfunction with filaggrin-deficient mice, prompting further investigation to elucidate the mechanistic drivers of AD.



Unlocking microbiome medicine for the human skin

Viduthalai R. Regina[1,2], Tarun Chopra[3], Kwok Weihao[3], Sreelakshmi Cheruvalli[1], Ang Sabrina[3], Hashmath Fatimah Binte Jamal Mohamed[1], Kesava Priyan Ramasamy[1], Kay Sarah[1], Chong Yik Yan[1], Eganathan Kaliyamoorthi[1], Rohan Williams[1], Liu Xianghui[1], Vedula Krishna[3], Nasrine Bourokba[3], Anjali Jhingan[4], Steven Thng Tien Guan[4], Olivier Da Cruz[5], Sylvie Riu[7], Romain De Dormael[6], Kahina Abed[6], Olivia Touriguine[7], Roland Jourdain[6], Sylvie Cupferman[5], Luc Aguilar[6], and Scott A. Rice[1,8,9]

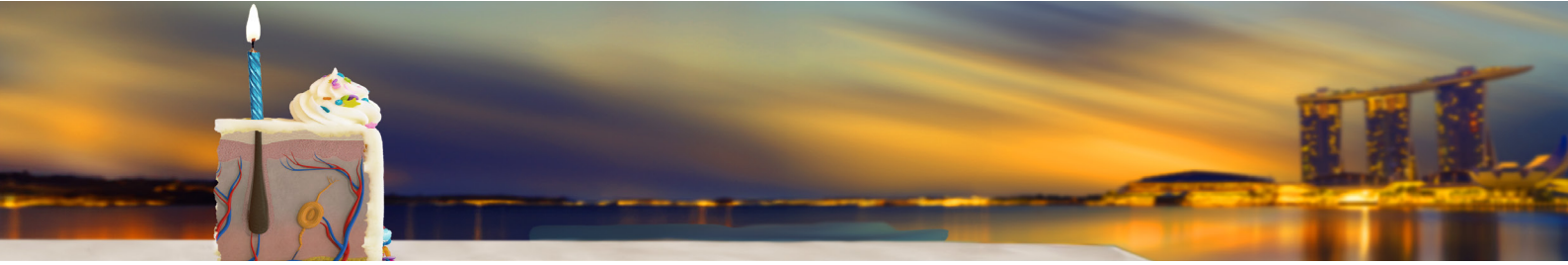
[1]Singapore Centre for Environmental Life Sciences and Engineering, Nanyang Technical University, Singapore; [2]Skin Research Institute of Singapore, Singapore; [3]L'Oréal Research and Innovation Singapore, Singapore; [4]National Skin Centre, Singapore; [5]L'Oréal Research and Innovation, France; [6]L'Oréal Research and Innovation, France; [7]L'Oréal Research and Innovation, France; [8]Australian Institute for Microbiology and Infection, University of Technology, Australia; [9]CSIRO Agriculture & Food, Microbiomes for One Systems Health, Australia

ABSTRACT

For over a decade, research on the human skin microbiome have employed advanced metagenomic sequencing methods to map out the members of the microbiome community that are associated with healthy and diseased skin. A handful of studies have ventured further, attempting to unravel the functional roles of individual skin microbes using the information derived from the metagenomic data. While the volume of data generated by sequencing and analysis has been instrumental in formulating several hypotheses on how the microbiome function, the lack of a robust laboratory-scale experimental system to test these hypotheses has posed a significant challenge in translating these microbiome insights into practical applications. In this talk, I will present my work on developing a multi-species in vitro model that represents the human skin microbiome. This in vitro model enhances our understanding of the complex interactions among the member of the skin microbiome and has laid a solid foundation for uncovering previously unknown skin microbiome-driven processes and the discovery of microbiome derived metabolites. This knowledge is essential in inventing methods to steer the skin microbiome towards a healthier state and opening new avenues in skin health and dermatological treatments.

BIO

Dr. Viduthalai Rasheedkhan Regina (@Vidu) carried out his Ph.D. in microbial adhesion and biofilm formation under the guidance of Prof. Rikke Meyer at the Interdisciplinary Nanoscience Centre (iNANO) at Aarhus University in Denmark. After a post-doc at Aarhus University, Denmark, and a brief entrepreneurial venture in Netherlands, he moved to Singapore and joined SCELSE-NTU as a Research Fellow in 2016. Dr. Vidu's research focuses on the development and study of niche-specific synthetic microbial communities, in vitro. By employing molecular techniques and community ecology frameworks, he investigates inter-species interactions facilitated by secreted metabolites to uncover novel targets and strategies for microbiome engineering. Currently he is a principal research fellow, leading the Skin Microbiome Research Program, at SCELSE, and is the deputy research director at the L'Oreal-SCELSE joint laboratory at NTU.



Bioactive lipids mediating epidermal barrier functionality

Anna NICOLAOU

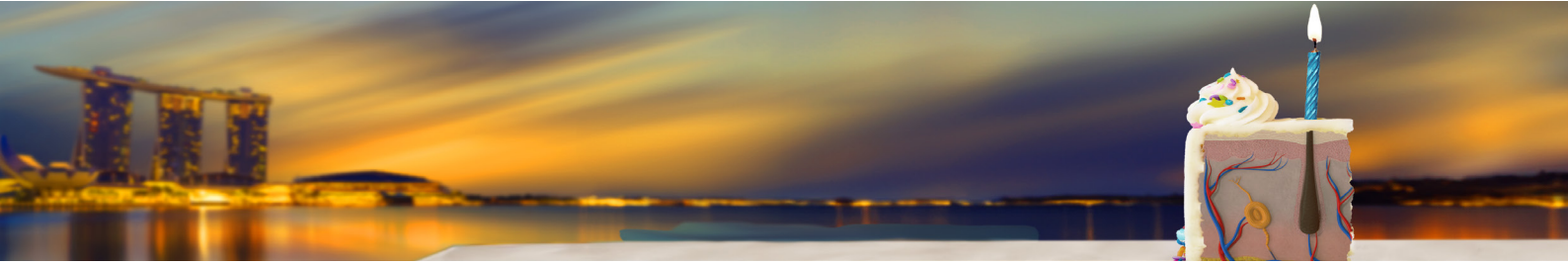
Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK

ABSTRACT

The skin presents a multifaceted barrier protecting the body from external threats, and is reliant on a vast array of bioactive lipids. The epidermal physical barrier is directly dependent on a mixture of free fatty acids, cholesterol and ceramides, found in the stratum corneum. Sebum- and keratinocyte-derived acylglycerols, fatty acids and oxylipins cover the skin's surface, controlling pH and the chemical barrier, whilst directly affecting the cutaneous microbiome and microbiological barrier. Lipid mediators such as eicosanoids, octadecanoids, endocannabinoids and sphingolipids, signal between resident and infiltrating cutaneous immune cells, driving processes underpinning the immunological barrier. These bioactive lipids are necessary for maintaining homeostasis in healthy skin, regulate inflammation and its resolution, and are implicated in cutaneous diseases, systemic conditions with cutaneous involvement, and natural processes such as ageing. The study of the cutaneous lipidome is supported by lipidomics, a mass spectrometry-based platform providing quantitative and qualitative information about the network of skin lipids. Given their central role in all aspects of the epidermal barrier function, lipids can provide valuable resource for the exploration of cutaneous processes, local and systemic disease mechanisms, discovery of biomarkers, and development of preventive measures and interventions to maintain healthy skin function.

BIO

Professor Anna Nicolaou is professor of Biological Chemistry at the Faculty of Biology Medicine and Health, University of Manchester, UK. Anna's research focuses on bioactive lipids and lipidomics, exploring the molecular mechanisms underpinning the role of fatty acids, lipid mediators and complex lipid networks in inflammation, cellular communications and tissue responses. Her lab has a long-standing interest in the cutaneous lipidome and the vital role lipids play in the structure and barrier function of human skin, in health and disease, and the impact of ageing. Other current projects explore the involvement of lipids in chronic inflammation and immune-metabolic diseases, neurodegeneration, cancer, reproductive tissues, and the cardiovascular system. Professor Nicolaou is President Elect of ISSFAL, chair of the Lipidomics division of EuroFedLipid, and serves at the editorial boards of Progress in Lipid Research and BBA Molecular and Cell Biology of Lipids.



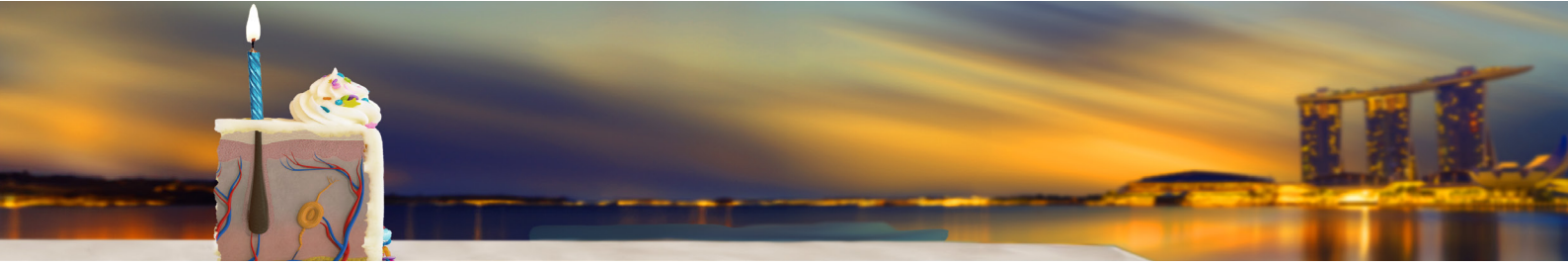
Short talk

The dynamic interplay between dermal adipocyte lineage cells and macrophages in regulating the acne-related skin inflammation and fibrosis

Yiman Liu[1], Qian Yao[2], Kangjun Jiang[2], and Lingjuan Zhang[2]

[1]State Key Laboratory of Cell Stress Biology, School of Life Siences, Xiamen University, Xiamen 361102, China; [2]State Key Laboratory of Cell Stress Biology, School of Pharmaceutical Sciences, Xiamen University, Xiamen 361102, China

Acne vulgaris is a cutaneous chronic inflammatory disorder of the pilosebaceous unit with complex pathogenesis. Excessive skin colonization with Cutibacterium acnes (C.acnes) is considered to be the trigger of skin immune activation during acne pathogenesis. Dermal adipocyte lineage cells, including adipocytes and their progenitors, are highly plastic and can undergo reversible differentiation and dedifferentiation in response to various stimuli. But their roles in acne pathogenesis remain poorly studied. Here, we performed comprehensive analysis of the C.acne-induced acne model, and found that during the early inflammatory phase, preadipocytes and adipocytes, rapidly expanded around the central abscess, and subsequently adipocyte lipolysis was observed in concomitantly with the onset of fibrogenesis. By lineage tracing of adipocyte and/or their progenitors by the AdipoqERTCRE;mTmG or PdgfraERTCRE;mTmG mice, we confirmed that acne inflammation triggered a rapid dermal reactive adipogenesis response followed by a profound adipocyte lipolysis event during which adipocytes dedifferentiated into collagen-producing THY1+ fibroblasts, contributing to dermal fibrosis. Furthermore, by in vivo and in vivo co-culture approach, we found that this dynamic interplay between adipogenesis and lipolysis during acne pathogenesis is regulated by the cellular interaction between adipocyte lineage cells with macrophages through the CCL2-CCR2, TNF, and TGFβ signaling pathways. Depletion of macrophage resulted in reduced C acne-induced adipocyte lipolysis and dermal fibrosis. Together, these data suggest that the dynamic interplay between adipogenesis and lipolysis plays a role in regulating the development of acne inflammation and the subsequent fibrotic pathology.



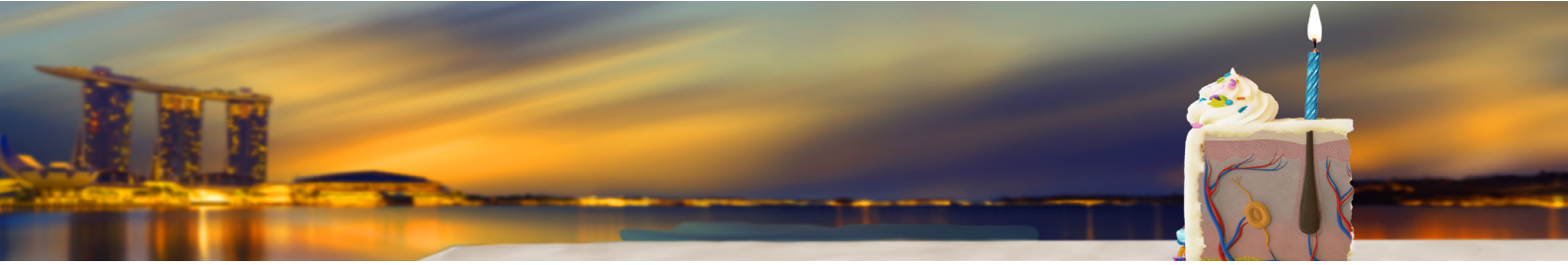
Short talk

Investigating the Intrinsic Regulation of the Hair Follicle Stem Cell Niche by MEF2C

Tracy Zhijun Tien[1,2], Nikolaos Pantelireis[1,3], Claire Higgins[3], Carlos Clavel[1,2]

*[1]Hair Pigmentation and Development Group, A*STAR Skin Research Labs (A*SRL), Agency for Science, Technology and Research (A*STAR), Singapore; [2]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore; [3]Department of Bioengineering, Imperial College London, London, United Kingdom*

Within the hair follicle, the crosstalk between the hair follicle stem cells and the mesenchyme-derived dermal papilla (DP) initiates hair follicle morphogenesis and controls the hair regeneration cycles. The exact mechanism by which DP cells regulate the hair follicle stem cell niche remains elusive. Recently, we screened different 2D vs 3D cultures of hair-inducing human DP and non-hair-inducing fibroblast cells, where myocyte enhancer factor 2c (MEF2C) was identified as a gene of interest in hair follicle induction. To assess its role in hair induction and growth, we have generated DP-specific conditional knockouts (cKO) of Mef2c using our recently characterized genetic tool, LeprCre. Interestingly, histological examination of the hair cycle revealed that Mef2c cKO hair follicles showed a significant delay in the early stages of catagen. Thus, to elucidate the mechanisms behind how Mef2c contributes to the DP's role in hair cycling, we are analyzing the DP niche transcriptome. Interestingly, preliminary findings reveal that SRY-box transcription factor 18 (Sox18), a known binding partner of Mef2c, is upregulated in the DP of cKO mice. Then, to corroborate the role and interaction between Mef2c and Sox18 in regulating hair growth, we are knocking down Sox18 in DP cells and optimizing various tools such as hair reconstitution assays. Elucidating whether and how Mef2c and Sox18 interact to regulate hair growth will provide new opportunities for disease modelling and product testing.



The latest and greatest on sebaceous glands

Maurice van Steensel

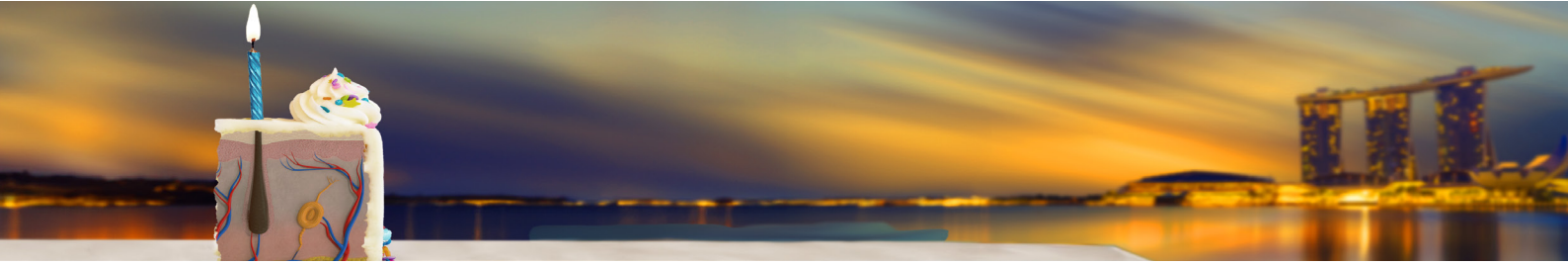
Lee Kong Chian School of Medicine and Skin Research Institute of Singapore, Singapore

ABSTRACT

In my presentation I will discuss the latest insights in sebaceous gland development and homeostasis. Small it may be, but the sebaceous gland is mighty in its influence on skin physiology and pathology. It is an interesting model in which to study stem cell (niche) maintenance and differentiation that also provides a microcosm of lipid metabolism. As such, the sebaceous gland deserves more attention than it is (still) getting and I hope my talk will help to achieve that.

BIO

Maurice van Steensel is Professor of Dermatology and Skin Biology at Lee Kong Chian School of Medicine (Nanyang Technological University, Singapore) and Research Director in the Skin Research Institute of Singapore. A dermatologist with a PhD in molecular genetics, Maurice brings over 2 decades of internationally recognized experience in the full breadth of skin research, ranging from molecular biology to clinical trials for rare diseases and development of novel personal care interventions. He earned his PhD cum laude from the University of Maastricht, the Netherlands.



How can mass spectrometry-based proteomics help us elucidate mechanisms of disease in dermatology?

Beatrice Dyring-Andersen

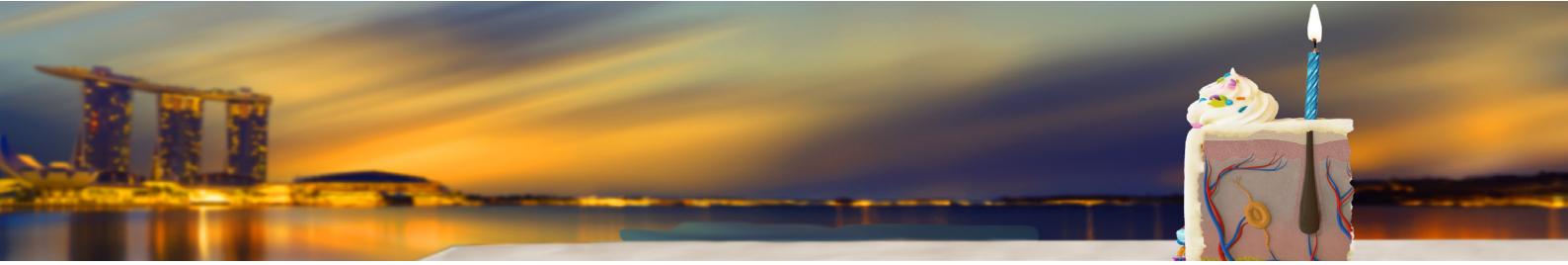
University of Copenhagen, Denmark

ABSTRACT

The rapid technological advances in the field of proteomics are an opportunity for defining disease pathways at the proteome level. It presents opportunities to characterize the end-products of our genetic code. Dr. Beatrice Dyring-Andersen will present findings from the Skinatlas project, a project that explores the proteomes of skin layers and associated immune cells. Additionally, she will present the recent addition to the Skinatlas study elucidating the proteome of skin-derived innate lymphoid cells and their significance in skin biology. The talk will also include recent insights from a melanoma study investigating the transition from benign nevi to malignant melanoma using laser microdissection and mass spectrometry. Here, differential expression analysis unveiled 1,725 proteins distinguishing nevi and nevi-associated melanomas, providing insights into cancer hallmarks, tumor suppression, and metabolic regulation. Pathway analysis revealed dysregulated PI3K-AKT-mTOR and Hippo-YAP pathways, shedding light on potential therapeutic targets.

BIO

Beatrice Dyring-Andersen, M.D. Ph.D., is a physician-scientist specializing in translational dermatology and clinical proteomics. Currently serving as an Associate Professor of Dermatology and Clinical Proteomics at the University of Copenhagen's Novo Nordisk Foundation Center for Protein Research, Denmark, and a Physician and Group Leader at University Hospital Herlev-Gentofte. After earning her Medical Doctor degree in 2007 and Ph.D. in 2014 from the University of Copenhagen, her research has focused on innate lymphoid cells and gamma delta T cells in inflammatory skin diseases. With postdoctoral fellowships at Brigham and Women’s Hospital, Boston, US, and the University of Copenhagen, her work spans healthy human skin immunology, psoriasis and cutaneous oncology. Funded by the Danish Cancer Society and the Novo Nordisk Foundation, she bridges research and education, mentoring students and advancing precision dermatology. Dr. Dyring-Andersen's commitment to translational research aims to improve patient outcomes by characterizing the proteomic landscape of inflammatory skin diseases and melanoma.



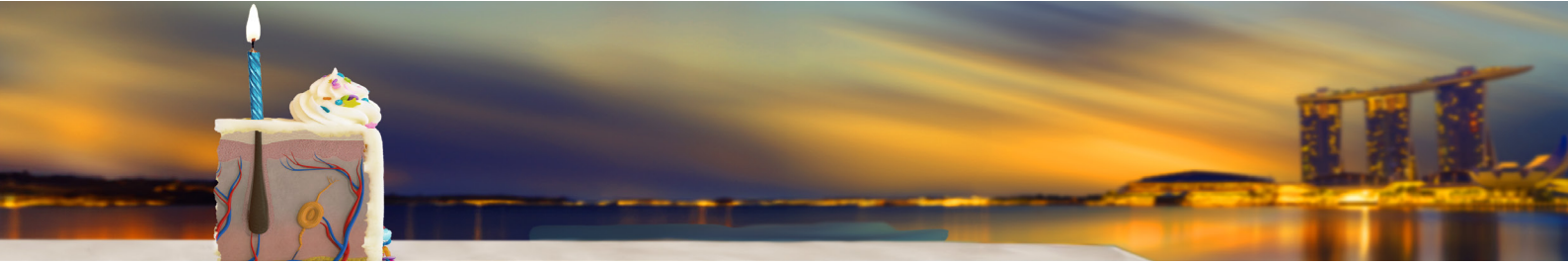
Short talk

Nanopore sequencing enables allelic phasing of FLG loss-of-function variants, intragenic copy number variation and methylation status in atopic dermatitis and ichthyosis vulgaris

Colin Wong[1], Cheng-Yong Tham[2], Lin Yang[2], Miles C. Benton[2], Vipin Narang[3], Simon Denil[1], Kaibo Duan[3], Yik Weng Yew[4], Bernett Lee[3,6,7], Paola Florez de Sessions[2], John E. A. Common[1,5]

*[1]A*STAR Skin Research Laboratory, Agency for Science, Technology and Research (A*STAR), Singapore; [2]Oxford Nanopore Technologies, Singapore; [3]Singapore Immunology Network, Agency for Science, Technology and Research (A*STAR), Singapore; [4]National Skin Centre, National Healthcare Group, Singapore; [5]Skin Research Institute of Singapore, Singapore; [6]Centre for Biomedical Informatics, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore; [7]A*STAR Infectious Diseases Labs (A*STAR ID Labs), Agency for Science, Technology and Research (A*STAR), Singapore*

Loss-of-function (LoF) variants in the FLG gene are associated with ichthyosis vulgaris (IV) and atopic dermatitis (AD). IV and AD patients with two FLG LoF variants are expected to have more severe disease but subsets of compound heterozygous patients display milder phenotypes. The underlying genetic mechanism of this phenotypic variability is unknown. One possibility is that two LoF FLG variants could be located in cis (on the same allele), thus altering the predicted gene dosage. To investigate the allelic contribution of compound heterozygous FLG LoF mutations to IV phenotypic variability, we utilised two long-range nanopore sequencing methodologies; amplicon-sequencing (n=21) and adaptive sampling (n=2) to phase the entire coding region of FLG and the epidermal differentiation complex (EDC) into parental alleles in a cohort of 21 compound heterozygous subjects with IV and AD. This enabled detailed investigations into the allelic distribution of FLG LoF variants and intragenic-repeat copy-number variations (CNV). All LoF variants were in trans which suggests alternative mechanisms that determine IV and AD severity in our cohort. Nanopore sequencing facilitated deep analysis of FLG genetic structure. Allelic phasing allowed us to link recurring LoF variants with specific CNV alleles and identified single-nucleotide polymorphisms (SNPs) were informative for CNV-calling. The use of native DNA template in adaptive sampling generated methylation profiles for FLG (mean CpG > 85%) and the EDC. These results highlight the utility of nanopore sequencing and provide a framework for future in-depth genetic analysis of the FLG gene and other highly repetitive genes for genetic stratification related to clinical phenotypes.



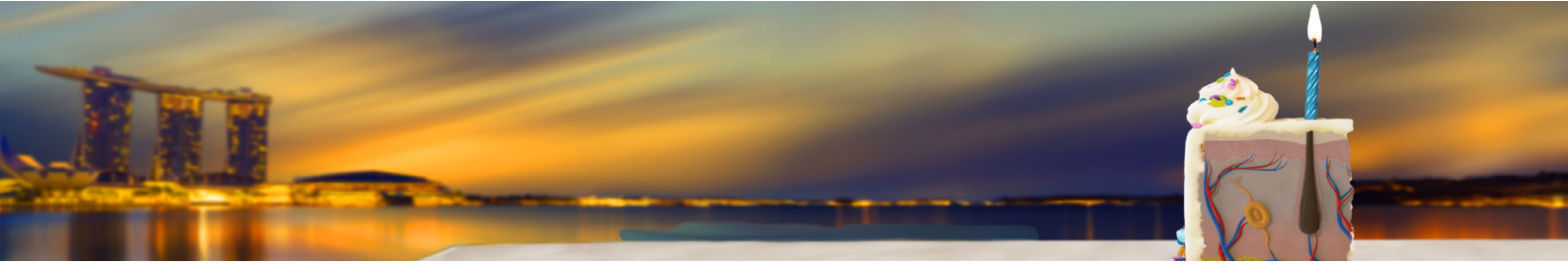
Short talk

A sustainable strategy for generating highly stable human skin equivalents based on fish collagen

Shi Hua Tan[1], Shaoqiong Liu[2], Swee Hin Teoh[3], Carine Bonnard[1,4], David Leavesley[4], Kun Liang[1]

*[1]A*STAR Skin Research Labs (A*SRL), Agency for Science, Technology and Research (A*STAR), Singapore; [2]School of Chemical and Biomedical Engineering, Nanyang Technological University, Singapore; [3]College of Materials Science and Engineering, Hunan University, People's Republic of China; [4]Skin Research Institute of Singapore (SRIS), Asian Skin Biobank, A*STAR, Singapore*

Ahed (attenuated hematopoietic development) is a newly identified gene based on in vitro screening assay of the homozygous mutant mouse embryonic stem cell bank, and found to be essential for hematopoiesis. Mice with Ahed deletion specifically in the hematopoietic lineage showed fetal anemia due to impairment in proliferation of differentiated blood cells. Here, we investigated whether Ahed also plays a critical role in proliferation and / or differentiation of epidermal keratinocytes, similar to in hematopoietic cells. To the end we generated epidermal-specific Ahed deficient mice by crossing Ahed flox mice and K5.Cre mice. Ahed conditional knockout (Ahed cKO) mice were born in accordance with the Mendelian expectation and showed no significant abnormality at birth. However, Ahed cKO mice were clearly distinguishable from control littermates by growth retardation, thinning of the skin at postnatal day 2 (P2) and lethality around P3. Ahed cKO mice showed a marked increase of transepidermal water loss at P2, indicative of barrier disruption. To overcome neonatal lethality of the mice, we generated inducible-Ahed KO mice by crossing K5.CreERT2 mice with the Ahed flox mice. The inducible KO mice showed atrophic epidermis and cell death in hair follicles by topical treatment of high dose 4-OH Tamoxifen (Tam) at day10. In contrast, low dose 4-OH Tam treatment led to generation skin lesions with histological features such as acanthosis, hyperkeratosis and inflammatory cell infiltrates. Collectively, the results suggest crucial roles of Ahed in development and maintenance of the epidermis.



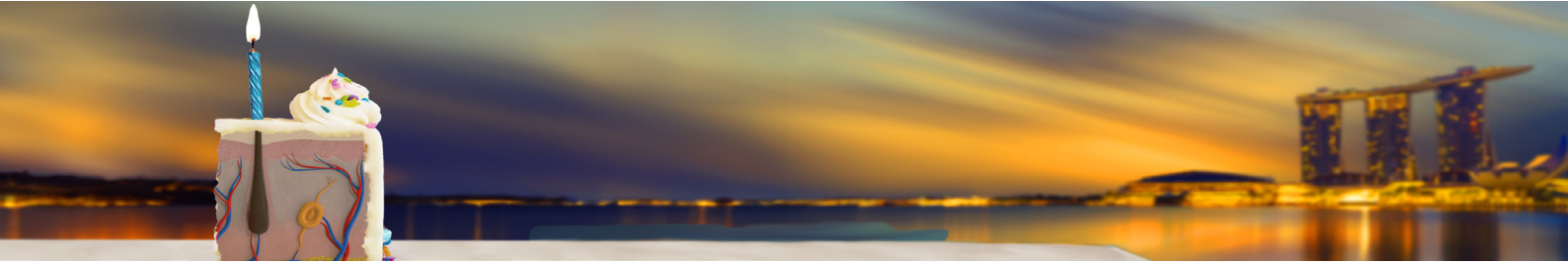
Short talk

Going beyond the surface: transepidermal microbiome microbiome sampling using 3D-printed microprojection arrays

Kun Liang[1,2], Jia Min Loh[1], Larissa Lim[1], Cheryl Leong[1], Thomas Dawson[1,2,3], and Hong Liang Tey[4,5,6]

*[1]A*STAR Skin Research Labs (A*SRL), Agency of Science Technology and Research (A*STAR), Singapore; [2]Skin Research Institute of Singapore (SRIS), Singapore; [3]College of Pharmacy, Department of Drug Discovery, Medical University of South Carolina, Charleston, USA; [4]National Skin Centre (NSC), Singapore; [5]Lee Kong Chian School of Medicine, Nanyang Technological University (NTU), Singapore; [6]Yong Loo Ling School of Medicine, National University of Singapore (NUS), Singapore*

The skin microbiome plays an important role in skin health and disease. Most of current human skin microbiome sampling have been performed using methods such as swabbing and tape stripping which collect microbes solely on the skin surface With the emergence of studies showing that the distribution and abundance of skin microbes varies with skin depth, there has been increasing recognition of the gap in knowledge of microbiota colonization in deeper skin layers. However, apart from the invasive skin biopsy being the only way to sample deeper skin microbiome, there are limited means to collect such samples. To address the shortcomings of skin biopsies, we have previously developed a simple and minimally-invasive sampling tool with a depth component – a transepidermal microprojection array (MPA). The MPA was fabricated by customizable computer-aided design and 3D printing and systematically optimized for the microbial extraction efficiency and skin penetration depth. In a proof-of-concept trial on human subjects, we investigated the microbial extraction efficacy and the downstream metagenome sequencing quantification of the MPA samples in comparison with the conventional swab and tape strip. MPA was found to be comparable in sensitivity to swab and superior to tape strip, especially for non-standard skin surfaces. We also observed differences in species abundance and diversity, indicating that the transepidermal microbes collected using MPA likely colonized the deeper skin layers. Overall, this work delivers a novel approach for skin microbiome sampling to potentially address gaps in our understanding of microbiota role in health and disease.



Single Cell and spatial transcriptomics reveal enhanced immune infiltration and aging signatures in Atopic Dermatitis

Tsukasa Kouno[1], Tomohiro Miyai[1], Yoshinari Ando[1], Mika Sawane[2], Miki Kojima[1], Piero Carninci[1,3], Kentaro Kajiya[2], Masayuki Amagai[4], Hiroshi Kawasaki4, Jay W. Shin[1,5]

*[1]Center for Integrative Medical Sciences (IMS), RIKEN, Yokohama, Japan; [2]Shiseido, Japan; [3]Human Technopole, Milan, Italy; [4]Keio University, Tokyo, Japan; [5]Genome Institute of Singapore (GIS), A*STAR, Singapore, Singapore*

ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by heterogeneous manifestations in a spatial-temporal manner. Understanding the cellular and molecular heterogeneity across these states is crucial for elucidating AD's pathophysiology and identifying potential therapeutic targets. Here, we employ scRNA-seq and spatial transcriptomics to profile the cellular landscape of healthy skin, non-lesional, lesional, and excoriated (scratched) skin samples from AD patients. Our comprehensive analysis reveals a pronounced immune infiltration in excoriated skin, surpassing that in non-lesional and lesional counterparts. Specifically, we observe an increased presence of T cells and neutrophils, highlighting the impact of skin barrier disruption on immune responses in AD. In addition to immune dysregulation, our study identifies a distinct aging signature in the stromal cell populations of the AD samples. This aging phenotype is characterized by alterations in extracellular matrix composition, cellular senescence markers, and reduced regenerative capacity, mirroring the stromal cell aging observed in chronologically aged skin. These findings suggest that AD may accelerate skin aging processes, contributing to disease chronicity and severity. Together, our results provide unique insights into the cellular and molecular dynamics of AD, highlighting the role of immune infiltration and stromal cell aging in its pathogenesis. These insights open avenues for targeted therapies aimed at modulating immune responses and rejuvenating the skin microenvironment in AD.

BIO

Dr. Jay W. Shin, a distinguished scientist in gene regulation and genomics, developed a novel single-cell gene expression profiling method focusing on the 5' end to map genetic networks, particularly in non-coding genome regions. Dr. Shin's PhD from ETH Zürich and research at Harvard Medical School were pivotal in his gene regulation studies during skin inflammation angiogenesis. Joining RIKEN Yokohama in 2008, he held a Special Postdoctoral Research Fellowship and later became a Principal Investigator, collaborating with major industries on stem cells and clinicians on regulatory RNAs research. With 13 years at RIKEN, Dr. Shin transitioned to the Genome Institute of Singapore, A*STAR, launching a Regulatory Genomics program and spearheading single-cell genomics and autonomous molecular phenotyping platforms. As a Human Cell Atlas organizer and HCA Asia steering committee member, he promotes equity in genomics representation and research. Additionally, he is a NRF Investigator, adjunct associate professor at NUS, and adjunct team leader at RIKEN, Japan.