Professional Development Dermatology

UCD CHARLES INSTITUTE SEMINAR SERIES

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Charles Institute of Dermatology

Under the skin of psoriasis

*Attendees at UCD's Charles Institute Seminar Series heard a presentation from **Dr Mark Mellett** of University Hospital Zurich on the mechanisms behind inflammatory skin diseases*

The Charles Institute, Ireland's national dermatology research and education centre, played host to a range of guest speakers who covered a variety of topics ranging from skin cancer to psoriasis, among others. The series, which was sponsored by RELIFE (part of the A.Menarini group), was designed to provide expert advice from a range of distinguished national and international experts in their respective fields and was chaired by Prof Desmond Tobin, Full Professor of Dermatological Science at UCD School of Medicine and Director of the Charles Institute of Dermatology. The seminars were broadcast to attendees with a special interest in dermatology in other locations, who accessed the talks remotely via an audio-visual link.

Attendees at the series heard a presentation from Dr Mark Mellett of University Hospital Zurich, where he is conducting investigations into the underlying disease mechanisms of dermatological skin disorders, with a particular focus on common and rare chronic inflammatory skin diseases, drug-induced eruptions and skin toxicities. Among his research in a number of institutions, Dr Mellett performed postdoctoral research at the Institute of Immunology in Maynooth University and was a Marie Curie Research Fellow in the Dermatology Department at University Hospital Zurich.

Dr Mellett delivered a talk titled 'Regulation of Interleukin-36γ and its Role in Inflammatory Skin Disease' and told the attendees that inflammatory skin diseases such as psoriasis are characterised by a combination of autoimmune and autoinflammatory immune responses, which dictate disease manifestation and clinical presentation. Important in this process is the contribution of the innate immune response in triggering inflammatory skin disease in genetically-susceptible individuals, he pointed out, and the keratinocyte signalling molecule CARD14 and Interleukin-36 cytokine family have emerged as significant factors in kindling the inflammatory response in keratinocytes.

Trigger

"In genetically-susceptible individuals, when people harbour some risk allele, a stressor or infection causes a trigger in the skin. Stressed or dying keratinocytes release nucleic acid, which is bound by antimicrobial peptides, which are cationic in nature and bind to negatively-charged nucleic acids. It has been shown that one in particular — although there are others — LL-37 binds to DNA and can activate Toll-like receptor 9 on plasmacytoid dendritic cells," said Dr Mellett.

"These will then secrete interferon-alpha, which activates dermal dendritic cells, which then migrate to the lymph node and polarize naïve. The T-cells then infiltrate to the skin to produce TNF-alpha, or Th17 cells will produce IL-17 and IL-22cytokines, which drives the inflammatory milieu and hyperproliferation of keratinocytes."

He also described how keratinocytes are not "innocent bystanders", but pump-out antimicrobial peptides, chemokines and cytokines of the innate immune system, including IL-19, , IL-17C and IL-36 cytokines. More than 80 risk genes have been identified that are associated with psoriatic skin disease in Caucasian and Han Chinese populations, Dr Mellett added. He discussed CARD14, which is a protein expressed in keratinocytes and is also known as CARMA2.

Disease mechanisms

Dr Mellett provided an overview of research he and his colleagues have conducted on mouse models in order to gain a greater understanding of mechanisms of inflammatory skin disease. "We found that the CARD14 pathway in the keratinocytes from the mice is hyperactive," Dr Mellett told the seminar. "Looking at the transcripts of proinflammatory cytokines, such as IL-19, IL-36 gamma, IL-17C, antimicrobial peptides in the primary keratinocytes from the mutant mice are significantly upregulated."

The transcriptome of these mice matches very well with human plaque psoriasis, said Dr Mellett, and demonstrated infiltration of neutrophils, myeloid cells, and also Th17 cells. There is significant expression of IL-17 and IL-22 in the epidermis of the CARD14 mutant mice, he added. IL-23 maintains polarisation of Th17 cells, which produce proinflammatory cytokines IL-17 and IL-22 that contribute to human psoriasis, therefore he set about neutralising IL-23 in the mice in an effort to alleviate symptoms. Ear thickness in the mice decreased significantly when the IL-23/IL-17 axis was blocked, and overall symptoms improved significantly, he said, which could have significance to the pathogenesis in human disease.

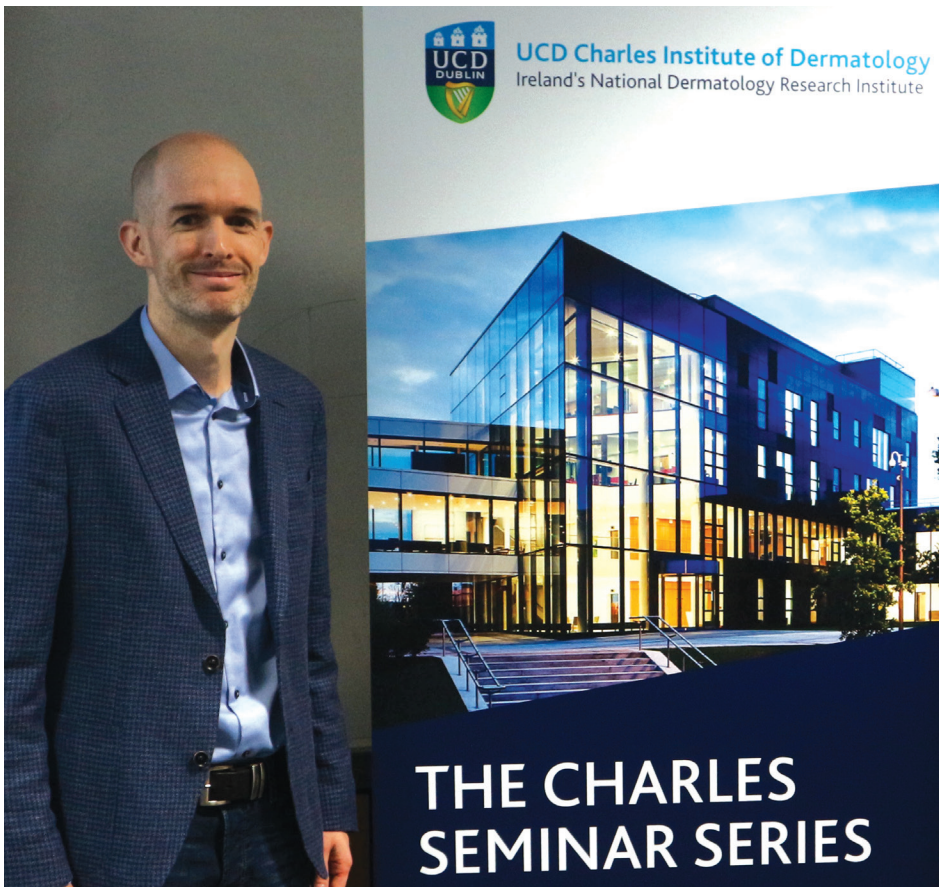
Dr Mellett summarised the first part of his presentation by telling attendees: "Gain in function in CARD14 alone is enough to drive the full-blown physiological effects of human skin disease in vivo," he said. "We looked at the histological, clinical, transcriptome and immune cell infiltrate and we found it matched very well with human disease. From other mouse data, we also saw that the CARD14 knockout mice are protected from psoriasis pathogenesis. This would suggest that the signalling pathway of CARD14 in keratinocytes is critical for psoriasis pathogenesis."

Other recent research also suggests that loss of function mutations in CARD14 has also been associated with a severe form of atopic dermatitis, Dr Mellett added. "CARD14 seems to be playing a pivotal role in the epidermis to protect us from infection," he said. "However, mutations in CARD14 can drive the Th17 response that we associate with psoriasis. It makes sense that it can do this, because it is tailoring the immune response at the epidermis against fungal or bacterial infection."

In the second part of the seminar Dr Mellett spoke about the role of Interleukin-36 cytokines in driving inflammation in the skin. He said that IL-36 cytokines are found at significantly elevated levels in the skin of individuals who are affected by both pustular and plaque forms of the disease.

Furthermore, clinician scientists have reported that patients who lack a functional IL-36 Receptor antagonist develop severe pustular psoriasis, Dr. Mellett told the audience.

While we know a lot about the effects of IL-36 in shaping the immune response we know less about how IL-36 comes to be activated and released from keratinocytes, he explained. Unlike, other cytokines, IL-36 cytokines lack a signal that tells the cell to secrete them so they remain trapped within the cell. He went on to describe how danger signals in the skin led to the release of IL-36 cytokines and how these might act as early triggers in psoriasis pathogenesis.



Dr Mark Mellett

Dr Mellett summarised the second part of his presentation by telling the seminar: "that when a psoriasis patient has a cut or other trauma to the skin and a new lesion occurs, this is known as the Koebner phenomenon and we believe that IL-36 release process could be mediating this new lesion".

Human disease

During a Q&A session following the presentation, Prof Tobin pointed out that there is currently a debate about whether psoriasis is an autoimmune disease, "…if it is , then where is the autoantigen and what is the trigger for that autoantigen to be perceived, either appropriately or otherwise by the immune system? To my knowledge, humans are the only mammals that get psoriasis. So, what is the first trigger for the disease in humans, and so can animal models really inform us in terms of driving therapeutic discoveries?"

Dr Mellett responded: "I believe the early trigger is in the skin — something akin to a danger signal that in susceptible individuals will precipitate and result in a response that can't be controlled.

"The adaptive T-cell response is absolutely required, so mutant CARD14 mice crossed with RAG knockout mice are protected — the T-cell infiltrate is a necessary component of the disease," added Dr Mellett. "In terms of the autoantigens, a lot of excellent research has been done on HLA CW6 by the laboratory of Prof. Jörg Prinz, who found that an antigen from melanocytes, ADAMTS-like protein 5, was detected by HLA CW6, which activates a cytotoxic CD8+ cell response. Some of these CD8+ T cellsare perhaps not inducing cytotoxicity; there may be a subset of CDAT cells that do not do this, and that could be why psoriasis patients do not have a significant correlation with vitiligo, for example… but it's a complex question and it's difficult to say that it's all keratinocyte-driven, or all adaptive immune cell-driven.

"It's probably a combination," he told the seminar. "You need the trigger in the skin and the immune cell infiltration. The way I try to describe the importance of CARD14 is that it is a pathway in keratinocytes and I think in most people with psoriasis, that pathway is being activated, whether they have a mutation or not."

Speaking to the ***Medical Independent (MI)*** following his presentation, Dr Mellett touched on his aspirations to take his research from the bench to the bedside and create a greater understanding of the potential practical applications. "Not all patients have equal access to expensive biologics that are effective," he explained. "Some of these biologics lose responsiveness in patients, while some patients do not respond at all".

"But also, there are some psoriasis sufferers who do not have severe disease where perhaps other types of treatment may be effective," he told ***MI***. "I think a greater understanding of what's happening with the skin may lend itself to developing topical treatments that could be more effective and good topical treatments could complement other therapies.

"We would also like to see other systemic therapies that might come out of this work. The fact that it is keratinocyte molecules that we study means that topical treatments might be a more immediate application.."

RELIFE has had no input into the content of this article or series of seminar