Clinical Dermatology

UCD CHARLES INSTITUTE SEMINAR SERIES

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Big challenges, bigger opportunities in wound-healing

Attendees at UCD's Charles Institute Seminar Series recently heard the penultimate presentation in the first series from ***Prof Mat Hardman*** *on advances in wound-healing research*

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 recently heard a presentation from Prof Mat Hardman, Chair in Wound Healing and Director of Research at Hull York Medical School, UK. During his 25 years' experience in the field of skin biology, Prof Hardman developed a specific focus on skin ageing and wound-healing. He currently leads the Advanced Wound Care Cluster at Hull York Medical School and his interests in the group include: The host-microbiota axis in wound repair; the effects of ageing and menopause on skin structure and function; and developing more predictive pre-clinical models for skin and wound research.

Prof Hardman delivered a talk titled 'Understanding Pathological Wound-Healing: Opportunities for Translation'. He discussed the current understanding of chronic wound pathology and emerging areas for potential wound intervention, as well as outlining the significant economic burden that chronic wounds place on health services. Prof Hardman pointed out that high numbers of chronic wounds are infected, which drives considerable patient morbidity and results in a high risk of lower-limb amputation.

The chronic wound treatment pathway remains largely ineffective, Prof Hardman explained, and he presented findings from his group, as well as other researchers, to provide new insights into wound pathophysiology. Emerging studies are revealing new potential therapeutic targets to promote wound-healing, from hair follicles, to the microbiome and senescence, to wound metallomics, Prof Hardman said.

Epidemic

He told the attendees: "Many of you will be aware of the chronic wound epidemic we are currently experiencing. One-in-20 older people will at some time develop a chronic wound, whether that's a venous ulcer or a diabetic ulcer, or pressure ulcer," he said. "The underlying aetiology of these wounds is very different in terms of the causes. Those could be venous insufficiency, diabetes or extended periods of pressure, but the local changes are actually very similar and there are certain factors that really drive wound pathology. As we get older, our ability to heal a wound changes, so everyone will take longer to heal a wound as we age, but many people will take so long to heal a wound that they transition into a chronic wound state."

Prof Hardman explained that up to 70 per cent of such wounds are infected and in addition to the impact on the patient, he described the resulting expense to health services as "staggering", with chronic wounds costing the NHS approximately £5 billion per year: "This is a major area of unmet clinical need." He added that research into the area is chronically under-funded and this creates a significant clinical and societal problem.

There are two main risk factors across all types of healing, Prof Hardman told the attendees, namely ageing and diabetes. "By 2050, there will be 1.5 billion people aged over 80 years — all of those people will need advanced healthcare and all of them will develop chronic conditions." He described current treatments for chronic wounds as "inadequate" and explained that they essentially consist of either sharp debridement, or using live maggot debridement to eat necrotic tissue.

"Obviously, neither of these could be described as optimal treatment options," said Prof Hardman. "The reason for this is that the cellular molecular processes that underpin wound-healing are still poorly understood, a point that I have been making for several years. I am a big proponent of translational research and it is fundamentally important in this area, to be thinking about both humans and translational models."

Microbome

In terms of the microbiome, Prof Hardman explained that there are different bacteria present in healing and non-healing wounds and "diversity is significantly reduced in non-healers. This is fundamentally important — we have shown that the bacterial profile in a human wound can predict whether or not it will heal. We know that there are a range of different bacteria-sensing Toll-like receptors in tissues but in fact, it's not the Toll-like receptors that are altered in these wounds, rather we identified an atypical pattern recognition receptor, Nod2, altered in wounds that did not heal."

He noted: "Historically, wound infection has been viewed in a very reductive way. Bacteria like strep (streptococcus), MRSA, and staphylococcus are clearly involved in wound pathology, but the microbiome is actually incredibly complex," he said. "The wound-healing field still has not got to grips with this level of complexity; wound infection is more than just a few pathogens."

Iron

Referring to research published by his group, he explained that iron is altered in wounds that don't heal. Cells that take up iron will deposit high levels of collagen and the mechanism behind this extracellular matrix deposition is likely due to an accumulation of oxidative stress, he told the seminar. "Oxidative stress is one of the key drivers of cellular senescence. We see that increasing concentrations of iron drive a clear linear increase in cellular oxidative stress measure, and this can also be seen cytochemically," he said. Antioxidant treatment can abolish oxidative stress and diminish collagen production, Prof Hardman added.

Iron signalling in cells is complex, but Prof Hardman explained that STEAP3 is important for the conversion of biologically-inactive Fe3+ to biologically-active Fe2+. "When we look at real tissue, we see a clear up-regulation of STEAP3 as healing progresses, with iron accumulation and matrix deposition... in vitro, we see the same thing — iron treatment induces STEAP3 in mice and when we treat with an siRNA to STEAP3, we completely abolish the effects of iron; there is no extracellular matrix production and there is no increase in oxidative stress."

Prof Hardman told the seminar: "We think STEAP3 is fundamentally important for the iron-mediated effects on extracellular matrix production. In the absence of iron, there is less STEAP3 activation, less iron signalling and less extracellular matrix, which leads to poor healing" said Prof Hardman. In fact, iron is also sequestered by macrophages, "so there is probably a whole other story about iron influencing macrophage biology. We know that macrophage polarisation is skewed in response to iron, and that changes the local immune response."

Increasing awareness

During a lively Q&A session following the presentation, Prof Tobin commented on iron and the ageing process: "BMP6 is involved in iron metabolism, and bone morphogenetic proteins in general have been strongly associated with both morphogenesis, as well as carcinogenesis, and BMPs in general are very much involved in tissue modelling," he said. "Have you and your team looked at BMPs as members of the TGF-beta family, in the context of the how iron may be influencing these processes?"

Prof Hardman responded: "I'm not sure how much literature is out there in that area with regards to wound-healing, but I do believe it would be a very interesting area that we could potentially examine." He added that he and his team can now profile every single bacterium species in a wound, but there is a need to assess how that changes a clinician's approach to treating a wound and the overall treatment pathway. "That's the challenge, but it's also a massive opportunity," he said. "Ideally, we would use a personalised medicine approach and profile the bacteria, which would then influence treatment decisions."

Speaking to the ***Medical Independent (MI)*** following his presentation, Prof Hardman remarked on what his field of research can learn from work that has already been done on the gut microbiome. "Skin and wound microbiome research is relatively new compared to the gut (ie, there are around 32,000 published scientific papers on gut microbiome, 2,000 on skin microbiome, and just 600 on wound microbiome), but actually, many of the underlying mechanisms whereby our gut and our skin interact with bacteria are going to be the same.

"So all of the existing gut knowledge in areas such as bacterial dysbiosis driving disease, the beneficial effects of probiotics, and dealing with antimicrobial resistance gives us a major head-start when is comes to new skin/wound studies. We also have to remember not to think about tissues in isolation. The gut and skin are directly linked via the gut-skin-brain axis, so your diet can absolutely influence your skin health, and vice versa."

Prof Mat Hardman

Prof Hardman was also asked about the importance of making practising clinicians more aware of the results of research conducted by he and his colleagues and how this increased awareness might be implemented. "This is a really important question," he told ***MI***. "All too often, research scientists make great discoveries that could make a real difference to patients, but they don't ever make it to the clinic.

"We work closely with wound clinicians, patients and other stakeholders from the very beginning of the research process, to maximise applicability of our work. Building a solid evidence base that then informs clinical policy is really the best way to get the message to the wider clinical community — unfortunately, this takes time.

"I also want to mention the importance of industry (ie, companies developing advanced wound care treatments and diagnostics). Scientists and clinicians can only take research and development so far. Working with commercial partners who are willing to make the (large) investment needed to get a new treatment to the clinic is essential."

Prof Hardman concluded by reiterating the need for serious investment into wound research in order to improve patient outcomes. " We need to build upon and develop the dedicated and talented pool of clinicians and scientists working in this area," he told ***MI***. "Chronic wounds are a growing problem, but are also an area of huge research opportunity."

To find out more about Prof Hardman's work visit the Hull York Medical School website at www.hyms.ac.uk

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