Clinical Dermatology

UCD CHARLES INSTITUTE SEMINAR SERIES

UCD School of Medicine
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Charles Institute of Dermatology

Protecting the skin we're in

Attendees at UCD's Charles Institute Seminar Series recently heard a presentation from ***Prof Mark Birch-Machin*** *on the various influences on skin ageing*

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 Mark Birch-Machin, Professor of Molecular Dermatology and Dermatological Sciences, Translational and Clinical Research Institute at Newcastle University, UK, and Director of Business Development at the University's Faculty of Medical Sciences. Prof Birch-Machin's research work is focused on the response of human skin to the environment, particularly in the context of skin ageing. Among other achievements, Prof Birch-Machin played a central role in pioneering the use of mitochondrial DNA as a biomarker of sun damage in skin and he is currently focusing his efforts on understanding the role of mitochondria in UV and environment-induced oxidative stress, skin cancer, and the relationship between oxidative stress, nutritional status, pigmentation and skin ageing, as well as the use of sunscreens and the science behind it.

Prof Birch-Machin delivered a talk titled 'The Relationship between Nutritional Status, Antioxidants, Bioenergy and Interventions on Human Skin Ageing' and spoke about how the skin is subject to stress from both internal and external influences and how oxidative stress results from redox imbalances and is linked to ageing in a range of tissues, including skin. As well as exposure to environmental pollution and sunlight, stressful lifestyles and dietary habits also have an influence on the ageing process in the skin. However, differences in skin bioenergy are linked to the mitochondrial theory of ageing, particularly as mitochondria have been identified as the major source of cellular oxidative stress, he explained.

Prof Birch-Machin presented the attendees with an overview of how the different theories of ageing have evolved. "What we see in skin ageing on the surface, such as fine lines, wrinkles and even skin tone, actually starts much lower down in the skin," he said. "The damage that happens below the outer layers of the skin is important in terms of what we manifestly see on the surface."

UV rays

He explained that there is differential penetration when it comes to UV rays — the longer the wavelength, the deeper the UV rays can penetrate the skin. "UVB tends to have a direct effect in terms of damage, causing pyrimidine dimers and photoproducts, and UVA in longer wavelengths affect their damage using oxidative processes," he said. "They combine to disrupt various processes, one of which is the upregulation of metalloproteinases (MMP), which serve to degrade collagen, leading to one aspect of photoageing," said Prof Birch-Machin, adding that there are other aspects that also influence the process.

The various theories of ageing have now been refined to the mitochondrial theory of ageing, he pointed out. "Essentially, this theory encapsulates the free radical theory but because mitochondria produce 90 per cent of all the free radicals in the cell, mitochondria are central to how the cells in our body age," he told the seminar.

A simplified overview of this process breaks it down into two aspects, he explained. "As we get older, our bioenergy declines and our free radicals increase," he said. "Mitochondria produce the ATP [adenosine triphosphate], which is the energy source for all of the tissues in our body and we know that as we get older, the amount of bioenergy our organs have declines, and then there is an issue related to the increase in free radicals.

"These two components are combined in the 'Vicious Cycle' theory, which is shown in a triangle with three components — generation of reactive oxygen species; mitochondrial DNA damage; which then affects the function of the mitochondria, making them dysfunctional. Therefore, they can't produce enough ATP, and therefore you have lower bioenergy," he explained.

Mitochondrial DNA are situated very close to where free radicals are produced, which is why mitochondria are damaged so quickly, Prof Birch-Machin explained, leading to the rapid 'Vicious Cycle'. "However, this gives us the potential to intervene by slowing-down the Vicious Cycle, therefore slowing-down the rate of ageing," he added. "That's the 'Holy Grail' that we are striving for."

He explained that a certain amount of free radicals, such as superoxide, are useful for cellular signalling and presented the attendees with a distillation of some 200 research papers on mitohormesis. "Mitohormesis basically shows us that the relationship between superoxides and free radicals in terms of ageing is not linear — in other words, a little bit is good, but too much of it is bad, and that in a nutshell is mitohormesis," said Prof Birch-Machin.

He discussed the effects of various pollutants on mitochondria and told the seminar: "At the moment [because of Covid-19], we are getting very little environmental air pollution because there is not much traffic on the roads but normally, there will be an effect from pollution, diesel particulate matters, as well as the effect on our skin of our diet, components of sunlight such as UV, infrared and invisible light, and of course lifestyle factors, such as sleep."

DNA damage

Mitochondrial DNA is unique, in the sense that it has "very compromised repair mechanisms," said Prof Birch-Machin. "Essentially, it has no nucleotide excision repair — for example, patients with xeroderma pigmentosum have very suppressed, or non-existent, nucleotide excision repair and therefore are unable to repair their photoproducts. It's the same for mitochondria — they do not have nucleotide excision repair, so therefore photoproducts accumulate in mitochondria. Because there are lots of copies of mitochondria in a cell, that damage can be tolerated within the cell, so damage can be accumulated without killing the cell, and that leads to an increasing 'tower' of sun-induced DNA damage." It is now possible to measure this damage and this acts as a type of "sun diary" of the damage caused by this exposure, he told the attendees.

Prof Birch-Machin presented an overview of data on research he conducted with colleagues on the use of mitochondrial DNA damage as a biomarker for sun-induced damage in skin. Samples of the dermis and epidermis were taken from different body sites with varying degrees of sun exposure, showing an increase in mitochondrial DNA damage on the Y-axis, depending on the site on the body and degree of sun exposure.

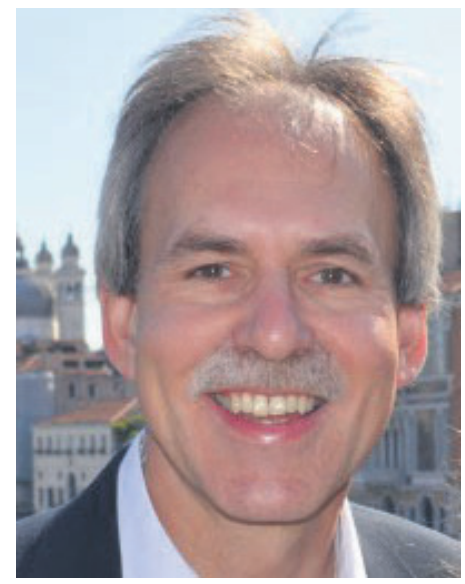
"As sun exposure increases, we see an upward curve in the amount of mitochondrial DNA damage, with more damage in the dermis than the corresponding epidermis," said Prof Birch-Machin. Assessment of the amount of mitochondrial DNA damage can also have commercial applications, such as evaluating the efficacy of suncreams, he added. "We can grow cells in a dish and use solar-simulated light or a sunbed or infrared light, and we can actually irradiate the sample and put sunscreen on it to measure how good the sunscreen is at protecting against UV-induced mitochondrial DNA damage."

Whilst protecting against skin ageing needs to be a holistic approach, involving a range of factors such as lifestyle and diet, Prof Birch-Machin and his team have developed apps that measure how much sunscreen should be applied relative to sun exposure and remind the user when it is time to re-apply the creams.

"We also did a number of trials looking at nutritional benefit to skin," he told the seminar. "Rather than just looking at the skin alone, we also looked at blood samples to examine the level of loading there — we are looking at ageing as a body phenomenon, so we wanted to see if dietary intervention would benefit the blood in terms of being able to withstand oxidative stress," he explained. "We developed a technique whereby we can do this on only two microliters of blood… we found that when people eat blueberries regularly, oxidative stress declined in normal controls and highly-trained athletes alike; different profiles with different oxidative starting levels. The best result we had was a 50 per cent benefit in people who ate 200g of blueberries per day."

Epidermis

During a wide-ranging Q&A session following the presentation, Prof Tobin commented: "Given that the inheritance of mitochondria between dividing cells is relatively passive and each donor cell has a relatively equal complement of mitochondria, what are the implications for the epidermis, where one of the daughter cells goes toward differentiation, and the other daughter cell remains as a progenitor cell in the basal layer? Have they actually inherited the same mitochondrial context for their lifetimes, or is there any additional requirement for mitochondrial behaviour in a progenitor cell versus a cell that undergoes differentiation?" he asked.



Prof Mark Birch-Machin

"An excellent question," Prof Birch-Machin responded. "A point related to that is, within those progenitor stem cells, if there is damage, are those cells more prone to accumulate damage, or are they better at removing damage? Secondly, in terms of rates of mitophagy, which will involve recycling of dysfunctional mitochondria… I don't think the rates of mitophagy have been studied in the context of the scenarios you have outlined. That would clearly affect the balance of the mitochondrial DNA ratio within those two cells."

Speaking to the ***Medical Independent (MI)*** following his presentation, Prof Birch-Machin was asked about the importance of the mitochondrial theory in the development of medical therapies, not just for ageing, but also in terms of curative treatments for diseases. "The mitochondrial theory of ageing is important for the ageing process in all tissues, as bioenergy declines and free radical production increases. But it is important in those diseases where these two processes are involved, and also where senescence is involved with the disease process."

Regarding a take-home message from his presentation, Prof Birch-Machin commented: "There are many processes involved in bioenergy decline and increase in free radical production, which affects many parts and processes of the cell. Mitochondria and their DNA can be used as a biomarker, or 'memory', which reflects the stress that each cell in the body is undergoing," he told ***MI***. "This is useful for monitoring progression of stress in cells, but importantly, for measuring the effectiveness of interventions that interact with nuclear DNA and other cellular processes."

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