Professional Development Dermatology

UCD CHARLES INSTITUTE SEMINAR SERIES

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The missing links in cellular dysfunction

Attendees at UCD's Charles Institute Seminar Series heard a presentation on how centrosomes contribute to the activities involved in DNA damage responses and repair

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, 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 seminar series heard a presentation from Prof. Ciaran Morrison of NUI Galway, an expert in biochemistry and cellular mechanisms with a wide range of distinctions both nationally and internationally. These include three Science Foundation Ireland Investigator Awards and a range of senior posts in locations ranging from Vienna to Japan. Prof Morrison's primary research focus is on the cellular mechanisms that allow accurate cell division and prevent damage to genetic material, in particular those that involve the centrosome.

Referring to the calcium-binding protein centrin-2, Prof Morrison provided a synopsis of his key findings to date. "Centrin is not required for centriole formation in human or chicken cells," he told the seminar. "It is, however, required for the efficient repair of nucleotide damage caused by solar UV. It is also required for primary cilium formation — we have separated the two elements of centrin, in that the calcium-binding functions of centrin-2 are required for ciliogenesis, but not for nucleotide excision repair," Prof Morrison explained.

"That's where we are in our exploration of centrin-2. It's a centrosomal and cilium-related protein that is intimately linked with key DNA repair processes in the nucleus." However, Prof Morrison also discussed centrobin, another protein that displays different functionality of centrosomal proteins in genome stability and about which little is known about to date, he said.

Prof Morrison told the attendees: "The main points to take away regarding centrobin are that there is a requirement for centrobin for efficient centriole duplication and for ciliogenesis, and this had not been described in mammalian cells until we conducted our work," he said. "We have also noted that centrobin is required for efficient DNA double-strand break repair, and our data thus far suggests that this involves homologous recombination repair pathways."

However, there are a number of questions that remain unanswered, said Prof Morrison. "What we are very interested in finding out is whether either of these genes of interest might be involved in human ciliopathies, diseases where the capacity for forming and regulating primary and multiple cilia give rise to a complex developmental spectrum of human disorders, particularly affecting the kidney, brain and retina. These are tissues known to be very sensitive during development to fluid motion, such as would be detected by primary cilia," he said.

DNA damage

"Another ongoing and underlying question is whether the DNA damage response is linked to the primary cilium or to the process of primary ciliogenesis," Prof Morrison continued. "Is this just related to the cell cycle arrest, which is required for quiescence to induce primary ciliogenesis, or are there different or specific activities related to the centriole or the primary cilium that can then communicate with the nucleus?" In this regard, a number of ciliopathy genes have been implicated in different DNA damage responses and there is a range of ciliopathy genes that encode various functions related to the cilium. The symptoms of the ciliopathies derive from ciliary dysfunction and some have an impact on genomic stability through different aspects of the DNA damage response, Prof Morrison pointed out.

"One might then pose the question of how centriolar or ciliary gene products might be communicating with genome maintenance activities within the nucleus," he told the seminar. "A very simple idea is a direct role in DNA repair within the nucleus… it is possible that centrobin and centrin play a role by acting within the nucleus to perform DNA repair, in addition to their centriolar or ciliary activities, and that seems possible.

"Another idea is that their functions at the centrosome may somehow impact on functions that the centrosome has in communicating with the nucleus," Prof Morrison continued. "If we ablate them, then we see a DNA repair defect, because their centrosomal roles, or the ciliary signalling roles… might impact on their DNA repair functions. Our current model of interest is that the main centrosomal functions that impact on the nucleus could be directed by microtubules through components that span the nuclear membrane, and thus communicate centriolar or ciliary signals through the nuclear membrane and into the membrane-adjacent chromatin to change DNA repair activities within the nucleus.

"It would be very instructive to try to link the strong phenotypes that we see relating to centrosomal and ciliary dysfunction to the nuclear impacts that these changes may have in the cells that we are looking at."

Future research

During a lively Q&A session, Prof Tobin highlighted the links referred to by Prof Morrison between sources of DNA damage stress and genotoxic stress, transitioning in interphase cells, potentially to neoplastic cells. Prof Tobin asked whether the onset of quiescence "is associated with the triggering or induction of ciliogenesis… at the same time, normal duplication of centrioles occurs when moving into a mitotic cycle — so, what is the connection between the re-use of the same materials for proliferation versus quiescence? Are you randomly using the same infrastructure of the cell for the two opposing cellular states, or is there somehow another reason for that?"

Prof Morrison replied: "The short answer is, this mechanism is not fully understood. It's clear that for this structure to be used for a spindle-pole, it has to be brought into the cell and not docked at the membrane. So for cells that are entering the cycle after quiescence, the cilium is ablated and there is a whole process for removing it," he said. "Whether that is a necessary prelude to re-entry into the cell cycle, or simply a consequence of the exit cycle into quiescence, is not fully understood at the moment. We don't yet know all the 'players' that ablate the process of cilium removal, or conversely, that direct docking of the centriole to the plasma membrane.

"It's an area of great interest," he continued, "to establish why it switches from one state to the other… unfortunately, some of the enzymes that are driving the loss of quiescence and ablating the cilium are those that are required for viability. If the full mechanism were to be established, that could be very interesting."

Prof Morrison added that there is a significant amount of research interest in ciliary and DNA repair in eye diseases, as a key structure in the eye is a modified primary cilium, making it one of the significant target organs for ciliopathies.

Renaissance

Speaking with the ***Medical Independent (MI)*** following his presentation, Prof Morrison spoke about the current state of specific research into his areas of interest. "Ciliary research has enjoyed something of a renaissance in the past decade," he said. "Particularly our understanding of how genes or proteins give rise to ciliopathies in the human spectrum — there really is a lot going on in that area.

"In the area specifically linking DNA repair to cilia — that's more specialised. You could say there are two reasonably separate domains that researchers work on and we [Prof Morrison and his research team] are working on both of these areas."

Prof Morrison was also asked if his work could potentially lead to better identification of biomarkers in the future. "From the cancer genome, for example, or any of the mutation databases, we have not seen that there is a huge number of these genes being mutated in cancer in general," he explained. "It may be of interest to look at particular types of cancer, given the DNA damage specificity that we see. That is definitely an area of interest, but we are not quite there yet where we can identify obvious biomarkers."

Prof. Ciaran Morrison

However, he added: "Microscopy of the centrosome can be used in tissues or cells to identify which cells have undergone DNA damage or have multiple centrosomes, which is a particular phenotype of potential interest in pathology," he said. "We have used it as a means of assessing radiation-induced damage, to establish whether this could be used to detect short-term DNA damage exposure in the event of a malevolent dose of radiation. Amplification of multiple centrosomes themselves, rather than the proteins or genes involved, is an unusual pathogenic indication of responses to DNA damage that could be of interest in other circumstances — that's what we had thought about and researched. That was [the basis for] a large EU-funded project called BOOSTER. That study received some attention and was successful to a certain extent in terms of how centrosome numbers may be of use for further investigation."

In terms of future research priorities and aspirations, Prof Morrison concluded: "I think there are a lot of open questions about the links between centrosomes and cilia, and the nuclear responses to genotoxic stress," he told ***MI***. "[The challenge is] working that out in relevant conditions, such as cancer and ageing, as well as in debilitating diseases related to centrosomal or ciliary problems. That is our main goal, to make this research useful [for the purposes of clinical interventions]."

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