RECENT HIGH-IMPACT PAPERS FROM RADBOUDUMC RESEARCHERS

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Summary

With over 3,000 publications each year, scientific research is a cornerstone of the Radboud university medical center [1]. In this section, recent high-impact papers with an impact factor higher than ten – published by researchers from the Radboudumc – will be discussed.

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A role for the innate immune system in cancer treatment

Immunotherapy is an anti-cancer treatment that makes use of the patient's immune system. The immune system consists of an innate and an adaptive part. As the innate immune system was believed not to have a memory, most immunotherapies target the adaptive immune system. However, recently, it has been shown that the innate immune system can be trained as well—trained immunity—, making it a major research topic within the research group of prof. dr. Mihai Netea (Department of Internal Medicine and Radboud Center of Infectious Diseases). In collaboration with other Radboudumc research departments, TU Eindhoven, and Mount Sinai Medical School New York, an article on trained immunity was published in *Cell* (impact factor = 38.6). A nanobiologic therapeutic, MTP10-HDL, was developed, and its effect on tumour growth was investigated in a melanoma mouse model (B16F10). MTP10-HDL significantly inhibited tumour growth by inducing trained immunity ($p = 0.0039$). In addition, via epigenetic mechanisms, MTP10-HDL stimulated bone marrow progenitors, resulting in more myeloid immune cells and increased cytokine production. These effects, in turn, resulted in a more pro-inflammatory tumour micro-environment (TME), favouring tumour destruction by the immune system. In addition, the effectiveness of checkpoint inhibitors, another type of immunotherapy, can be impaired by an anti-inflammatory TME. As MTP10-HDL treatment results in a more pro-inflammatory TME, adding MTP10-HDL improves the effectiveness of checkpoint inhibitor therapy. Finally, MTP10-HDL was not only found safe in mice but also in non-human primates. This offers possibilities for the application of MTP10-HDL as an anti-cancer treatment in humans. Before this clinical translation can be done, more extensive longitudinal studies using animal models are needed, which can also be used to investigate other types of cancers [2].

Does apathy predict cognitive deterioration or vice versa?

Apathy can be defined as a lack of motivation, initiative, and concern, and apathy is one of the main features of frontotemporal dementia (FTD), a well-known type of dementia. However, it has not been investigated before whether apathy is a predictor of cognitive deterioration in patients with FTD or the other way round. In collaboration with the University of Cambridge, prof. dr. Rogier Kievit (Department of Cognitive neuroscience, Donders Institute) answered this research question in *Alzheimer's and Dementia* (impact factor = 17.1). In this study, 304 carriers of mutations associated with FTD, as well as 296 of their relatives (non-carriers), were included. Study participants were pre-symptomatic and had a follow-up period of two years. The subjects underwent MRI scans and tests for apathy and cognitive function three times. Latent growth curve modelling was performed to assess relations between volumes of different brain regions, apathy, and cognitive decline. Apathy increased significantly during the period of follow-up in the carrier-group ($p = 0.004$) but not in the non-carrier-group ($p = 0.300$). In addition, apathy was found to be a predictor of cognitive deterioration in this group within two years ($p = 0.008$) but not the other way round ($p = 0.323$). Finally, low brain volumes of the frontal lobe and cingulate gyrus at the start of the study were associated with increasing apathy severity during follow-up in the carrier-group ($p = 0.038$ and $p = 0.037$, respectively). These results show that apathy could be identified as a marker of FTD-related cognitive decline. However, additional supporting evidence from studies with a longer follow-up period and larger sample size is required. Large sample sizes would also make it possible to investigate the previously reported findings in patient groups with different mutations separately. Together, those analyses could further increase insight into the role of apathy in the clinical course of FTD. Potentially, apathy could be an intervention target to decrease the risk of dementia [3].

Bone formation is less complicated than expected

The unique properties of bone tissue allow, among others, for organ protection, movement, and haematopoiesis. The traditional bone model assumes that bone consists of collagen fibrils and carbonated hydroxyapatite platelets (HAp crystals). According to this traditional model, the HAp crystals are organised parallel to the collagen fibrils in a structured deck-of-cards like manner. This organisation would presumably be guided by specific interactions with large biomolecules in the collagen. Sommerdijk *et al.* (Department of Biochemistry, Radboud Institute for Molecular Life Sciences) challenged this traditional model, and their results were recently published in *Nature Communications* (impact factor = 12.1). High-resolution electron microscopy confirmed that the HAp crystals were oriented parallel through the collagen. However, the orientation seemed to be random instead of in an organised deck-of-cards like manner. X-ray analysis revealed the structure of collagen, containing so-called gap regions. An *in vitro* model for bone growth showed that those gap regions provide HAp crystal organisation in the length direction of collagen. This type of crystal growth requires the least amount of energy, implying that crystal organisation is mainly determined by the laws of chemistry and not so much by specific molecular interactions. These results show that bone growth is less complicated than previously thought, as a highly complex matrix with specific biomolecules does not seem to be the main driver of crystal formation in bone anymore. This study opens doors for synthetic bone formation and regeneration, which, for example, could be valuable for patients with bone loss due to disease or fractures [4].

References

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