RECENT HIGH-IMPACT PAPERS FROM RADBOUDUMC RESEARCHERS

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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 – published by researchers from the Radboudumc – will be discussed.

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How much should you exercise for a healthy heart and a longer life?

Exercise and physical activity have been commonly associated with a healthy heart and a long life. But, how much should you exercise to yield cardiovascular health benefits? In an attempt to answer this question, Bakker et al. performed a cohort study involving ~145,000 individuals from three northern provinces of the Netherlands (PLOS Medicine, impact factor = 11.07) [2]. The participants were divided into three groups: 1) healthy group, 2) group with increased risk of cardiovascular disease due to hypertension and diabetes, and 3) group with a history of heart attack or stroke. The sample population was asked multiple questions regarding topics such as self-reported physical activity and occupation. The results were correlated with mortality and major adverse cardiovascular events within a ~7 year timeframe ($p<0.05$) . The analysis indicated that the ideal amount of exercise differs per group. For healthy and at-risk individuals (group 1 and group 2), a higher amount of exercise correlates to a lower risk of mortality and heart disease. However, the benefits plateau after 10-15 hours of moderate to vigorous physical activity every week. On the other hand, individuals with cardiovascular disease history (group 3) actually showed sustained increases in cardiovascular benefits from physical activity . The more they exercise, the lower their risk of acquiring a new cardiovascular disease. Aside from this, the study also investigated people's daily physical activities, including biking commutes, nature of work, spare time, and household chores. Surprisingly, individuals who perform intensive physical work as part of their jobs do not have a lower risk of heart disease or death. The researchers have no definite explanation for this phenomenon, but they hypothesise that it occurs because this group does not exercise sufficiently outside of their working hours. Additional causes that could have led to this result will be investigated in a future study. The general results of this study support that a physically active lifestyle is crucial in preventing and managing heart diseases. As such, this helps medical practitioners provide evidence-based lifestyle advice, especially to patients that have a history of cardiovascular disease.

Uncovered: enzyme responsible for hypoxia-induced metastasis in tumours

Hypoxia is a hallmark of cancer that drives metastasis and collective tumour invasion in various cancer types. In environments with normal oxygen levels, different forms of cancer cell masses collectively survey and invade surrounding tissues for further growth. On the contrary, hypoxic environments prompt cancer cells to individually detach from the primary tumour and probe the rest of the body for suitable growth sites. During this process, hypoxia induces epithelial cell transition to mesenchymal cells. Mesenchymal cells, then, can acquire amoeboid cell movement features. This type of movement allows a cell to move alone, mimicking the ancient movement of single-cell amoebas. However, the main drivers of this process remain to be uncovered. A paper published by te Boekhorst et al. in Current Biology (impact factor = 10.83) identifies the enzyme calpain-2 as a key regulator in hypoxia-induced amoeboid cell transition [3]. This enzyme regulates the degradation of integrins, which are adhesive proteins that attach tumour cells together to form a mass. Thus, an increase in calpain-2 detaches a cell from the primary tumour. Additionally, the enzyme also prompts the cell to go into an "energy-saving" mode while travelling to other parts of the body to prevent metabolic burnout. After some time, the cells revert to their previous adhesive state and form new tumours in other tissues. To validate the role of calpain-2 and its pharmacologic targeting potential, the researchers added drugs that inhibit the enzyme in tumour cells in a hypoxic environment. In this condition, the tumour cells were unable to transition, and significantly lower levels of metastasis were observed ($p<0.0001$). These findings demonstrate that calpain-2 is a potential target for therapy, which warrants further drug discovery and translational research studies.

DeepRank: a novel tool to accelerate protein-protein interaction research

Protein-protein interaction networks are essential for the coordination of complicated cellular processes. Therefore, gathering insight into how these interactions take place in 3D space helps to understand their function and to use this knowledge for drug design, immunotherapy, and other clinically relevant research. Different types of experimental methods, such as X-ray crystallography and cryogenic electron microscopy, have produced numerous atomic-resolution 3D structures of protein complexes. To derive complex interaction patterns from these experimental 3D structures, current machine learning and deep learning methods are used but still need further refinement to increase predictive accuracy. Aiming to circumvent this problem, a novel deep learning framework for data mining 3D protein-protein interfaces called DeepRank has been developed and published in Nature Communications (impact factor = 14.92) by Renaud et al. Using this deep learning approach, scientists can train software to analyse protein structures for specific patterns and predict their interactions [4]. The researchers tested DeepRank's performance based on two challenges in structural biology, being: 1) classification of biologically relevant structures in crystallography products, and 2) ranking of docking models to predict binding between proteins. Results show that DeepRank is comparable and sometimes even outperforms other state-of-the-art methods. The deep learning framework has a variety of applications in medical sciences. For example, in Radboudumc, it is currently used to aid in the development of a novel cancer vaccine [5]. DeepRank is publicly available through GitHub, which makes it accessible for any scientist interested in studying 3D protein interactions. Ultimately, this open-source framework can help accelerate a variety of fundamental and translational research efforts.

References

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