RECENT HIGH-IMPACT PAPERS FROM RADBOUDUMC RESEARCHERS

Janneke Elzinga[1]

With over 3000 publications per year, scientific research is a cornerstone of the Radboud university medical centre [1]. In this section, recent high-impact papers – published by researchers from the Radboudumc – will be discussed.

[1]Master Student Molecular Mechanisms of Disease, Radboud university medical center, Nijmegen, the Netherlands

How emotional memories are stored

While everyday memories slowly wear down with time, emotional events are often longer and more vividly remembered. It is known that noradrenergic activation of the amygdala, involved in emotional processing, enhances the initial formation of memory in the hippocampus. In the long term, memory traces are reorganised and partly transferred to neocortical networks, called systems consolidation. This is accompanied by the transformation of memory quality and time- and brain-specific epigenetic modifications. However, whether this process can be actively influenced by emotional arousal status is unknown. In a study by researchers from the Donders Institute, rats were subjected to a so-called inhibitory avoidance discrimination task training (footshock versus no footshock), after which they were treated with either norepinephrine (NE) or saline [2]. It was demonstrated that NE treatment supports accurate memory of the shock-context association and thus affects systems consolidation dynamics. This was shown to be dependent on hippocampal activity and accompanied by time-regulated epigenetically driven changes in transcription of memory-related genes in hippocampus and neocortex. The study contributes to further understanding the neuronal pathways involved in long-term accuracy of memory.

Non-haploinsufficiency in neurodevelopmental disorders

Intellectual disability (ID) and other developmental disorders (DDs) are often caused by de novo mutations in protein-coding genes. Previously, haploinsufficiency (i.e. the loss of one copy of a gene) was thought to be the main mechanism by which dominant mutations exert their disease-causing effect. Opposed to this is non-haploinsufficiency (NHI), of which gain-of-function and dominant-negative mechanisms are examples. In the case of NHI, mutations are often spatially clustered, affecting only particular regions of a gene. Researchers of the Department of Human Genetics exploited this phenomenon to identify genes with significant spatial clustering patterns of de novo mutations in large cohorts of people with ID and DDs [3]. From the 15 genes with clustering mutations identified, 12 had already been associated with neurodevelopmental disorders, of which 11 indeed had been associated with NHI mutation mechanisms. The three newly-identified genes opened new diagnostic possibilities. The results were complemented with 3D modelling of the affected proteins, which showed that the majority of the clustered mutations probably does not affect the overall structural integrity and may possibly act through another mechanism than haploinsufficiency. Furthermore, it was found that NHI-associated genes are less tolerant to normal genetic variation. The study shifts the focus of study to a mutation mechanism that may contribute to a larger extent to ID/DD than previously thought.

From mRNA modifications to an autism spectrum disorder

The field of epitranscriptomics investigates the biochemical modification of RNA and its effect on RNA metabolism, as in line with epigenetics (e.g. splicing, translation and degradation). The most common and well-understood mRNA modification is the addition or removal of m6A. This is a mRNA nucleotide modification commonly found in mammalian cells and has been linked to (patho)biological processes including cancer, obesity and fertilisation. The mechanism by which m6A influences RNA homeostasis is not exactly known. The so-called YTH-domain has previously been identified as a potential "m6A-reader" domain, but the existence of other interacting proteins, either attracted or repelled by m6A, remains elusive. Researchers from the Department of Molecular Biology, in collaboration with international partners, screened for m6A readers in various cell types and mRNA sequence contexts [4]. They demonstrated the conservation of YTH-domain-containing proteins across cell-types. In addition, sequence-context-dependent m6A readers were identified, including FMR1, of which loss is known to lead to fragile X-linked mental retardation. On the opposite, other proteins were shown to be repelled by m6A modified mRNA. This study demonstrates the effect of m6A modifications on mRNA homeostasis by regulating, for instance, mRNA stability or translation rates. Moreover, this study is the first to report a link between a mRNA modification and the fragile X-linked mental retardation syndrome.

Linking magnesium homeostasis to metabolic disorders

Magnesium (Mg^{2+}) homeostasis is tightly regulated by renal reabsorption. Disturbed levels of this cation have been associated with metabolic disorders, but the main genes regulating renal Mg^{2+} handling, however, remain to be identified. In a multidisciplinary, international collaboration, researchers from the Department of Physiology performed a genome-wide meta-analysis of Mg^{2+} homeostasis to identify genetic components [5]. They combed existing data on genetic and biological (e.g. plasma and urine) parameters from over 9,000 individuals. This resulted in the identification of two loci associated with urinary magnesium: one was located near a gene coding for a Mg^{2+}-channel (TRPM6), the other was located on a gene (ARL15), which previously had been linked to obesity and insulin biology, respectively. Next, ARL15 was demonstrated to regulate TRPM6-mediated currents in human kidney cells. This *in vitro* data was complemented with *in vivo* data from zebrafish. The expression of ARL15 zebrafish orthologue was regulated by dietary Mg^{2+} and its knockdown resulted in Mg^{2+} wasting and metabolic disturbances. Finally, in the population-based studies, the association between urinary Mg^{2+} and metabolic phenotypes were modified by a genetic variant of ARL15. This study increases insight in Mg^{2+} homeostasis in relation to metabolic disorders and identifies ARL15 as a novel key player in these processes.

References

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