Controlling magnesium flux: a central role for the PRL-CNNM complex

Magnesium is an essential metal ion for human health. However, its ability to act as a supplementary therapy against disease is a poorly understood area of science. Professor Michel L. Tremblay and his team at McGill University in Montreal, Canada, are looking to change this though, and are currently investigating the role of the newly discovered pathway, PRL-CNNM, in controlling magnesium’s mechanism of action. This breakthrough discovery has implications for our understanding of cancer, metabolism, circadian rhythm and infectious disease.

Magnesium (Mg²⁺) is a metal ion found in the earth, sea and all living creatures, and is essential to life. Present in every single cell of the body, it serves many important functions – especially in supporting biochemical reactions. Notably, it’s an intrinsic component of adenosine triphosphate (Mg-ATP), the universal energy store found in all forms of life. Its most widely understood function is its ability to support the physiological processes behind the metabolism of food into energy. Magnesium contributes to the creation of new proteins from amino acids, the contraction and relaxation of muscles, and the regulation of neurotransmitters – chemical substances that transfer messages throughout the brain and nervous system. It also supports gene transcription and replication. It therefore makes sense that magnesium is a vital component of adenosine triphosphate (ATP) – the organic chemical that provides cellular processes with the energy required to drive them.

As yet, it is unclear whether these interactions play a role in magnesium transport, or if they simply act as a magnesium sensor for cells. Nonetheless, results currently show that the more PRL-CNNM protein complexes there are, the higher the level of intracellular magnesium. Think of it like three people (PRL proteins) getting a choice of four cars (CNNM transporters) to drive – driving these cars around causes intracellular magnesium to increase. Indeed, the central role of the PRL-CNNM complex is supported by the fact that it is evolutionarily conserved across all chordates.

**MAGNESIUM MUTATIONS**

Mutating one of the PRL proteins in a study using mice, Professor Tremblay and his colleagues proved this phenomena to be true – establishing a decrease in intracellular magnesium production when PRL-CNNM interactions were inhibited. Through their work, they also found that the PRL enzymes and CNNM proteins worked together and that their collaborative function modulated magnesium levels in cells.

**PRL-CNNM: A CANCER-CAUSING PATHWAY?**

The implications of this research are huge. The prominence of PRL gene expression in almost all human cancers, and the fact that PRL levels are higher in metastatic (spreading) tumours compared to non-metastatic tumours, suggests PRL is involved in the process whereby cancers spread.

Professor Tremblay and his team therefore turned their attention towards furthering understanding of this area, investigating the influence of PRL enzymes on cancer growth.

Again using mice as models, their research found that – amazingly – reducing the number of PRL proteins in cancer cells significantly reduced the rate of tumour growth. In other words, lower levels of PRL enzymes, lower levels of cancer growth.

Not only that, but the team also found that mutations in PRL or CNNM genes reduce intracellular levels of magnesium and lead to a decrease in the metabolism of cancer cells – preventing them from invading other tissues. This could therefore explain the oncogenic role of the PRL-CNNM pathway, the outcomes of which could be life-changing: should this process occur similarly in humans, different approaches to cancer prevention and therapeutics may be developed.

**THE COMPLEX AND THE CANCER**

So far, Professor Tremblay and his team have found an association between the balance of intracellular magnesium and the pro-oncogenic function of PRL-2 enzymes, pinpointing CNNM complexes as key PRL-binding partners.

Interestingly, the team uncovered that, to ensure PRL is sufficiently present in normal cells, a lower magnesium concentration is needed for PRL-2 enzyme expression. Conversely, a higher magnesium concentration is needed to inhibit PRL-2 enzyme expression – maintaining the balance of magnesium concentration within the cell. The researchers therefore propose that you need one person to push up and the other to pull down to create an equilibrium.

However, cancer cells operate differently. These cells rely on a higher magnesium concentration to increase the activity of the PRL-CNNM pathway, ensuring their survival and replication. It therefore makes sense that PRL expression is often higher in metastatic tumours – instances where cancer spreads to surrounding tissue. Because of Prof Tremblay and his team’s findings, the role of the PRL-CNNM pathway has now been identified as a major part of cancer’s ability to metastasise.

**PRL-CNNM: OTHER IMPLICATIONS**

Although the initial focus of the PRL-CNNM complex research was on cancer, the McGill University group have since found it to have other important metabolic functions. They demonstrate that PRL-2 deficient mice have an abnormal physiology, leading to growth retardation, altered body composition and higher mortality rates after birth. Some of these effects appeared to be sex-dependent – especially in brown adipocytes important for maintaining body temperature – due to PRL being found at higher levels in females.
than in males. It is possible that female hormones may have a positive effect on PRL gene expression, increasing the amount of available PRL.

PRL2 deficient mice also showed alterations in their circadian rhythm – the internal clock system that regulates energy expenditure, sleep pattern and metabolism. The importance of this mechanism was recently highlighted by the award of the 2017 Nobel Prize in Physiology or Medicine to Jeffrey C. Hall, Michael Rosbash and Michael W. Young for their discoveries in this field. The complex at the membrane promotes the entry of magnesium to support increased metabolic activities in their respective tissues.

On the right panel, once evening arrives, a decrease in the need for magnesium occurs causing a reduction in the expression of both PRL and CNNMs. A consequent drop in magnesium concentration is followed by a decrease in metabolism favouring during the incoming night. In cancer, higher levels of magnesium are needed to sustain the high-energy metabolism of cancer cells. This occurs either through a positive feedback mechanism that is initiated when magnesium is required; thus, increasing expression of the PRL and CNNMs induced by various oncogenes that leads to high magnesium levels, increased cell metabolism and a strengthening of tumour and metastatic burdens.

The implications of Prof Tremblay’s area of work could be massive, especially within the field of cancer research.