PUSI: Special issue on Purinergic Signalling and Calcification

Editorial by Isabel R Orriss & Timothy R Arnett

Over the last two decades a new role for ATP as an extracellular regulatory molecule has emerged. Many independent studies have now shown that extracellular ATP additionally functions as an important inhibitor of tissue calcification, particularly in the skeletal and cardiovascular systems. This novel action of ATP may occur not only via 'classical' P2 receptor-mediated pathways but also because extracellular ATP is hydrolysed by ecto-nucleotide pyrophosphatase/phosphodiesterase 1 (NPP1), to yield pyrophosphate (PP_i), a critical physiochemical inhibitor of mineralisation that acts as the body's ubiquitous 'natural water softener'. The short collection of papers presented here offers diverse new insights into this fascinating avenue of extracellular nucleotide research.

Matrix vesicles (MVs) are a class of extracellular vesicles involved in initiation of mineralisation processes and contain NPP1 and tissue non-specific alkaline phosphatase (TNAP). TNAP cleaves ATP and PP_i to produce phosphate (P_i), a promoter of calcification/mineralisation processes. The paper by Andrilli and colleagues describes a proteoliposome biomimetic model of MVs to investigate how these enzymes function together to regulate biomineralisation. By engineering the proteoliposomes to contain one or both enzymes, the authors were able to determine the rates at which they consumed ATP and the impact this has on the rate of mineralisation. They conclude that when TNAP and NPP1 are present at equal levels, these enzymes function synergistically to produce a P_i/PP_i ratio conducive to mineralisation.

Alterations in the P_i/PP_i ratio can have a significant negative impact on the mineralisation of the skeleton, for example, in hypophosphatasia, a genetic disease caused by mutations in the TNAP gene. In contrast, in blood vessels, increased P_i relative to PP_i can lead to pathological calcification. The review by Villa-Belosta provides an overview of the important role that purinergic signalling and extracellular ATP play in regulating vascular calcification. It focusses on the importance of ATP as the principal source of PP_i and how the ATP/PP_i metabolism cycle represents an area that could be targeted therapeutically.

The final contribution in this special issue concerns the role of the P2X4 receptor in osteoblasts, the cells responsible for bone formation. It is shown that ATP signalling via this receptor favours osteogenic, rather than adipogenic differentiation of progenitor cells.

The papers collected here illustrate the importance of purinergic signalling in the regulation of calcification processes. There will surely be more developments in this exciting area in the future.