Purinergic Signalling (2006) 2:325–326
DOI 10.1007/s11302-006-9005-3

Editorial

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Received: 21 December 2005 / Accepted: 23 December 2005 / Published online: 5 April 2006

"Make everything as simple as possible, but not simpler"

Albert Einstein

Nucleosides and nucleotides are primordial biological molecules derived from glycosylamines (comprising nucleobases and variably phosphorylated pentose sugars) that serve all biological processes. These molecules are responsible for the transmission of genetic information and provide currency units for biological energy transfer and generate crucial intermediates for intracellular signaling processes. In keeping with Occam's razor and the parsimony of Nature, these ubiquitous compounds are also released from cells to provide what we consider to be integral elements of extracellular signaling. Within such "purinergic systems", specificity and regulation can be dictated by the source of the extracellular nucleotides, expression and/or desensitization of specific receptors for these molecular transmitters and derivatives that are generated by specific catalytic factors or ecto-enzymes. Arrays of such receptors are widely distributed in neuronal, glial, immune, hepatic, bone, muscle, endothelial, epithelial and endocrine cells and induce multiple intracellular signaling cascades. To provide specificity, this process involves at least four subtypes of P1 (adenosine) receptors and currently over 15 subtypes of the ion channel and G protein-coupled families of nucleotide (P2) receptors.

Within the past decade, ecto-enzymes hydrolyzing and interconverting extracellular nucleotides belonging to several gene families have been discovered, then cloned and characterized. These include our own favorites, CD39 and the ecto-nucleoside triphosphate diphosphohydrolases (E-NTPDases). Other equally intriguing ecto-enzymes include those of the ecto-nucleotide pyrophosphatase/phosphodiesterases (E-NPPs), alkaline phosphatases, diadenosine polyphosphate hydrolases, adenylate kinases, nucleoside diphosphate kinases, CD38/NAD glycohydrolases (NADases), ADP-ribosyltransferases (ARTs) and ecto-protein kinases.

These distinct families of ecto-nucleotidases appear to provide key components responsible for P2 receptor modulation and functional integrity by the removal or conversion of nucleotides to derivatives (inclusive of nucleosides). They also dictate cellular purinergic responses by the conversion of P2-responses to adenosine-P1-mediated events with ultimate nucleoside salvage by cells. These functions influence both acute, transitory processes such as neuronal transmission or platelet secretion and also impact upon long-term (trophic) signaling in the control of cell proliferation, differentiation, motility and death in tissue regeneration, wound healing and cancer.

In this Special Issue of Purinergic Signalling, we address the ensemble of key cell surface-located ecto-enzymes. We, as guest editors, have assembled an array of leaders in their respective fields to summarize key areas of interest. Articles range from those detailing the

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pathophysiological significance of ecto-enzymes to others that chiefly address structural biology and molecular features. It is our wish that these articles illuminate, and possibly clarify, many of the controversial points in this ever enlarging and increasingly disparate field. We also hope this issue will increase interest in the roles of purines and pyrimidines in physiological and pathophysiological conditions and help provide for further acceleration of therapeutic applications in human disease. Finally, we are grateful to Geoffrey Burnstock for his vision in establishing this forum and for the invitation to prepare what we believe to be a state-of-art overview of this area.

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Christmas, 2005.