AUTHOR COMMENTARIES - 2009

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Vera Ralevic

Featured Scientist from *Essential Science Indicators*SM

According to Essential Science Indicators *from Thomson Reuters, the most-cited paper in the field of Pharmacology & Toxicology for the period of January 1, 1998 to August 31, 2008 is "Receptors for purines and pyrimidines," (*Pharmacol. Rev. *50[3]: 413-92, September 1998), by Dr. Vera Ralevic and Professor Geoffrey Burnstock. This paper currently has 1,968 cites.*

Dr. Ralevic is an Associate Professor and Reader in the School of Biomedical Sciences at the University of Nottingham. Professor Burnstock is the President of the Autonomic Neuroscience Centre at Royal Free and University College Medical School, University College London.

In the interview below,* ScienceWatch.com *talks with Dr. Ralevic about this paper and its impact on the research community.

SW: What factors motivated you to write this review?

The main aim of this review was to categorize some of the extensive literature on endogenous purine receptors according to the new nomenclature developed around cloned receptors. In the 10 years before the review was published, 16 out of 19 different receptors for purines and pyrimidines were cloned, including all four subtypes of adenosine P1 receptor, all seven subtypes of P2X purine receptor, and five (out of eight) subtypes of P2Y purine receptor. This contributed to a worldwide renewed interest in purinergic signaling. Importantly, it led to the development of a new nomenclature for purine receptors, based on the newly cloned receptors; this superceded the established nomenclature, expanded and refined since the first formal recognition of purine receptors by Professor Geoffrey Burnstock in 1978.

The field was moving so rapidly that a comprehensive review was timely. The intention was that this review would be a useful reference article for both experts in, and newcomers to, the field of purine research. The review is coauthored with Geoffrey Burnstock, the "grandfather" of purinergic signaling, and is a testimony to the time that I spent with him as a Ph.D. student and postdoctoral research fellow.

"There is still an enormous amount that we do not know about purine receptors."

SW: Would you sum up the main points of your review for our readers?

Purines and pyrimidines are important extracellular signaling molecules that have diverse biological effects via cell-surface receptors known as purine receptors. This review describes briefly the history of the discovery of purine receptors, and details their current classification; firstly into two main families of P1 and P2 receptors, with a

further subdivision of P1 receptors into four subtypes, and P2 receptors into P2X receptors (seven subtypes) and P2Y receptors (now eight subtypes). The review matches endogenous purine receptors, characterized mainly using pharmacological, electrophysiological, and immunohistochemical methods, with their cloned counterparts.

The review additionally reports the important and diverse biological actions of purines and pyrimidines, including modulation of cardiac function, smooth muscle contraction, neurotransmission, exocrine and endocrine secretion, immune and inflammatory responses, pain, and platelet aggregation. It seems that every single cell in the body expresses one or more subtypes of purine receptor and is, therefore, regulated by purines and pyrimidines.

SW: How has our knowledge of these receptors changed in the 10 years since this paper was published?

There has been a tremendous increase in the breadth and depth of our understanding of purine receptors in the last 10 years. Two further P2Y receptors, $P2Y_{12}$ and $P2Y_{13}$, were cloned in 2001, and the $P2Y_{14}$ receptor was identified (it was first cloned in 1994 as an orphan receptor).

More generally, we are starting to know increasingly more about each of the specific receptor subtypes: their tissue expression, signaling, regulation, and patho/physiological roles. For example, the stoichiometry of P2X receptors has been clearly defined as 3 subunits, and we now know that adenosine P1 receptors (A_1 subtype) can dimerize with certain P2Y receptors ($P2Y_1$ and $P2Y_2$). Through the development and use of knockout animals, small interference RNA and subtype-selective ligands, patho/physiological roles of different purine receptor subtypes have been newly identified or confirmed, including: A_1 receptors in regulation of pain, anxiety, neuroprotection and tubuloglomerular feedback; A_{2A} receptors in inflammation; A_3 receptors in immunity and ischemia-reperfusion injury; $P2X_1$ receptors in platelet aggregation, fertility and reproduction and tubuloglomerular feedback; $P2X_{2/3}$ receptors in nociceptive and mechanosensory transduction; $P2X_4$ receptors in regulation of blood pressure and vascular remodeling; $P2X_7$ receptors in inflammation and pain, bone formation and resorption; $P2Y_1$ receptors in platelet aggregation; $P2Y_2$ receptors in epithelial chloride secretion in airways and potassium secretion in the gastrointestinal tract; $P2Y_4$ receptors in epithelial potassium secretion in the gastrointestinal tract; $P2Y_{12}$ receptors in platelet aggregation and microglial chemotaxis; $P2Y_{13}$ receptors in regulation of hepatic HDL endocytosis.

"Purines and pyrimidines are important extracellular signaling molecules that have diverse biological effects via cell-surface receptors known as purine receptors."

Changes in purine receptor expression have been shown in response to physiological stimuli (e.g., noise upregulates expression of $P2X_2$ mRNA and protein in the cochlea), as well as in development, ageing, and disease (e.g., $P2X_1$ and $P2Y_2$ receptor mRNA levels are increased in congestive heart failure). Some premises have been overturned. For example, it had long been believed that, in blood vessels, P2X receptors are expressed on the smooth muscle and P2Y receptors on the endothelium; it is now known that different subtypes of both P2X and P2Y receptors are expressed on both smooth muscle and endothelium, with diverse roles in regulation of contractility, tissue growth, and development. There is increasing evidence that these important discoveries about purine receptors can be exploited clinically, e.g., in the development and use of $P2Y_{12}$ antagonists to inhibit platelet aggregation, and in the development of $P2Y_2$ antagonists to treat chronic bronchitis, cystic fibrosis, and dry eye.

SW: Are there things we still don't know about these receptors?

There is still an enormous amount that we do not know about purine receptors. A number of the different receptor subtypes are still largely enigmatic, mainly because of a lack of selective ligands and knockouts available to give clues as to their physiological roles. Overall, relatively little is known about the sources, stimuli, and mechanisms of release and metabolism of the endogenous ligands of purine receptors, especially of the pyrimidine nucleotides UTP and UDP. This limits our understanding of purine receptors, through not knowing the circumstances leading to their activation.

Our understanding of the physiological roles of purine receptors in humans is still in its infancy compared to that in other species. Similarly, although there is evidence of an involvement of purine receptors in many different animal models of disease, including cardiac disease, immune and inflammatory

disorders, and cancer, relatively little is known about the roles of purine receptors in pathophysiological conditions in humans.

SW: What should the "take-away lesson" about your work be?

It is clear that purines and pyrimidines, through actions on specific purine receptors, have important and diverse effects on many different biological processes. There is a rapidly growing increase in our understanding of all aspects of purinergic signaling—especially the expression, signaling mechanisms, and physiological roles of different subtypes of purine receptors—which is being driven by the tantalizing prospect that they can be targeted clinically.

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Vera Ralevic's current most-cited paper in *Essential Science Indicators*, with 1,968 cites:

Ralevic V, Burnstock G, "Receptors for purines and pyrimidines," *Pharmacol. Rev.* 50(3): 413-92, September 1998. Source: *Essential Science Indicators* from Thomson Reuters.

Keywords: purines, pyrimidines, receptors, cloned receptors, purinergic signaling, extracellular signaling, biological actions, receptor subtypes, expression, physiological roles.

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