Editorial

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The P2X₇ receptor was functionally identified as the “ATP⁴⁻ receptor” (later P2Z) in the early 1980s, and cloned in 1996. Despite its intriguing functional properties, it was never seriously considered a physiologically relevant receptor, in part in consequence of the stubborn skepticism that surrounded the purinergic hypothesis until recently. With hindsight, we must admit that it was undoubtedly difficult to make a rationale of a receptor that caused a reversible permeabilization of the plasma membrane via an utterly undefined molecular mechanism. This scenario has changed dramatically over the last five years, with the identification of the elusive P2X₇ “large pore” by Pelegrin and Surprenant (doi:10.1007/s11302-009-9141-7), and the unveiling of the P2X₇-inflammasome connection. We now know that P2X₇ is not merely a hole in the plasma membrane inevitably associated to cell death. Converging interest from different fields such as biochemistry, immunology and cell biology generated a surprising cross-fertilization that led to the identification of an additional mechanism of activation of P2X₇ by covalent modification of arginine residue(s) by ecto-ribosyltransferase-catalyzed ADP-ribosylation (see Schwarz et al. doi:10.1007/s11302-009-9135-5). Arginine residues in the P2X₇ ecto-domain

seems to play an important role in ligand-receptor interaction, as mutations affecting these residues, as discussed by Adriouch and co-workers (doi:10.1007/s11302-009-9134-6) may change sensitivity to ATP ten to thirty fold. A tight regulation of P2X₇ activation by ATP is absolutely necessary in view of the increasingly recognized role of this receptor in host-pathogen interaction and inflammation as a whole. Qu and Dubyak (doi:10.1007/s11302-009-9132-8) discuss how activation of P2X₇ affects multiple facets of membrane trafficking and recycling, phagosome-lysosome fusion and release of secretory lysosomes included. P2X₇ modulates innate immunity on a variety of fashions, ranging from NADPH oxidase activation and generation of reactive oxygen species to gene transcription (Lennertz et al. doi:10.1007/s11302-009-9133-7). One of the best characterized inflammatory pathways set in motion by P2X₇ is the caspase-1/IL-1 β maturation pathway, as described by Wewers and Sarkar (doi:10.1007/s11302-009-9131-9). Therefore it is no surprise that the P2X₇ receptor is a central player in the continuing struggle against intracellular pathogens (Coutinho-Silva et al. doi:10.1007/s11302-009-9130-x). The immune system and bone share many features and are targets to many common pathways, to the point that osteoimmunology has been proposed as a novel branch for biomedical investigation, thus it was not surprising to find that P2X₇ has an important role in the regulation of bone formation and resorption as well as in the response to mechanical stimulation (Grol et al. doi:10.1007/s11302-009-9139-1). The P2X₇^{-/-} mouse was an invaluable tool in these studies. It is well known that the issue of whether the P2X₇ receptor is expressed by all cells the Central Nervous System (CNS) is a *vexata quaestio* (a contentious issue). While there is no doubt that P2X₇ is present and functional in microglia, there are serious doubts that neurons express this receptor. However and very

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interestingly, some of the most clear indications of the pathophysiological role of this receptor come from the CNS. Cotrina and Nedergaard (doi:[10.1007/s11302-009-9138-2](https://doi.org/10.1007/s11302-009-9138-2)) show that activation of P2X₇ is crucial in spreading damage after spinal cord injury, and Bianco et al. (doi:[10.1007/s11302-009-9137-3](https://doi.org/10.1007/s11302-009-9137-3)) describe the different pore-forming properties of the P2X₇ receptor of astrocytes isolated from the cortex versus those isolated from the hippocampus. Since pore formation is necessary for P2X₇-dependent IL-1 β processing and release, these observations will certainly have far reaching implications in neuroinflammation. Nervous tissue is very sensitive to pressure changes and the ensuing mechanical stress. These factors release ATP which might reach in the pericellular space concentrations sufficient to activate P2X₇. A paradigmatic example is the retina, where P2X₇ is implicated in pressure-induced ganglion cell damage (Mitchell et al. doi:[10.1007/s11302-009-9142-6](https://doi.org/10.1007/s11302-009-9142-6)). Glaucoma is a likely candidate disease for P2X₇ blockers.

Most of the emphasis on P2X₇ pathophysiological functions has been as a cytotoxic receptor. But this might not be the whole truth. Data from Di Virgilio and co-workers (doi:[10.1007/s11302-009-9145-3](https://doi.org/10.1007/s11302-009-9145-3)) now suggest that low level P2X₇ stimulation is beneficial as it increases total cellular ATP and stimulates growth. Finally, Fuller and co-workers (doi:[10.1007/s11302-009-9136-4](https://doi.org/10.1007/s11302-009-9136-4)) shed light on a fascinating aspect of P2X₇ genetics: the presence of a high number of single nucleotide polymorphisms (SNPs). Some of these have important effects on the receptor function and its associated release of pro-inflammatory cytokines. Genetic association studies in a number of human diseases has uncovered a role for genetic variants of P2X₇ in diseases as diverse as tuberculosis, Chlamydia and post-menopausal osteoporosis. These very recent acquisitions bring now P2X₇ at the very heart of human disease. Surely the future will reserve us many more exciting surprises on this very unconventional receptor.