Role of the purinergic receptor P2X7 in the shedding of transmembrane molecules in diseases

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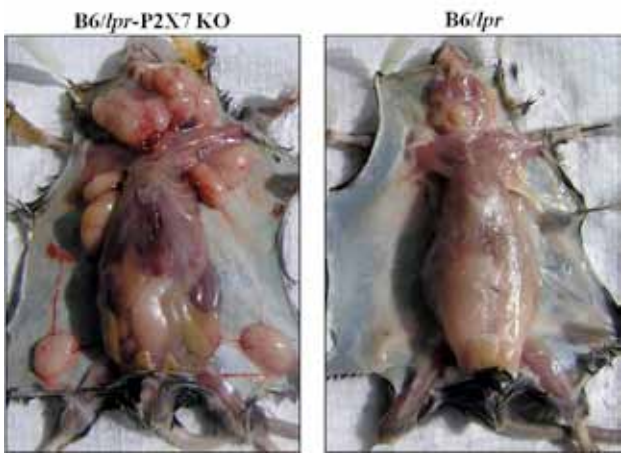
Major Aims of our projects

1)Study the role of the purinergic receptor P2X7 in the proteolytic cleavage of the amyloid precursor protein (APP) and identify the biochemical pathways leading to the shedding of the soluble fragment of APP (sAPPα).(Partner N °1, Kanellopoulos Jean)
2) Study the role of P2X7R in the homeostasis of T lymphocytes (Partner N°2, Bobé Pierre)



RESULTS

We have shown that P2X7R activation stimulates the proteolytic shedding of sAPPα from neuroblastoma cells and mouse astrocytes or neural progenitor cells. The release of sAPPα is specific of P2X7R and is not observed in mouse astrocytes from P2X7R-deficient mice. The P2X7R-dependent α-secretase cleavage of APP is strongly inhibited by metalloprotease inhibitors. However, siRNA of ADAM9, 10 and 17, known to have α–secretase activity, does not block the non-amyloidogenic pathway triggered by P2X7R. Using pharmacological inhibitors, we show that inhibition of the mitogen-activated protein kinase modules Erk1/2 and JNK strongly decreases the P2X7R-dependent α-secretase activity.

The mutation of the death receptor Fas in both MRL/lpr mice and humans (ALPS patients) causes a lymphoproliferative syndrome due to the accumulation of B220+ CD4–CD8– T lymphocytes, and autoimmune syndromes. However, Fas deficiency cannot account for the entire autoimmune syndrome of MRL/lpr mice because B6/lpr mice develop mild lymphoproliferation and no autoimmune disease. Since P2X7R plays a major role in the processing of pro-inflammatory cytokines, the proteolytic cleavage of transmembrane proteins such as leukocyte homing CD62L, and cell death, we have determined the role of P2X7R in T-cell homeostasis and autoimmunity. Thus, we have generated a mice deficient for Fas and P2X7R (B6/lpr-P2X7R KO mice). While B6-P2X7R KO mice do not develop lupus and B6/lpr mice present a mild type of lupus, the B6/lpr-P2X7R KO mice develop a massive lymphoproliferation (Figure 1) due to the accumulation of B220+ DN T cells in lymph nodes and the spleen, suggesting that Fas and P2X7R synergize to maintain T-cell homeostasis.

PERSPECTIVES

We are currently trying to identify, using *in vitro* and *in vivo* approaches, the biochemical pathways activated by P2X7R which produce the sAPP fragment. In addition, we plan to analyze how P2X7R controls the expansion and/or accumulation of T lymphocytes in peripheral lymphoid organs. Furthermore, we will study the role of P2X7R in autoantibody production, overproduction of cytokines and shedding of transmembrane protein such as Fas ligand (FasL) because these parameters are strongly correlated with the severity of the autoimmune disease.

PUBLICATIONS

• Le Gall SM, **Bobé P**, Reiss K, Horiuchi K, Niu XD, Lundell D, Gibb DR, Conrad D, Saftig P, Blobel CP. **Mol Biol Cell**. 2009;20(6):1785-94.
• Delarasse C, Auger R, Gonnord P, Fontaine B, Kanellopoulos JM. **J Biol Chem**. 2011;286:2596-606.
• Legrand J, SM Le Gall, M Benbijja, P Gonnord, MG Tovey, K Benihoud, JM Kanellopoulos, and P Bobé. Down-regulation of P2X7 receptor expression on CD4⁺ effector T cells and DN regulatory T cells in B6 mouse. **Submitted**
•Le Gall SM , Legrand J, M Benbijja, MG Tovey, K Benihoud, JM Kanellopoulos, and P Bobé. Synergistic role of death receptor Fas and purinergic receptor P2X7 in maintaining homeostasis of peripheral T lymphocytes. **Submitted**

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