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Poster Board #-Session: 775-I

**New Role for ATP P2X1 Receptors in the Control of Neutrophil Apoptosis and Respiratory Burst Activity.**

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**Abstract**

P2X receptors are membrane non-selective cation channels thatopen in response to the binding of extracellular ATP. Sevengenes encode P2X receptor subunits (P2X1–7) in vertebrates.Channels form homo- or hetero-multimers of several subunitsthat are highly permeable to Ca2+. P2X receptors are widelydistributed. In recent years, increasing attention has beenpaid to extracellular ATP as a candidate danger signal locallyreleased at the inception of inflammation. One of the most strikingfeatures of ATP is its ability to promote P2X7 receptor-mediatedmassive release of mature IL-1ß from LPS-primed mononuclearphagocytes. On neutrophils, ATP rises intracellular Ca2+ concentrations,contributes to degranulation, adhesion, oxidative burst anddelays apoptosis, events that may partly depend on the G-proteincoupled P2Y2 receptor and on P2X7. In the present work, RT-PCR,Western blotting and immunofluorescence experiments reveal thatneutrophils also express P2X1 and P2X5 receptor subtypes. Amicroarray analysis indicates that a 3-hour treatment of humanperipheral blood neutrophils with the selective P2X1 and P2X1/5receptor agonist, a,ß-meATP, changes the expressionof genes mainly involved in the control of cell fate. Accordingly,this agonist causes an increase of phosphatidylserine exposureon neutrophil membranes, maximally occurring after 3 hours andlasting until 18 hours of culture. In the presence of the proteinsynthesis inhibitor cycloheximide, a,ß -meATP promotescaspase-3-dependent neutrophil apoptosis after 3 hours, whichis correlated with highly reduced Fc RIII (CD16) membrane expression.In addition, a 1 min pretreatment of neutrophils with a,ß-meATP potently increases tumor necrosis factor-a (TNF- )-drivenpriming (30 min) of the respiratory burst induced by the bacteriallyderived peptide N-formyl-methionyl-leucyl-phenylalanine (fMLP).Furthermore, a,ß -meATP produces L-selectin (CD62L)shedding by its own and in an additive manner with TNF- . Thisagonist also induces rapid and reversible phosphorylation ofthe survival kinases ERK (starting after 2 min) and Akt (15min) as well as phosphorylation and degradation (after 2 min)of I- B , an inhibitor of the anti-apoptotic transcription factorNF- B. Hence, neutrophil P2X1 receptors might have a dual rolein inflammation; they would both contribute to neutrophil activationand promote cell death of neutrophils that have reached theend of their useful life span. Activation of P2X1 receptorsby extracellular ATP may thus represent novel regulatory mechanismsthat govern neutrophil function.

**Footnotes**

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