Underlying purinergic signaling contributes to T lymphocyte activation in tissue repair. Focus on “Shockwaves increase the T-cell proliferation and IL-2 expression through ATP release, P2X7 receptors, and FAK activation”

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Even though I have worked in the “purinergic field” for a number of years, I continue to be amazed by the range of cellular and tissue systems and experimental settings in which purinergic signaling (i.e., extracellular signaling by ligands such as ATP, ADP, 5’-AMP, and/or adenosine) is demonstrated. This deepening of data cannot be accidental. It is likely that these small molecules were among the first in a primitive and evolutionary sense that could be utilized by early biological cells. Seemingly unrelated to these concepts is the evidence that electrical, thermal, and/or mechanical stimulation is therapeutic for skeletal muscle repair after sports injury. Indeed, virtually ‘every day’ a professional athlete treated in this manner rebounds from a musculoskeletal injury to play in the next big game.

A recent compelling article by Yu et al. (10), integrates the fields of extracellular ATP signaling and T cell-driven tissue repair by describing an important local form of signal transduction within tissues, including skeletal muscle, that promotes healing. It is increasingly apparent that ATP release (secretion, efflux, exocytosis) is stimulated by mechanical perturbations (membrane stretch, changes in tissue mechanics, mechanical strain or stretch on a ‘stretchable’ support). Arguably, this was first described in comprehensive analyses by Forrester in skeletal muscle many decades ago (3). It is well known, principally from the work of Dubyak and coworkers (5, 8) and di Virgilio and colleagues (1, 6), that P2X7 receptors play critical physiological roles in hematopoietic cells. P2X7 receptors and other P2X receptor subtypes are stimulated by extracellular ATP binding to a large extracellular domain. The same transmembrane protein forms a calcium-permeable cation channel that is gated by the extracellular ATP. P2X7 receptors are also centrally involved in apoptosis as either an apoptotic signaling effector and/or a conduit of large dye uptake, which is monitored as an apoptotic endpoint (1, 2, 5, 6, 8, 9). Finally, it has been documented that P2X7 activation leads to stimulation of focal adhesion kinase (FAK) (8); however, the precise signaling cascade steps in this action remain to be elucidated fully.

In their study, Yu et al. (10) demonstrate that various frequencies and intensities of shockwaves (routinely used in skeletal muscle therapy for sports injury) stimulate ATP release from Jurkat T cells. This stimulation of ATP secretion occurred at a middle range of shockwave intensity and was of a duration that did not affect cell viability. In fact, this extracellular ATP signaling augmented T cell proliferation, which is not a complete surprise, because ATP has been described as a mitogen and comitogen in some cellular systems (2, 4). The authors provide additional data to show that the stimulation of ATP release (as well as peak effect of a 1 μM dose of exogenous ATP) markedly stimulate p38 mitogen-activated protein kinase (MAPK) kinase and FAK kinase activities within T cells. These effects promoted proliferation of the Jurkat T cells and production and secretion of interleukin-2 (IL-2). Importantly, the effects of shockwave stimulation were markedly attenuated by a P2X7 receptor antagonist KN-62 and by the ATP/ADP scavenger apyrase. These experiments solidify the conclusion that endogenous ATP is being produced to engage P2X7 receptors to produce the signaling events observed. A schematic illustrates the major concepts and findings from this study (Fig. 1).

This study is very compelling and lays the groundwork for future studies to validate its conclusions. Arguably, similar data should be demonstrated in primary human T lymphocytes to verify that these signaling events occur in primary cells derived from human subjects. Similar observations should be

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**Fig. 1. Illustration of shockwave-induced ATP release from muscle and T cells and resultant T-cell autostimulation and the underlying consequences of extracellular purinergic (ATP) signalling. Details are provide in the text and supportive references.**
made on T cells derived from skeletal muscle undergoing such ‘shockwave’ therapy after injury. It is also often true that ATP’s principal end-metabolite adenosine has physiological roles in the same cellular system. Its role should be examined in this experimental context, especially from the fact that adenosine is touted as therapeutic in ischemia-reperfusion injury and in other vascular paradigms (7). One caveat is that the relative effects of extracellular ATP versus adenosine are often cell specific and tissue specific.

This study thus provides an example of the need to examine the effects of endogenous ATP and adenosine in additional cellular systems. Often, the role of ATP and adenosine is to augment or attenuate the effects of endocrine hormones and neurotransmitters at the local level within a cellular or tissue microenvironment. Moreover, as the results by Yu et al. (10) imply, discovery and development of purinergic receptor ligands represent an important area for future, novel therapeutics.

DISCLOSURES

No conflicts of interest are declared by the author.

REFERENCES


