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Editorial

T Cells Continue to Play on the ATP Circuit

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Editorial

The generation of immune responses involves the coordinated communication between cells through direct cell-to-cell contact and the release of various soluble factors binding to their respective receptors. Of the many soluble factors and receptors known, there is growing evidence that the release of extracellular adenosine triphosphate (ATP) and its subsequent activation of cell-surface ligand-gated cation channels belonging to the family of P2X receptors (P2X1-7) play important roles in communication between immune cells [1]. Much of what is understood about the roles of extracellular ATP and the activation of P2X receptors during an immune response has been inferred from *in vitro* studies requiring the addition of exogenous ATP or from studies using rodent models of inflammation and immunity [2]. Nevertheless our understanding of the extracellular ATP-P2X receptor axes operating between immune cells, including $CD4^+$ T cells, during immune responses is limited.

Previous studies have demonstrated that extracellular ATP can modulate T cell function in an autocrine fashion. ATP released following $CD4^+$ Tcell activation and its subsequent binding to P2X1, P2X4 and P2X7 receptors can promote interleukin (IL)-2 production and cell proliferation [3-5]. Alternatively, activation of P2X receptors by extracellular ATP can inhibit the generation and immunosuppressive function of regulatory T cells, and promote the development of IL-17 producing $CD4^+$ Tcells [6]. Now in a recent study by Wang and colleagues [7], evidence is provided that extracellular ATP can also function in a paracrine manner to induce calcium waves between activated and bystander $CD4^+$ T cells to limit their motility in lymph nodes during priming by dendritic cells.

Wang and colleagues used ultraviolet (UV) photolysis of caged inositol 1,4,5-triphosphate (IP3) in single cells to mimic the cellular signaling events downstream of T-cell receptor activation. Using this system with human peripheral blood $CD4^+$ T cells, Jurkat T cells or murine lymph node slices, the authors not only observed calcium influx in cells exposed to UV light but also the propagation of calcium signals to bystander T cells not exposed by UV light. This phenomenon of spreading calcium signals, termed calcium waves, is observed in many cell types and represents a rapid spatio-temporal movement of information across tissues [8]. Through use of the ATP hydrolyzing enzyme, apyrase, Wang and colleagues established that extracellular ATP was responsible for the calcium signals in both an autocrine and paracrine fashion. Furthermore, UV photolysis of caged IP3 resulted in the release of detectable amounts of extracellular ATP, comparable to that released from T cells following activation with anti-CD3 and anti-CD28 antibodies.

Suramin, a broad-spectrum P2X receptor antagonist, also blocked this calcium increase in bystander cells, to an extent similar to that of apyrase, supporting a role for P2X receptors in this process. Real-time PCR analysis of human peripheral blood $CD4^+$ T cells and Jurkat T cells found that the only P2X receptors common to both cell types were the P2X1, P2X4 and P2X7 subtypes. Subsequent analysis of naive, central memory and effector memory T cells revealed the absence of P2X1 receptors in memory T cells, despite observing calcium waves in each of these T cell populations. Collectively this supported the notion that P2X4 and P2X7, but not P2X1, receptors were involved in the bystander activation of T cells. Use of antagonists specific for P2X4 and P2X7 receptors confirmed the role of these two receptors in this process, as well as calcium influxes in T cells induced by exogenous ATP. Notably, pharmacological inhibition of both P2X4 and P2X7 receptors completely abrogated these processes indicating that these purinergic receptors act in concert to mediate ATP-induced calcium waves in T cells. Similar results were also observed with small interfering RNA specific for P2X4 and P2X7 receptors, although gene silencing was not used directly to assess the bystander activation of T cells.

Finally, the authors examined the functional significance of these calcium waves in T cells. ATP impaired the *in vitro* migration of human $CD4^+$ T cells to the chemokine CXCL12, and this process was prevented by suramin indicating a role for P2X receptors. Further, this ATP-induced impairment of T cell migration required an influx of calcium. Notably, using the transgenic OT-II mouse model, the authors demonstrated a role for the ATP-P2X receptor axis in the bystander activation of T cells in lymph node slices. Stimulation of ovalbumin-specific T cells by ovalbumin-loaded dendritic cells resulted in the reduced motility of bystander T cells non-specific for ovalbumin, and this process was prevented by the addition of either apyrase or suramin. Notably, neither of these two compounds altered the motility of ovalbumin-specific T cells contrasting the role of autocrine ATP in calcium fluxes in caged-IP3 T cells stimulated by UV exposure. These differences remain to be reconciled.

Collectively the study by Wang and colleagues demonstrates that extracellular ATP, via P2X4 and P2X7 receptors, can function in a paracrine manner to induce calcium waves between $CD4^+$ T cells to limit their motility in lymph nodes during priming. However a number of questions remain. Reduced motility of T cells during antigen stimulation has been previously observed [9,10], but the immunological significance of this process remains to be established. Reduced T cell motility has been postulated to be an important strategy in the improved scanning of dendritic cells by T cells [7],

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but direct evidence is lacking. The intracellular signaling mechanism by which ATP-induced calcium waves impair T cell motility also remains unknown. Based on migration studies of amoeba, Wang and colleagues propose that calcium influx impairs T cell movement by the phosphorylation of the myosin heavy chain IIA. In this regard, it is interesting to note that extracellular ATP dissociates myosin heavy chain IIA from the P2X7 receptor complex to regulate the function of this receptor [11,12], although whether this alters T cell migration or if P2X7 (or P2X4) receptors are associated with the myosin heavy chain IIA in T cells remains unknown. Finally as suggested by Wang and colleagues, it will be of importance to determine if ATP released by T cells during an immune response acts in a paracrine fashion on other lymphocytes. Extracellular ATP can activate dendritic cells to drive T cell responses against tumors [13], and in diseases such as asthma [14], graft-versus-host disease [15] and psoriasis [16], while extracellular ATP can stimulate $CD8^+$ T cells and B cells to induce the shedding of L-selectin [17] and CD23 [18]. Thus, these cell types may also serve as potential targets of paracrine ATP within lymph nodes.

In the meantime, the study by Wang and colleagues continues to highlight the importance of extracellular ATP-P2X receptor axes in modulating T cell function during immune responses. As such, it appears that studies of T cells on this ATP circuit will continue for some time to come.

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