Published in final edited form as:

Transplantation. 2016 September ; 100(9): 1789–1790. doi:10.1097/TP.0000000000001429.

Blurring the Lines between Innate and Adaptive Immunity

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...T cell inflammasome activation is required for both human and murine T cells to differentiate into IFN γ -producing Th1 effector cells.

Traditional thinking differentiates innate immunity, defined as inborn, evolutionarily conserved cells and molecules that rapidly recognize and respond to pathogens, from adaptive T and B cell immunity that is highly specific, albeit slower to respond, and capable of forming immune memory. Both innate and adaptive immunity are essential for protection against invading organisms, and both participate in pathogenic immune responses directed at transplanted organs. Among the many constituents of innate immunity are the complement system and inflammasome-activated myeloid cells.

The complement system is comprised of greater than 30 proteins, the majority of which are produced predominantly by the liver and circulate in the plasma [reviewed in ¹]. Plasma complement activation initiated via the classical, mannan binding lectin or alternative pathways converge at the formation of C3 convertases, the central amplification step of the cascade. Following C3 cleavage to C3a and C3b, activation of the common terminal pathway results in cleavage of C5 to C5a and C5b, and subsequent formation of the C5b-C9 membrane attack complex (MAC). Plasma complement activation results in inflammation and vasodilatation, principally mediated by binding of the anaphylatoxins C3a and C5a to their specific G-protein coupled receptors (C3aR and C5aR respectively). Complement activation also results in opsonization (eg via C3b/iC3b binding to CR3/CR4) and MAC dependent a) cell lysis or b) in the case of most nucleated cells, NF- κ B mediated cell activation.

It is now recognized that many cell types, including endothelial cells, renal tubular cells and various immune cells produce complement components and that activation of such nonliver-derived complement has crucial physiological significance ¹. Studies performed since 2005 uncovered a fundamental role for immune cell derived-complement in T cell activation, differentiation and expansion ^{2,3} (see schematic Fig 1). This body of work showed that during cognate T cell/APC interactions, T cell receptor (TCR) engagement along with

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Disclosure:

Conflicts: P.H has grant funding from Alexion Pharmaceuticals and served on a scientific advisory board for Chemocentryx in 2016.

costimulatory signals induce both T cells and APCs to release alternative pathway complement components and to upregulate C3aR and C5aR on their surfaces. Subsequent local alternative pathway complement activation results in production of C3a and C5a which ligate their respective receptors on both interacting partners via paracrine and autocrine loops. Downstream signals mediate protein kinase A-(PKA)-, phosphoinositide-3-kinase-gamma-(PI-3K γ) and pAKT-dependent effector T cell proliferation, survival and differentiation, and induce APC activation. The same immune cell-derived, complement-dependent C3aR/C5aR signals inhibit regulatory T cell (Treg) induction, function, and stability, amplifying local development of effector T cell responses against pathogens, autoantigens and transplant antigens ^{1,4,5}. Together, these paradigm shifting observations revealed that T cells have incorporated the evolutionarily older complement system as part of their activation machinery. While these findings were principally documented using murine systems, identical mechanisms are operative during human T cell responses ⁴⁻⁶.

Innate immune activation by pattern recognition receptors (including toll like receptors and NOD receptors, among others) in myeloid cells (eg monocytes and neutrophils) results in an assembly of a multimeric intracellular complex called the inflammasome ⁷. The inflammasome regulates caspase-1 cleavage, and as a consequence, the activation of IL-1 β and IL-18 as key mediators of inflammation and inflammatory cell death. Inflammasome activation is required for protective immune responses against certain pathogens and participates in a wide array of disease processes, including ischemia reperfusion injury with relevance to transplantation. Previously published work has additionally shown that complement activation and insertion of the MAC into myeloid cells triggers inflammasome activation, delineating an interactive crosstalk mechanism between these 2 innate immune systems ⁸.

Building upon this background, Kemper and colleagues now show in their publication in *Science* the unexpected finding that inflammasomes are present in human and murine T cells ⁹. Using genetic knockouts and pharmacological inhibitors, the authors demonstrate that T cell inflammasome activation is required for both human and murine T cells to differentiate into IFN γ -producing Th1 effector cells. The authors provide some evidence that the human T cell inflammasome is induced by a reactive oxygen species-dependent mechanism requiring intracellular formation of C5a that binds to intracellular C5aR (Fig 1).

The observation that human T cells employ intracellular complement as part of their activation process confirms a process reported previously by the same group in which they demonstrated that T cell activation is in part mediated by intracellular C3 cleaved by cathepsin-L ¹⁰. As noted above, whereas both murine and human T cell activation involves release, activation and autocrine/paracrine C3a/C5a binding to their receptors as a mechanism that activates Teff and inhibits Treg, the intracellular complement cleavage pathways seem only to be operative in human T cells (but have not been evaluated in murine or human Treg). It is also notable that in order to activate this intracellular, complement-dependent, inflammasome activation in human T cells, the authors needed to stimulate human T cells via their T cell receptor (TCR, using anti-CD3) along with an antibody that binds to (and likely crosslinks) the complement regulator CD46 without providing a standard costimulatory signal, eg CD28. In fact, anti-CD3/anti-CD28 stimulation in the

absence of the crosslinking anti-CD46 stimulus did not initiate inflammasome activation. While the findings linking CD46, C5a and inflammasome activation are intriguing, there is no known in vivo circumstance where isolated coligation of the TCR and CD46 is operative; thus the physiological relevance of the result for in vivo human T cell responses remains to be determined.

Nonetheless, the work by Kemper and colleagues⁹ illustrates the emerging consensus from several research groups that immune cell-derived complement crucially regulates T cell immunity (Fig 1). The *Science* publication newly shows that T cells have also incorporated the inflammasome into their intracellular activation/differentiation apparatus. Together with previously published reports, this new contribution further blurs the distinction between innate and adaptive immune responses and supports the need to test the efficacy of blocking complement and/or assembly and function of the inflammasome as strategies to limit pathogenic T cell immune responses, including those directed at transplanted organs.

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Figure 1.

Effects of immune cell-derived complement on T cell immune responses. TCR ligation in addition to costimulation results in immune cell production and local activation of alternative pathway complement components. Subsequently, C3a/C5a bind to their surface receptors expressed on a) T cells, initiating proliferative and survival signals, and b) on APCs, inducing upregulation of costimulatory molecules and release of innate cytokines. TCR ligation plus crosslinking of CD46 activates human T cell intrinsic inflammasomes via signaling that likely depends on intracellular formation of C5a. Inflammasome activation on T cells, in turn, enhances IFN γ production and Th1 differentiation.