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Shedding Light on Impaired Efferocytosis and Nonresolving Inflammation

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Abstract

Nonresolving inflammation contributes to tissue damage and organ dysfunction in a wide array of pathologies, including cardiovascular disease. At the interface between inflammation and inflammation-resolution is the macrophage. Macrophage engulfment of apoptotic cells (efferocytosis) during immune cell turnover triggers activation of intra- and inter-cellular immunosuppressive signaling networks. In diseases of aging and obesity, accumulating evidence indicates that efferocytosis is impaired; the underlying mechanisms of which are unclear. In the current issue of Circulation Research, Driscoll et al., reveal that deficiency of the metalloproteinase ADAM17 prevents shedding of the apoptotic cell receptor CD36 from macrophages to enhance efferocytosis and inflammation resolution during peritonitis. These findings implicate proteolysis of apoptotic cell receptors as one explanation for defective efferocytosis-directed inflammation resolution during disease. Future studies are warranted to test the significance of these findings during cardiovascular syndromes and in other cases of nonresolving inflammation.

Keywords

Efferocytosis; ADAM17; CD36

Efferocytosis-directed inflammation resolution

Removal of dying cells and pathogens by macrophages (MΦs) is coupled to activation of downstream intracellular signaling pathways that mobilize either pro- or anti-inflammatory signaling networks. In the case of efferocytic[1] engulfment of apoptotic cells (ACs), MΦs both suppress [2, 3] pro-inflammatory signaling and activate pro-resolving [4] cascades to uphold tolerance to self-antigen [5]. For example, injection of ACs *in vivo* represses the immune response to cell-associated antigens [6]. This is in contrast to MΦ engulfment of IgG-opsonized pathogens[7, 8, 9] by Fcγ receptors, which triggers release of pro-inflammatory cytokines [2, 10]. Thus, immune cells have evolved distinct mechanisms to differentially recognize and orchestrate inflammation, secondary to engulfment.

In the setting of nonresolving inflammation[11, 12], mis-calibration of the immune response (for example, over-exuberant inflammation during sepsis), or failure to clear initiating insults and activate resolving factors, in turn promotes an inflammatory milieu that is counterproductively harmful. In diseases such as cystic fibrosis, COPD, asthma, lupus, and atherosclerosis, prolonged inflammation is also associated with an accumulation of

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ACs [1, 13-15]. AC clearance in the absence of disease is typically efficient. Even in tissues with high rates of cell turnover, only a few ACs can be detected under homeostatic conditions [16]. Whether defective efferocytosis is a cause, consequence, or both within these underlying pathologies is not clear and likely context dependent. Nevertheless, inability to activate efferocytosis-directed anti-inflammatory pathways is a candidate contributing factor in the failure to promote healing. Consistent with this notion, studies in experimental gene-targeted rodents support the hypothesis that efferocytosis causally regulates disease progression, as described below.

Defective efferocytosis at the level of apoptotic cell (AC) receptors

Suppressors of efferocytosis can act at multiple stages, including phagocyte recruitment, AC binding to phagocytes, and engulfment. For reasons that are not entirely clear, in some disease states, such as atherosclerosis [17], efferocytosis becomes defective despite abundant MΦ presence, suggesting cell-intrinsic perturbations[13]. *In vitro*, inflammatory stimuli such as endotoxin and TNFα directly inhibit efferocytosis, at least in part through generation of superoxides [18]. In this scenario, inflammation initiates a reinforcing feedback loop of defective efferocytosis, promoting further inflammation *via* non-cleared apoptotic cells that become secondary necrotic. Little is known about mechanisms of defective efferocytosis *in vivo*, however, studies targeting phagocyte AC receptors support the idea that defective efferocytosis can promote inflammation and aggravate underlying disease. These cell-surface AC receptors directly, or through soluble bridging molecules, recognize AC ligands that include phosphatidylserine and oxidized membrane epitopes [19]. As an example, deficiency of the AC receptor Mer tyrosine kinase receptor (MERTK) delays AC clearance [20] and increases TNFα levels during endotoxemia. In chronic diseases, MERTK is required to clear dying cells during advanced atherosclerosis [21, 22] and deficiency of MERTK accelerates lupus-like autoimmunity [14].

Besides genetic proofs of principle, natural mechanisms of defective efferocytosis *in vivo* have eluded discovery. There are however molecular clues that implicate phagocyte AC receptors. Cultures from diseased patients reveal elevated levels of shed, or non-cell associated/soluble AC receptors. Typically, transmembrane AC receptors signal independently or in cooperation through membrane domains. This mobilizes intracellular cytoskeletal signaling to generate force required for AC internalization [23]. On the other hand, signal transduction capacity of AC receptors can be uncoupled from AC-binding domains [24]. Thus, AC receptor shedding not only depletes phagocytic capacity of the host cell, but also generates a potential competitive inhibitor that can block efferocytosis on neighboring efferocytes. Notable examples of soluble AC receptors during disease include CD36, lectin-like oxidized LDL-receptor-1 (LOX-1), low-density lipoprotein receptor-related protein-1 (LRP-1), and as described above, MERTK. Soluble LRP-1 is increased in patients with acute respiratory distress syndrome [25]. Circulating soluble LOX-1 is elevated in patients with acute coronary syndrome [26]. Evidence for soluble MerTK is found in patients with lupus, rheumatoid arthritis, cardiovascular disease, and endtoxemia [24, 27-29]. Finally, plasma CD36 elevation is associated with diabetes[30]. These illustrations highlight AC receptor shedding as an important phenotype of diverse inflammatory diseases. In the case of LOX-1, MERTK, and now CD36, the metalloproteinase ADAM17 (a disintegrin and metalloprotease) has been identified as an agent of AC receptor shedding.

Linking ADAM17 to defective efferocytosis and inflammation resolution

Proteases of the ADAM family juxtapose near neighboring membrane-bound proteins and trigger shedding/release of cell surface ectodomans into the extracelluar milieu [31]. First described for its role in shedding of pro-TNFα [32], ADAM17 is therefore intimately linked

with the regulation of inflammation. However, a direct requirement for ADAMs at the level of efferocytosis and efferocytosis-directed inflammation resolution had previously not been documented. In this context, and independent of effects on cytokine release, Driscoll et. al. [33] hypothesize an additional layer of ADAM17-mediated inflammatory control, specifically through control of efferocytosis efficiency. To test their hypothesis, the investigators measured AC clearance and markers of inflammation in a mouse model of ADAM17 deficiency. To focus their studies on MΦs, ADAM17 deficient cells were transplanted into irradiated mice to generate chimeras deficient for leukocyte ADAM17 in bone marrow. After eliciting inflammatory cells, ADAM17-deficient mice, relative to control, exhibited similar levels and kinetics of neutrophil turnover and monocyte entry in the peritoneum during acute phase peritonitis. Interestingly, after injecting ACs at later stages of inflammation, MΦs from ADAM17-deficient mice displayed a significant enhancement in uptake of exogenous ACs. This led to a marked reduction of MΦ numbers, consistent with resolution of inflammation. Although an alternative explanation for reductions in MΦ content is due to altered interactions with acute-phase neutrophils, it is important to note that ACs were injected after neutrophil egress and that reductions in MΦs were specific to injection of ACs. Evidence for enhanced efferocytosis was also discovered in mixed chimeras containing an equal ratio of control and ADAM17-null MΦs, supporting the notion that increased efferocytosis was MΦ-intrinsic rather than secondary to an altered extracellular milieu. Consistent with an overall anti-inflammatory phenotype, ADAM17 deficient MΦs expressed reduced levels of the pro-inflammatory marker iNOS and increased levels of resolution-associated arginase I [34, 35].

Linking ADAM17 effects on efferocytosis to cleavage of CD36

MΦs express multiple substrates of ADAM17, including some implicated in recognition or uptake of ACs [36-38]. Therefore, to focus their mechanistic questions, a screening approach was utilized. AC surrogates with known receptor specificities were loaded onto ADAM17-deficient phagocytes *in vitro*. Exploiting this approach, ADAM17-null MΦs bound more phosphatidylserine (PS)-containing liposomes, but not liposomes composed of phosphatidyl*choline*, suggesting that ADAM17 acts to inhibit recognition of PS on ACs. Recognizing that PS-receptors can further be distinguished by their ability to recognize modified atherogenic lipoproteins [39], Driscoll et al. zeroed-in on scavenger receptors after acetylated LDL prevented enhancements in liposome binding. Finally, CD36 was directly implicated after addition of blocking antibodies: CD36-blockade significantly decreased efferocytosis in ADAM17-deficient MΦs relative to control and during peritonitis.

Evidence for ADAM17-mediated shedding of CD36 was found in ADAM17-deficient MΦs after measuring increased surface levels of MΦ CD36 during peritonitis, independent of changes in messenger RNA. In addition, loss of ADAM17 decreased the ratio of soluble protein (by ELISA) from clarified supernatants *in vitro*, relative to cell-associated CD36. Relative to other AC receptors targeted by ADAM17, such as MERTK and LOX-1, which are type I and type II single-pass transmembrane (TM) proteins respectively, CD36 is unique. CD36 encodes a dual-pass TM, therefore requiring at least two separate cleavage events to liberate its soluble ectodomain. Immunoblot analysis provided initial evidence for proteolytic fragments of CD36 and mass spectrometry identified cleavage sites of CD36 at regions predicted to be proximal to the membrane, as has previously been documented with other ADAM17 substrates [40]. However, future experiments are necessary to resolve other candidate cleavage sites that may have been masked by shared trypsin cleavage sites during tryptic mass-spec analysis. Also, considerations for the involvement of other proteases must be made. In fact, this is a likely scenario as significant levels of soluble CD36 were still found in the absence of ADAM17 *in vitro. In vivo*, studies are also required to measure the extent and biochemical nature of ADAM17-dependent soluble-CD36 levels in serum.

Nevertheless, together these experiments provide strong evidence that ADAM17 promotes shedding of CD36, likely by direct proteolytic cleavage, thereby dampening efferocytosis of ACs and leading to delayed inflammation resolution (Figure 1).

Other future considerations

Interestingly, effects of ADAM17 on efferocytosis were independent of other AC receptors that had primarily been studied as *in vitro* targets of ADAM17 [24, 29]. One explanation is that unlike these other reports, CD36 cleavage by Driscoll et al. chiefly occurred independent of inflammatory triggers such lipopolysaccharide and TNFα. Therefore cleavage of alternative AC receptors may play a more significant role in other pathogenic or disease contexts. Also, the relative importance of specific ADAM17 targets may vary in homeostasis versus resolving inflammation versus non-resolving inflammation. In this context, it is tempting to speculate that ADAM17-directed cleavage of AC receptors may selectively target receptors to uniquely regulate efferocytosis and inflammation resolution in disparate inflammatory states. Such specificity could be controlled both spatially and temporally. For example, substrate-specific targeting could be regulated at the level of substrate-site affinity or conformational or proximal accessibility. Temporally, the investigators point out that CD36 expression was highest on MΦs at later stages of inflammation, consistent with involvement during inflammation resolution. This begs additional questions in an evolutionary context: What purpose does ADAM17 serve in blocking inflammation-resolution during efferocytosis, or is such a response maladaptive? One answer may be that cleavage represents a path to quickly reverse inflammation resolution if additional or persistent stimuli are detected. In a similar vein, suppression of efferocytosis could mobilize alternative mechanisms of phagocytic uptake that are more tailored, for example, to the uptake, metabolism, and/or cross-presentation of pathogens. In this setting, uptake of AC self-antigen may also be disadvantageous if “confused” with uptake of non-self, with implications on loss of tolerance and autoimmunity. At the level of CD36, this discussion must also consider the numerous other CD36 functions, independent of AC uptake, including phagocytosis of bacteria, uptake of modified lipoproteins during atherosclerosis, requirements for fatty acid import, and even effects of angiogensis [41-44]. Thus, cleavage of CD36 has broader implications, just as the activities of ADAM17 and its multiple substrates.

Finally, singular or combinatorial strategies to resolve inflammation must not only consider issues of specificity, but also the potential for compensatory feedback mechanisms that may further limit efficacy. In addition, therapies must not overly impair innate requirements to ward off infection and repair tissue injury. Thus, a more comprehensive understanding of the mechanisms described by Driscoll et al., beyond efferoctyosis-directed inflammation and at the level of infection and wound healing, will assist in development of future strategies. This is important in the setting of chronic diseases such as aging and obesity, which typically require long-term therapeutic administration. Also to be considered are diseases of acute inflammation, particularly in cases such as inflammation after myocardial infarction, wherein advanced age and therefore limited evolutionary pressures may set the stage for maladaptive responses, with the potential for therapeutic optimization. Thus, the present study by Driscoll et. al. is just the “tip of the iceberg” and provides an intriguing mechanistic starting point to test implications of protease-directed receptor cleavage during efferocytosis and inflammation in multiple settings of disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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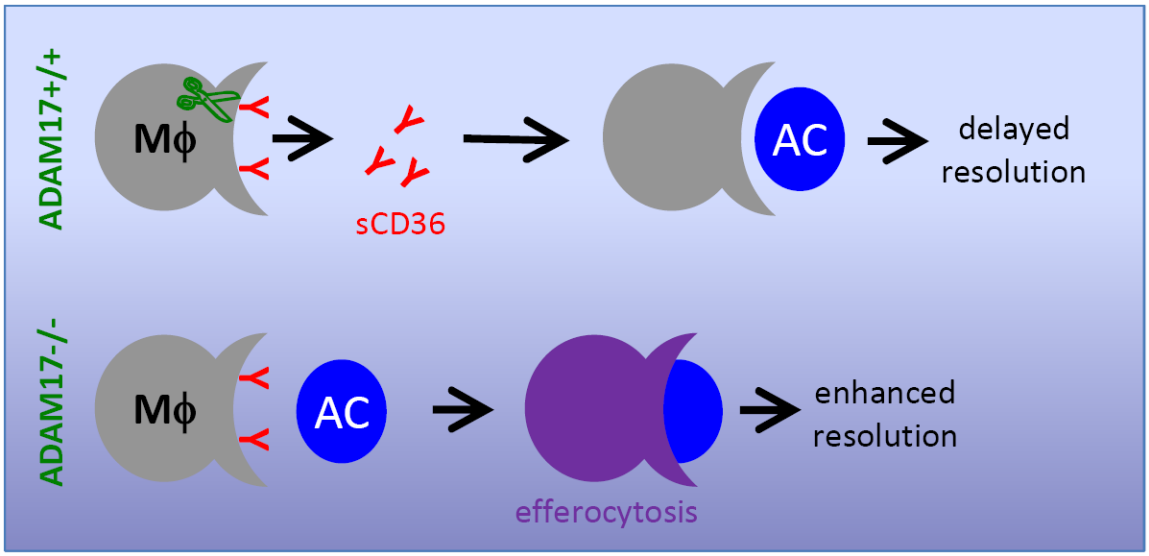

Figure 1. Proteolysis of CD36 by ADAM17 delays inflammation resolution by inhibiting efferocytosis

ADAM17 (green) cleaves membrane bound CD36 on macrophages (MΦs), leading to shedding of soluble CD36 (sCD36) into the extracellular milieu. Loss of CD36 reduces efferocytosis, i.e., macrophage engulfment of apoptotic cells (ACs), and in turn delays inflammation resolution. Absence of ADAM17 (ADAM17-/-) in contrast promotes efferocytosis and an anti-inflammatory response in MΦs, thereby enhancing inflammation resolution.