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## Processes of Sterile Inflammation

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### Abstract

Sterile inflammation occurs in acute conditions such as ischemia reperfusion injury and crystal-induced arthritis, and also with chronic diseases such as particle-induced lung diseases and atherosclerosis. The triggers of sterile inflammation are still being identified and the pathways that transduce sterile inflammatory signals are not completely clear. Currently, most of the innate immune pathways that sense infection have been implicated in sterile inflammation, although distinct signaling pathways of sterile inflammation exist. Whether immune pathology ensues after sterile inflammation depends on the balance of induced inflammatory and resolution pathways. Further identification of the molecular mechanisms of sterile inflammation will lead to novel therapeutics to treat a wide range of diseases.

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Over the last two decades our understanding of innate immunity has greatly increased. Although much of what has been learnt has come from examining how pathogens induce inflammation, it has become evident that non-microbial activators trigger inflammation. In certain conditions such as trauma, non-microbial and microbial activators both contribute to inflammation. In this *Brief Review*, we will discuss the conditions that result from sterile inflammation, the triggers of these conditions, signaling pathways of sterile inflammation, the implications of sterile inflammation and potential avenues for future investigation.

### Conditions that result from sterile inflammation

The acute conditions that result from sterile inflammation include ischemia reperfusion injury (IRI), trauma, crystal-induced inflammation, and toxin exposure. IRI is a condition in which the blood supply to an organ is abruptly halted and then re-instated (1). Not only does injury to the tissues result from the initial hypoxia but also from the restoration of blood flow and re-oxygenation, which exacerbates inflammation. Acute myocardial infarctions, cerebral infarctions, acute kidney injury and solid organ transplantation are all conditions in which IRI occurs. Some of these disorders (e.g., myocardial and cerebral infarctions, and acute kidney injury) may share common disease pathologies such as atherosclerosis in which acute atherosclerotic plaque rupture or thromboembolism leads to cessation of blood flow. In the case of organ transplantation, the harvest and procurement of the organ leads to tissue ischemia injury and is followed by further inflammation after implantation into the recipient when blood supply to the organ is restored.

Crystal deposition within joints leads to gouty arthritis and elicits the classic clinical signs of inflammation including redness, pain, heat, swelling and loss of function. Toxins, such as

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acetaminophen or cobra venom, induce hepatic and muscle injury, respectively. Trauma, including crush injury, triggers an abrupt inflammatory response, and endogenous and microbial triggers (from bacterial exposure) may contribute to inflammation in this context. How sterile inflammation is triggered is discussed in the next section.

Chronic conditions that trigger sterile inflammation include particle-induced lung diseases such as asbestosis and silicosis, cardiovascular diseases such as atherosclerosis, some causes of chronic heart failure, and certain cases of tumors (2, 3). Studies in germ free mice provide evidence that microbes are not essential for the development of experimental atherosclerosis (4). With atherosclerosis, the chronic deposition of cholesterol within the arterial wall induces an injury response characterized by the recruitment of immune cells including macrophages, dendritic cells (DCs), T and B cells, leading to the development of the atherosclerotic plaque, which is the hallmark of the disease.

## Triggers of sterile inflammation

Cellular necrosis that results from either acute or chronic inflammation leads to the release of immune triggers that are typically “hidden” in quiescent states. This contrasts with apoptosis that is the result of an orchestrated cell death program and is typically immunologically silent. Indeed, necrotic cells induce neutrophil infiltration when injected into the peritoneum of mice (5), indicating that the rupture of plasma membranes releases intracellular contents that activate inflammation.

Conceptually, a putative trigger of sterile inflammation would meet the following criteria. First, the levels of the trigger should correlate with immune activation in an experimental model of sterile inflammation or in relevant clinical samples. Second, the trigger should elicit a proinflammatory response in cultured cells, such as macrophages or DCs. Third, the trigger should provoke an inflammatory response after injection into disease free hosts. Evidence that the trigger is not contaminated by microbial motifs (e.g. LPS) should also be demonstrated. These last two criteria require modification with two-step activators, e.g., those which stimulate the inflammasome (see next section) after priming with another trigger such as TNF- $\alpha$  (6). Lastly, the inflammatory response should be abrogated with blockade of the receptor or inhibition of the signaling pathway of the trigger. This last criterion depends upon whether the receptor and the downstream signaling pathways of the trigger are known.

The triggers of sterile inflammation can be broadly divided into those that are intracellular and those that originate from the extracellular matrix (Table 1 and Figure 1A). Intracellular triggers include nuclear proteins (e.g. High-mobility group box 1 [HMGB1]), mitochondrial DNA and peptides, uric acid and cellular chaperones (e.g., heat shock proteins). Studies have provided evidence that HMGB1 meets several of the above criteria for a trigger of sterile inflammation. Specifically, HMGB1 is elevated in murine renal IRI models (7, 8). Furthermore, HMGB1 translocation from the nucleus to the cytoplasm is abrogated with treatment with ethyl pyruvate and this treatment significantly reduces inflammation in the renal IRI model (7). Importantly, administration of recombinant HMGB1 to disease free mice elicits a systemic inflammatory response (7). Another study also found that HMGB1 levels are increased after renal IRI and that administration of an anti-HMGB1 antibody reduces inflammation, whereas administration of recombinant HMGB1 exacerbates inflammation during renal IRI (8). Additionally, this latter study demonstrated that TLR4<sup>-/-</sup> mice are protected from renal IRI and are insensitive to the effects of HMGB1 manipulation. Recent studies have also implicated HMGB1 in hepatic IRI (9). Specifically, TLR4 expression in hepatocytes is important for HMGB1 release to promote inflammation within the liver (10).

Mitochondrial components, including mitochondrial peptides or DNA, trigger sterile inflammation. Mitochondria are organelles that may have originated from bacteria that existed in a symbiotic relationship with the host cell. Hence, the release of mitochondrial components during necrosis may lead to activation of inflammatory pathways that are typically stimulated by microbes. One study found that mitochondrial DNA was released into the plasma of patients that had sustained traumatic injury (11). Mitochondrial components stimulate inflammatory responses in neutrophils and transfer of mitochondrial components to rodents induces a systemic inflammatory response. Furthermore, the activity of mitochondrial components is reduced by either inhibition of formyl peptide receptor one (FPR1) or TLR9, indicating that the mitochondrial components that trigger inflammation are either formylated peptides or DNA. Other mitochondrial components, e.g., ATP may also enhance inflammatory responses. Evidence exists that ATP signals via a purinergic receptor P2X7, in combination with TLR activation, to induce inflammation via the inflammasome (see next section) (12). This indicates that ATP enhances inflammation, by priming the inflammatory response, rather than being both necessary and sufficient to induce sterile inflammation. ATP may also be released from the cytosol of neutrophils and platelets in addition to mitochondria (reviewed in (13)). Overall, mitochondrial formylated peptides and DNA meet criteria as sterile inflammatory triggers.

Two reports indicate that F-actin, a component of the cytoskeleton, acts as a ligand for the C-type lectin receptor CLEC9A (14, 15), which was previously shown to be expressed by DCs and activated by dead cells (16). However, it remains unknown whether F-actin induces sterile inflammation in relevant *in vivo* models.

Components of the extracellular matrix, including hyaluronan (HA), a glycosaminoglycan produced by mesenchymal cells, have been implicated in sterile inflammation. In quiescent states, HA is in a high weight form, but during inflammation HA is degraded into smaller fragments (135 KDa), which have been shown to activate macrophages via TLR2 and 4 *in vitro* (17). In a lung model of sterile inflammation in which bleomycin is administered to mice, HA levels are induced and inflammation is reduced in mice that are deficient in TLRs 2 and 4 (17). However, HA is important for resolving sterile inflammation induced by bleomycin as mice in which high weight molecular HA is overexpressed on lung epithelial cells exhibit protection from lung injury (17). However, the role that HA plays in inflammation resolution may depend on its context as overexpressing HA in myofibroblasts within the lung enhances severe lung fibrosis after bleomycin administration (18). Overall, there is evidence that HA promotes sterile inflammation within the lung, but it may also aid in inflammation resolution. Differential effects of HA may reflect the cellular source and the molecular weight of HA.

Uric acid is produced by all cells and is a product of purine metabolism. Upon cell necrosis, the increased uric acid concentration allows for formation of monosodium urate crystals (MSU) when exposed to extracellular sodium. Although not formally proven experimentally, this may explain why physiological circulating uric acid levels are not associated with inflammation. MSU activates DCs *in vitro* by upregulating costimulatory molecules and producing proinflammatory cytokines such as IL-1 and TNF (19). Direct injection of monosodium MSU into the peritoneum of mice induces neutrophil recruitment *in vivo*, an inflammatory response that is abrogated in IL-1R<sup>-/-</sup> and MyD88<sup>-/-</sup> mice (20). IL-1R expression on non-bone marrow derived cells is required for inflammation in this model. By employing transgenic mice, which overexpress uricase, it has been demonstrated that uric acid is required for inflammation induced by injection of necrotic cells (21). Uric acid also activates the NLPR3 inflammasome (see next section) to induce IL-1 production (22). Overall, there is clear evidence that uric acid is a trigger of sterile inflammation.

Cells that have not yet undergone necrosis but are damaged send signals that are sensed by the immune system. For example, DNA damage from tumorigenesis leads to the upregulation of NKG2D ligands, which are sensed by NKG2D receptors on NK cells and initiate anti-tumor immunity (23, 24). Although this pathway is not necessarily the result of tissue necrosis, it is a mechanism by which cellular damage alerts the immune system.

In sum, several triggers of sterile inflammation exist. However, it is likely that many more are yet to be identified. Most studies have focused on examination of one trigger when it is likely that several may contribute and synergize to induce inflammation. Un-biased approaches (e.g., proteomics or genomics) may be required to identify novel inflammatory triggers in sterile inflammation. Such approaches have been employed to identify triggers of inflammation in experimental models of organ transplantation (25).

## Signaling Pathways of Sterile Inflammation

The evolution of the immune system was likely shaped by the pressure to defend against pathogens. Although some sterile inflammatory conditions have been evident for many centuries (e.g., trauma and gout), some entities have arisen due to modernization of our society (e.g., organ transplantation and atherosclerosis). Evidence indicates that pathways that have evolved to respond to infection are also employed to respond to non-microbial triggers, although some distinct pathways exist.

TLRs are one of the principle innate immune receptors that have been implicated as mediators of certain sterile inflammatory conditions. These innate immune receptors respond to a broad range of microbial motifs and are expressed within the cell or on the cell surface on both hematopoietic and non-hematopoietic cells (reviewed in (26)). TLRs 2 and 4 have been implicated in IRI, specifically in coronary ligation models and models of acute kidney injury (27-30). In both models, TLR 2 and 4 have been shown to signal via the signal adaptor MyD88 to contribute to inflammation. In the kidney IRI model, TLR4 on epithelial cells contributes to inflammation (27). Furthermore, inhibition of TLR2 can reduce renal IRI in mice (31). Within the heart, cardiomyocytes and vascular cells express TLRs, and these cells have been shown to transduce inflammatory responses at least *in vitro* (32, 33). Not only are TLRs involved in acute sterile inflammatory conditions, but also chronic sterile vascular diseases as TLR 2, 4 and MyD88 enhance the development of atherosclerosis in mice (34-36). In hepatic IRI models, TLR 4 is critical for inflammation, yet this effect is independent of MyD88 and dependent on IRF-3 (37). As stated above, HMGB1 has been implicated in hepatic injury via TLR4 signaling on hepatocytes (38, 39). Although hepatic IRI models are likely sterile, it is possible that microbial motifs from commensal bacteria, such as LPS, enter the hepatic circulation with induction of ischemia. Acetaminophen-induced hepatic injury requires TLR 9, a TLR that is expressed within endosomes, by signaling in sinusoidal endothelial cells. Finally, TLR3, another TLR expressed within endosomes that typically responds to double stranded viral RNA, is required for macrophage inflammation after stimulation by necrotic neutrophils, indicating that TLR3 may respond to endogenous RNA (40). However, the *in vivo* implications of this finding has so far been tested in experimental models of septic peritonitis, which are not sterile inflammatory models (40).

The inflammasome is a multi-protein intracellular complex that upon activation of its receptors, the NOD like receptors (NLRs), leads to recruitment of apoptosis-associated speck-like protein contains a caspase recruitment domain (ASC). This leads to activation of caspase-1 and production of mature IL-1. Patients who died of acute myocardial infarction display ASC expression, implying that the inflammasome may have contributed to the pathology (41). Furthermore, ASC<sup>-/-</sup> mice exhibit increased heart function after cardiac IRI

via coronary ligation as compared to wild type mice (WT) (41). Although infarct sizes were similar between the groups, the degree of fibrosis was smaller in the ASC<sup>-/-</sup> mice as compared to the WT, indicating that the inflammasome is important for efficient inflammation resolution (41). This study also found evidence that inflammasome signaling within bone marrow cells and non-hematopoietic, cardiac resident cells (e.g., cardiomyocytes) contribute to sterile inflammation after cardiac IRI. In a complementary study, ASC formation occurred in mice subjected to permanent ligation of the coronary artery with subsequent acute myocardial infarction (42). Caspase 1 is activated in cardiomyocytes that are exposed to ischemia or to the combined effects of LPS activation and ATP stimulation *in vitro* (42). Furthermore, *in vivo* inhibition of the P2X7 receptor, a purinergic receptor that responds to extracellular ATP by increasing K<sup>+</sup> influx, reduces infarct size in the acute myocardial infarction model in mice (42). Hence, these two studies indicate that the inflammasome is essential for sterile inflammation in acute models of cardiac ischemia.

NOD-, LRR- and pyrin domain-containing 3 (NLRP3), is one of the best-studied NLRs in sterile inflammation. In a chronic murine model of cardiac inflammation induced by overexpression of calcineurin within the myocardium, increased IL-1 and NLRP3 activation was noted (43). Importantly, genetic ablation of NLRP3 decreases inflammation and improved cardiac function in this model (43). NLRP3 has also been implicated in atherosclerosis. Specifically, cholesterol crystals activate NLRP3 *in vitro* and LDLr<sup>-/-</sup> (atherosclerotic prone) mice, when reconstituted with NLRP3<sup>-/-</sup> bone marrow exhibit reduced atherosclerosis as compared to mice reconstituted with WT bone marrow (44). NLRP3 has been implicated in other sterile inflammatory disorders, including mechanical stretch-induced lung inflammation. In this latter instance, a study found that ventilator-induced lung injury in mice leads to increased reactive oxidative stress release from mitochondria that in combination with TLR4 signaling, activates NLRP3 to produce IL-1 and lung inflammation (45) in agreement with other recent reports in both humans and mice (46, 47). Another study found that mitochondria released from necrotic cells activate NLRP3 in macrophages *in vitro* and NLRP3 is required for maximal inflammation after renal IRI (12). Lastly, NLRP3 also contributes to inflammation in acute hepatic inflammation induced after acetaminophen (48) exposure and there is evidence that NLRP3 is important for particle-induced inflammation (49). In sum, NLRP3 has been implicated in several sterile inflammatory conditions. Whether other inflammasomes such as the Absent in Melanoma 2 (AIM2), which responds to DNA, contributes to sterile inflammation is yet to be determined.

Not all sterile inflammatory responses engage receptors that are also known to respond to pathogens. The receptor for advanced glycation end products (RAGE) is such a receptor. This receptor is a type 1 transmembrane protein that is expressed at low levels in vascular endothelial cells, cardiomyocytes and immune cells (e.g., neutrophils, DCs, and lymphocytes). It responds to a variety of ligands, e.g., advanced glycated end products, DNA, RNA, HMGB1, S100 proteins and  $\alpha$ -fibrin sheets. RAGE has been implicated in cardiac IRI (50) and in the development of atherosclerosis (51).

The release of bioactive cytokines from necrotic cells occurs with sterile inflammation and enhances the inflammatory response. In particular, IL-1 is released from necrotic cells and sensed by the IL-1 receptor to induce the production of neutrophil attracting chemokines (e.g., CXCL1) in mesothelial cells (52). In a murine model in which inflammation was induced by injection of MSU crystals into the peritoneum, IL-1 inhibition via an inhibitory antibody or injection of MSU in IL-1 receptor<sup>-/-</sup> mice reduces neutrophil recruitment into the peritoneum (53). The same group of investigators subsequently found that injection of necrotic T cell lymphoma cells into peritoneum of mice induces neutrophil recruitment via

an IL-1 $\beta$ -dependent (but IL-1 $\alpha$  independent) mechanism (20). IL-1 $\alpha$  also enhances adaptive immunity after sterile inflammation as shown in an experimental model, in which a human coronary artery is implanted into an immunodeficient mouse, which is reconstituted with allogeneic human peripheral blood mononuclear cells (54). In this model, IL-1 $\alpha$  is present in endothelial cells lining the human artery and inhibiting IL-1 $\alpha$  reduces subsequent T cell graft infiltration (54). This study also indicates that sterile inflammatory pathways may enhance subsequent adaptive immunity. A recent study has provided evidence that intracellular pro-IL-1 $\beta$  is not active after release from necrotic cells unless converted to an active form (55). This study also found that IL-1 $\beta$  release is controlled by intracellular IL-1R2, which prevents cleavage of IL-1 $\beta$ . Furthermore, cells found to induce inflammation after necrosis (e.g., vascular smooth muscle cells) either do not express IL-1R2 or have evidence of caspase 1 activation, which abrogates the effects of IL-1R2 (55).

## Resolution of Sterile Inflammation

Regardless of whether inflammation is sterile or microbial in origin, immunopathology will ensue without effective repair and resolution (reviewed extensively in (56)). One of the first cellular mediators of sterile inflammation are neutrophils, which home to sites of sterile inflammation within hours of injury and form clusters, as was recently shown by dynamic two photon imaging in murine models of cardiac IRI and burn injury (57, 58). Neutrophils are short-lived cells that propagate the initial inflammatory response. Effective resolution of inflammation requires that these cells be efficiently cleared after they undergo apoptosis or necrosis. Furthermore, it is important that recruitment of more neutrophils is inhibited to the inflammatory site for efficient inflammation resolution. In this regard, apoptotic neutrophils secrete mediators (e.g., annexin A1), which can impair further neutrophil recruitment. Furthermore, neutrophils upregulate signals (e.g., sphingosine 1-phosphate) that enhance uptake by macrophages, a process termed efferocytosis (59). The release of extracellular adenosine that occurs in IRI also dampens inflammation possibly by stabilizing hypoxia-inducible factor, which promotes a switch to glycolytic metabolism (60). Macrophages typically follow neutrophils into sites of inflammation and initially potentiate the inflammatory response. However, macrophages are dynamic cells and they can change their phenotype to one that enhances resolution. Indeed, a transcriptional analysis comparing macrophages isolated at either an inflammatory or resolution phase of murine peritonitis found that resolution-phase macrophages express genes such as TIM4 and TGF $\beta$ , which are involved in tissue repair and clearance of inflammatory cells (61). Macrophages also secrete VEGF, which enhances tissue angiogenesis and restoration of oxygen to the hypoxic tissue and immunosuppressive cytokines (e.g., IL-10), which may allow for recruitment of regulatory T cells that further assist in inflammation resolution. Finally, macrophages secrete pro-resolution mediators such as lipoxins, and resolvins that enhance inflammation resolution (reviewed in (62)).

Although macrophages have been implicated in inflammation resolution, a recent study provided evidence that eosinophils, which secrete IL-4, rather than macrophages are required to resolve acute muscle inflammation induced by cobra toxin (63). IL-4 produced by eosinophils is sensed by fibro/adipogenic progenitors (FAPs), a specific stem cell implicated in muscle cell regeneration, which enhances the ability of FAPs to clear necrotic cells, induce muscle cell proliferation and regeneration (63). Whether this pathway of inflammation resolution is relevant to other forms of sterile inflammation has not yet been determined.

There are reports that endogenous innate immune triggers can stimulate specific receptors, not known to respond to pathogens, to dampen sterile inflammation. For example, CD24 is a glycosyl-phosphoinositol-anchored protein that provides costimulation to T cells, but it also

signals in conjunction with a lectin Siglec-10, to dampen sterile inflammation (64). Specifically, CD24-Siglec-10 signaling suppresses sterile inflammation after acute hepatic injury induced by acetaminophen, possibly by inhibiting signals mediated by HMGB1 or heat shock proteins (64). Future research is required to determine how broadly applicable this pathway is to other forms of sterile inflammation.

## Activation of adaptive immunity by sterile inflammation: the case of organ transplantation

Before the molecular and cellular pathways of innate immunity were heavily investigated, it was postulated that innate immune activation enhances the induction of adaptive immune responses (65). Subsequent work using model antigens indicated that this is the case (66), which has been expanded to infectious models (reviewed in (67)). Although activation of innate immunity during sterile inflammation alerts the host to the presence of a noxious stimulus, which can lead to a repair response, it has been argued whether this enhances the induction of adaptive immunity as compared to inflammation induced by a pathogen. The example of organ transplantation indicates that sterile inflammation may enhance adaptive immunity. In this context, one study provided evidence that the re initiation of IRI led to acute allograft rejection in cardiac allografts that were accepted by the host for < fifty days (68). In another study, human coronary arteries were implanted into immune-deficient murine hosts that were reconstituted with allogeneic human peripheral blood mononuclear cells (69). Increasing hypoxic injury to the artery graft prior to implantation led to increased T cell recruitment to the graft (69). As both these studies employed sterile inflammation models of transplantation, they indicate that the presence or degree of IRI enhances anti-donor, adaptive T cell responses and provide evidence that sterile inflammation enhances adaptive immunity. Clearly, there is clinical evidence that increasing donor ischemic time, and thus IRI, enhances acute and chronic rejection (70). Furthermore, a clinical study revealed that IRI leads to innate immune cell migration into kidney allografts that precedes the recruitment of T cells (71). Thus, in the case of organ transplantation there is evidence that sterile inflammation enhances adaptive immunity. Whether this occurs in other forms of sterile inflammation and the molecular links between sterile inflammation and induction of adaptive immunity are yet to be determined.

## Conclusions

Sterile inflammation occurs in several broad medical conditions. Therefore, dissecting out the mechanisms by which sterile inflammation induces pathology will have a large biomedical impact. It is likely that there are many yet to be identified triggers of sterile inflammation, and exploratory approaches (e.g., proteomics, genomics or metabolomics) will be required to identify these triggers. Identifying relevant sterile inflammatory triggers may allow for the development of localized therapeutics that will dampen inflammation at the injury site without disabling systemic innate immune pathways that afford protection against infection (Figure 1B). This is particularly relevant in organ transplantation or in the setting of IRI due to acute myocardial infarction or stroke in which the host is either immune suppressed (i.e., organ transplant recipient) or likely to have compromised immune function (i.e., older people, who are at increased risk of vascular disease and exhibit immune senescence). In these susceptible populations, systemically inhibiting innate immune pathways that are employed both to respond to sterile and microbial-induced inflammation could lead to detrimental infectious complications. In conclusion, further investigation into the initiation and resolution of sterile inflammation will lead to novel therapeutics that could impact a wide array of human diseases.

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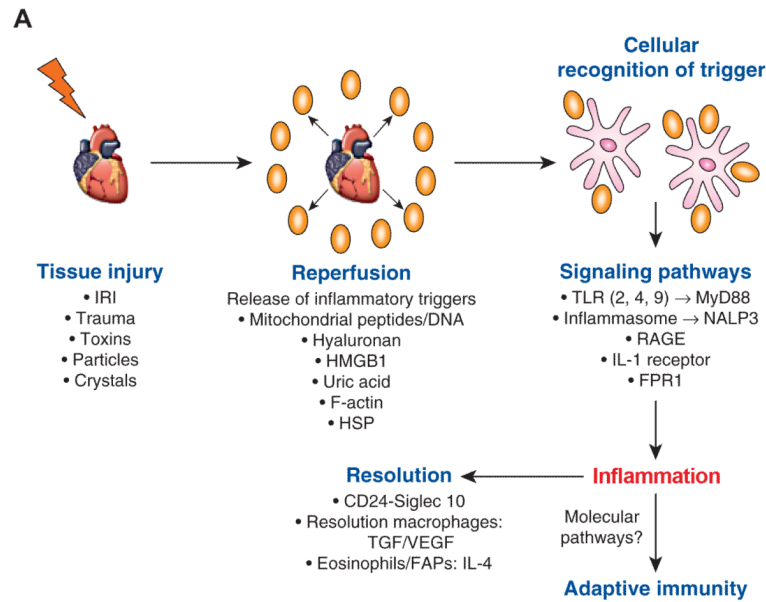


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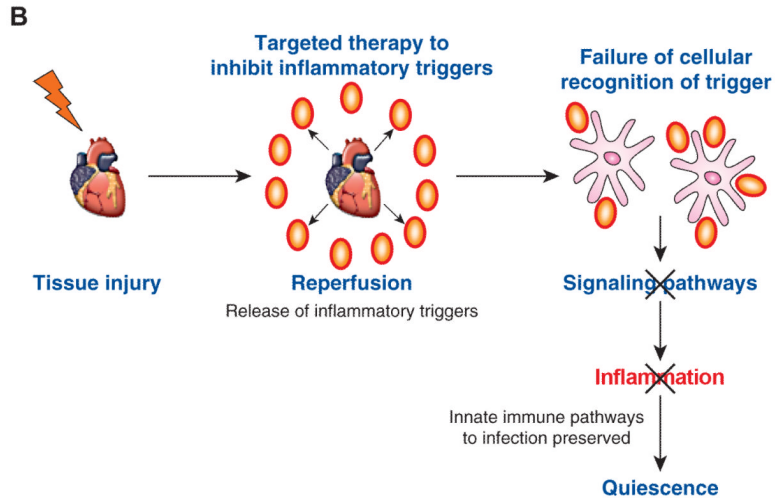
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### Figure 1A. Pathways of Sterile Inflammation

A variety of insults induce sterile inflammation. This leads to the release of inflammatory triggers that are sensed by immune (e.g., dendritic cells or macrophages) or non-hematopoietic cells (e.g., endothelial or epithelial cells). These cells respond to the trigger via a variety of pathways, some of which are shared with pathways that respond to microbes and others that are distinct to sterile inflammation (e.g., RAGE and IL-1). The induction of sterile inflammation leads to repair mechanisms that are mediated by macrophages that clear necrotic or apoptotic neutrophils and produce factors that enhance resolution (e.g., resolvins, TGF- $\beta$ ) or growth of blood vessels into the area (e.g., VEGF). There is evidence that IL-4 produced by eosinophils is sensed by fibro/adipogenic progenitors (FAPs) to mediate repair after acute skeletal muscle necrosis. Activation of sterile inflammation may also enhance adaptive immune responses as in the case of organ transplantation. The molecular pathways by which sterile inflammation enhance adaptive immunity remain to be fully elucidated.

HSP=heat shock protein



**Figure 1B. Therapeutic paradigm: localized inhibition of inflammatory triggers may reduce inflammation without compromising systemic innate pathways required for protection from infection**

As several pathways are shared between sterile inflammation and inflammation sensed by microbes, targeted localized therapy that is aimed at the triggers could reduce inflammation without impairing host defense to infection. Such a strategy may be beneficial for localized sterile inflammation that occurs with organ procurement and implantation. In this instance, the organ could be pretreated prior to implantation.

**Table 1**  
**Inflammatory Triggers, Signaling and Associated Diseases**

Trigger	Senor + signaling pathway	Associated diseases	References
Nuclear proteins • HMGB1	<ul style="list-style-type: none"> <li>• TLR2/4</li> <li>• RAGE</li> <li>• CD24</li> </ul>	<ul style="list-style-type: none"> <li>• Acute kidney injury</li> <li>• Acute hepatic injury</li> <li>• Acute allograft rejection</li> </ul>	(7-10, 72)
Mitochondrial components <ul style="list-style-type: none"> <li>• Formylated peptides</li> <li>• DNA</li> <li>• ATP</li> </ul>	<ul style="list-style-type: none"> <li>• FPR1</li> <li>• TLR9</li> <li>• ATP in combination with NLRP3</li> </ul>	<ul style="list-style-type: none"> <li>• Crush injury/trauma</li> <li>• Acute hepatic injury</li> <li>• Acute kidney injury (ATP + NLRP3)</li> </ul>	(10-12, 73)
Monosodium uric acid crystals	<ul style="list-style-type: none"> <li>• IL-1receptor + MyD88</li> <li>• NLRP3</li> </ul>	<ul style="list-style-type: none"> <li>• Gout</li> <li>• Acute lung injury induced by bleomycin</li> </ul>	(19, 20, 22, 74)
Components of extracellular matrix <ul style="list-style-type: none"> <li>• Hyaluronan</li> </ul>	<ul style="list-style-type: none"> <li>• TLR2/4</li> <li>• CD44</li> </ul>	<ul style="list-style-type: none"> <li>• Acute lung injury induced by bleomycin</li> </ul>	(17, 18, 75)
Cholesterol	<ul style="list-style-type: none"> <li>• NLRP3</li> </ul>	<ul style="list-style-type: none"> <li>• Atherosclerosis</li> </ul>	(44)
Particles <ul style="list-style-type: none"> <li>• Silica</li> <li>• Asbestos</li> </ul>	<ul style="list-style-type: none"> <li>• NLRP3</li> </ul>	<ul style="list-style-type: none"> <li>• Lung fibrosis</li> </ul>	(49)
IL-1	<ul style="list-style-type: none"> <li>• IL-1 receptor</li> </ul>	<ul style="list-style-type: none"> <li>• Acute allograft rejection</li> </ul>	(54)