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Scavenging Damage and Pathogen Associated Molecules

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Abstract

In response to exogenous and endogenous danger signals the immune system launches a carefully orchestrated response known as inflammation. However, these signals can be found in higher than normal levels leading to pathological inflammation resulting in the establishment and progression of many diseases. There is a growing appreciation for the ability of inflammation systems to exhibit both beneficial and deleterious effects. Investigators are developing novel approaches to reduce aberrant inflammation. This review will highlight some of the therapeutic approaches that arise from combining medicinal chemistry and bioengineering, and discuss the disease states that are being targeted with these novel approaches.

Keywords: Inflammation; Polymer; Scavenger; Fiber; DAMP; PAMP

Abbreviations: DAMP: Damage Associated Molecular Pattern; PAMP: Pathogen Associated Molecular Pattern; PRR: Pattern Recognition Receptor

Introduction

In order to establish host defense responses against harmful insults, e.g., infection and injury, the innate immune system launches a critical response known as inflammation, which serves to establish a physical barrier against the spread of infection and to repair damaged tissues [1]. Innate immunity has traditionally been discussed in the context of its ability to recognize ligands from pathogens known as Pathogen Associated Molecular Patterns (PAMPs) [2]. These ligands are often liberated from dead and dying cells as a result of bacterial, viral, or fungal infections. Recently, there is a growing appreciation for stimulation of innate immunity from endogenous ligands known as Damage Associated Molecular Patterns (DAMPs) [3]. Upon infection or injury, PAMPs and DAMPs are released into the blood and surrounding tissues and recognized by Pattern Recognition Receptors (PRRs) that are expressed on almost all mammalian cells. Activation of PRRs leads to the induction of inflammatory and innate immune responses.

Toll-Like Receptor (TLR) family is one of the most well characterized classes of PRRs. TLRs are expressed either on the cell surface or in the endosomal compartments and recognize a diverse set of structural motifs present in bacteria, viruses and cells [4]. Although TLRs are mostly expressed on immune cells, e.g., dendritic cells, macrophages and B cells, non-immune cells express and up regulate TLRs [5]. A relatively new addition to the PRR family, retinoic acid-inducible gene I (RIG-I)-like receptor (RLR) family [6] and nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family [7] are expressed in the cytoplasm of nucleated cells where they specifically recognize structural motifs in nucleic acids and bacterial membrane. TLRs, RLRs and NLRs work in concert to protect host from infection.

Uncontrolled activation of PRRs leads to the development of various inflammatory diseases, autoimmune diseases and cancers. Sepsis is among the most common causes of death of hospitalized patients and according to the Center for Disease Control and Prevention in 2008 nearly $14.6 billion dollars was spent on patients with sepsis from 1997 to 2008 [8]. Lipo polysaccharide (LPS) is a key membrane component of Gram-negative bacteria and a potent TLR4 ligand that is associated with the development of septic shock [9]. In the late 1990's Shoji et al. [10] developed a novel therapeutic strategy whereby circulating LPS was removed by polymyxin B (PMB) immobilized to a polystyrene-derived fiber (called PMX-DHP). PMB is a cyclic cationic polypeptide antibiotic isolated from *Bacillus polymyxa* that exhibits profound binding and neutralization of endotoxin [11]. However, systemic administration of PMB can cause

severe nephrotoxicity and neurotoxicityin humans [12]. To sidestep this shortcoming, the investigators developed covalently immobilized PMB to polystyrene derived fibers, which can then be used to filter blood outside of the patient using an extracorporeal circuit (Figure 1), thereby detoxifying the blood by removing nearly 90% of the circulating LPS [10]. To date, PMX-DHP has been implemented in the treatment regimen of over 100,000 septic patients with little to no reports of adverse reactions [13].

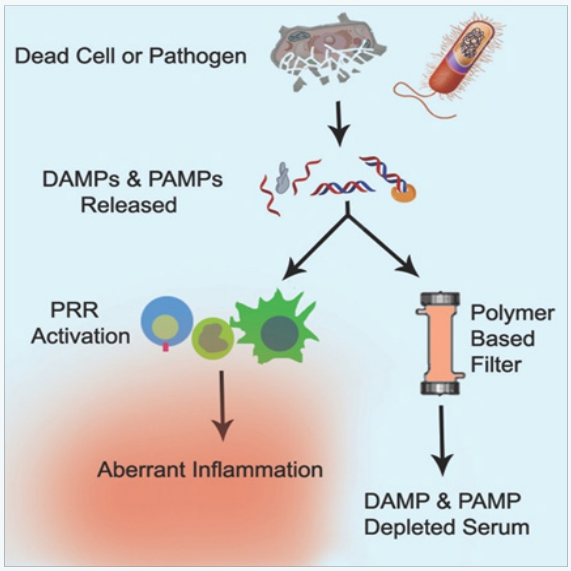

Figure 1: Clearance of DAMP and PAMP using extracorporeal scavenger cartridge. DAMPs and PAMPs are liberated from dead and dying cells and bacteria. These danger signals go on to activate PRRs ultimately leading to pathological or aberrant inflammation. Membranes coated with DAMP- and/or PAMP-binding polymers capture and remove DAMPs and PAMPs from patients' blood in an extracorporeal circuit.

As a result of massive tissue damage trauma patients produce a myriad of danger signals and high levels of DAMPs are found in the serum of these patients. Elevated levels of DAMPs are strongly correlated with the development of severe posttraumatic complications, including systemic inflammatory response syndrome (SIRS), thrombosis and multi-organ dysfunction [14]. In order to thwart the deleterious effects of excessive circulating DAMPs, we and others demonstrated that certain types of nucleic acid-binding polymers (NABPs), e.g., third-generation polyamidoamine dendrimer (PAMAM-G3), β-cyclodextrin-containing polycation (CDP) andhexadimethrine bromide (HDMBr),neutralized the ability of cell-free DNAs and RNAs to activate nucleic acid-sensing TLRs (e.g., TLR3, TLR7, TLR8 and TLR9) [15] and blood coagulation [16,17]. Interestingly, NABPs, e.g., PAMAM-G3 and branched polyethylenimine (PEI), immobilized onto electrospun microfiber mesh captured and removed extracellular DNAs as well as non-nucleic acid DAMP HMGB1 from extracellular fluids and neutralized the ability of DAMPs generated by ex vivo cell culture or DAMPs circulating in the blood of trauma patients to stimulate multiple TLRs, e.g., TLRs 2, 3, 4 and 9, and coagulation in vitro and in vivo [18].

Conclusion

Membranes coated with DAMP- and/or PAMP-capturing polymers have a potential use during hemofiltration, extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT) in intensive care units. Removing pro-inflammatory DAMPs and PAMPs from circulation is an unmet need in the treatment of critically ill patients. Cartridges containing such membranes can be developed as safe and effective anti-inflammatory therapeutics for the treatment of patients with traumatic injuries and infection.

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Conflict of Interest

We have no conflict of interest to declare.

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