Roles of Heat Shock Proteins and $\gamma\delta$ T Cells in Inflammation

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Elimination of activated inflammatory cells that infiltrate and damage host organs can reduce morbidity and mortality. A better understanding of the mechanisms by which these processes occur may lead to new approaches to prevent tissue damage. The lungs, gastrointestinal tract, and skin are particularly prone to infection and collateral damage by inflammatory cells. Specialized lymphocytes protect these organs from collateral tissue damage by eliminating neutrophils and macrophages from inflamed tissues. These lymphocytes recognize signals produced by inflammatory cells. One such signal is heat shock protein (Hsp) expressed on the cell surface of inflamed phagocytes. Mammalian Hsp molecules closely resemble their microbial equivalents, and therefore phagocytes decorated with these molecules are recognized as target cells. T lymphocytes bearing the $\gamma\delta$ T cell receptor (TCR) elicit cytotoxic activity toward macrophages and neutrophils that express Hsp60 and Hsp70, respectively, protecting host organs from collateral tissue damage by phagocytes.

Keywords: $\gamma\delta$ TCR; macrophages; neutrophils; inflammatory tissue damage; immunoregulation

Systemic inflammatory response syndrome (SIRS) secondary to trauma, hemorrhagic shock, or severe infections results in uncontrolled inflammation and the dysfunction of host organs (1). Inflammatory damage to the microvasculature, lungs, and liver is a major cause of post-traumatic morbidity and mortality of patients in intensive care. Despite extensive studies of the processes involved in SIRS, the events that lead to the initiation and the resolution of this inflammatory response are not completely understood. This lack of understanding limits the success of current treatments of trauma casualties and of patients with sepsis, despite the advanced therapeutic tools that are available (2). It has been shown that acute pulmonary and hepatic inflammatory injury is associated with accumulation and activation of various inflammatory cells, primarily polymorphonuclear neutrophils (PMN), within the parenchyma of these organs (3–5). Pulmonary inflammation results in acute lung injury (ALI) and can progress to acute respiratory distress syndrome (ARDS), which requires mechanical ventilation and is the cause of death of at least 50% of those patients who die in the intensive care unit (6). While the processes leading to ALI are not well understood, even less information exists on the mechanisms by which the host resolves inflammatory episodes in cases in which patients are able to recover from ALI to avoid ARDS. We have recently gained

CLINICAL RELEVANCE

This review describes the role of heat shock proteins in target cell removal by the immune surveillance system in the context of inflammatory diseases and cancer. Special emphasis is on the resolution of inflammation from the lungs.

a better understanding of these mechanisms, which might lead to new strategies to reduce ARDS in trauma patients (7).

RESOLUTION OF ACUTE INFLAMMATION

Although rapid protective responses to invading pathogens are critical for the defense of the host against infectious agents, appropriate termination of these responses is equally important to protect host tissues from excessive collateral damage after prolonged exposure to toxic mediators released in inflamed tissues. A good example for the importance of such balanced responses is pulmonary inflammation secondary to trauma or sepsis. The initial moderate inflammatory reaction in the lungs gives way to a destructive and ultimately lethal escalation of events that culminates in ARDS. Similarly, other clinical conditions such as tuberculosis, asthma, and glomerulonephritis are associated with a failure of the cellular immune response to appropriately terminate the inflammatory cascade. This leads to chronic diseases, characterized by extensive tissue damage and scarring, which seriously impairs organ system function (8, 9). The resolution of inflammatory responses coincides with a normalization of vascular tone and permeability, drainage of edema fluid, and the clearance of activated immune cells that have accumulated in inflamed tissues (8). Increased vascular permeability and edema formation are primarily mediated by inflammatory mediators such as amines, eicosanoids, nitric oxide, and cytokines released from activated phagocytes within inflamed tissues. Thus, removal of activated phagocytes is a necessary prerequisite for the resolution of inflammation.

Macrophages (M ϕ) can effectively eliminate inflammatory cells by phagocytosis. This process must be carefully controlled to avoid further host tissue damage. M ϕ must therefore be able to recognize appropriate target cells before engaging them. M ϕ accomplish this task via specific signals that are generated by target cells that are destined to be destroyed and eliminated from inflamed tissues (10, 11). Such signals may be chemical mediators released from the target cells or markers expressed on the cell surface of the target cells. The latter mechanism may be associated with an altered phenotype that initiates the phagocytosis of target cells by M ϕ . Such mechanisms have been demonstrated in several systems that result in the elimination of PMN or lymphocytes from inflamed tissues (9, 12, 13).

However, phagocytosis of apoptotic immune cells by M ϕ is not the only mechanism by which inflammatory cells can be cleared from inflamed tissue. Many inflammatory mediators such as endotoxin (LPS), chemotactic peptides, and prostaglandins are

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known to inhibit apoptosis in PMN, preventing subsequent clearance of PMN by M ϕ (14). The mechanisms by which M ϕ themselves are eliminated after completing their tasks are also not well understood. Similar to PMN, M ϕ have been shown *in vitro* to undergo apoptosis in response to various stimuli (15), but it is not clear how this apoptotic process is regulated or if it also occurs *in vivo* (16). Nevertheless, such mechanisms that facilitate the elimination of M ϕ must exist, because a large number of the leukocytes that accumulate in inflamed tissues are M ϕ and they, along with all the other phagocytes, are effectively cleared during the recovery from inflammatory episodes. Conversely, continued presence of large amounts of PMN or M ϕ within affected host tissues is a hallmark feature of chronic microbial or inflammatory diseases (17).

The clearance of inflammatory cells likely depends on alternative mechanisms in addition to apoptosis and subsequent phagocytosis by M ϕ . One such mechanism may occur through the externalization of stress proteins by inflamed target cells. These proteins serve as markers, designating target cells for elimination by immune cells. An important example of such a mechanism is the recognition of tumor cells by natural killer (NK) cells that recognize Hsp expressed on the cell surface of tumor cells (18).

HSP AND CELLULAR DISTRESS

Hsp comprise a large family of proteins that are constitutively expressed by prokaryotic and eukaryotic cells under normal conditions. Hsp are important housekeeping molecules that contribute to the appropriate folding, transport, and repair of various cellular proteins (19). When subjected to environmental stress, cells express increased amounts of intracellular Hsp molecules so as to protect the cells from damage by preventing erroneous protein folding (20). Table 1 lists some important eukaryotic Hsp, their molecular weight ranges, prokaryotic equivalents, and potential roles in protecting host tissues.

Hsp are typically found in the cytosol, as they lack specific leader sequences that are required for the expression of the proteins on the cell surface (20). Nevertheless, several recent studies have demonstrated that Hsp molecules can appear on the cell surface of normal and transformed cells (7, 17, 21–23). The mechanisms by which Hsp molecules are translocated to and expressed on the cell surface are poorly understood. Although Hsp70 expression by PMN requires *de novo* protein synthesis and the transport of the protein to the cell surface (7), the question of whether this mechanism is universal for surface expression of Hsp

in other cells as well remains to be investigated. Several studies have shown that cells can externalize Hsp molecules during apoptotic transformation (23–25). Another possible mechanism is through the binding of Hsp molecules that are produced by other cells. These molecules may be bound to the cell surface by specific receptors (26, 27) or via lipid anchorage (24). These possible mechanisms are consistent with the results of immune precipitation experiments, which revealed that externalized Hsp molecules are not truncated and have full length (22).

In contrast to the well-defined roles of Hsp in the intracellular compartment, the functions of Hsp molecules on the cell surface of normal (28), infected (21), transformed (18, 22), and apoptotic cells (23, 24) remain poorly understood. Increasing evidence suggests that Hsp molecules may serve as surface markers that are involved in intercellular communication and as triggers for target cell elimination by the immune surveillance system (7, 17, 18, 29–31). Another function of Hsp may be to stabilize plasma membranes that are damaged by toxins and stress-related metabolites generated in response to infections or inflammation (32). Surface localization of Hsp may also represent an intermediary step involved in the secretion of Hsp into the extracellular space. The possible mechanisms by which Hsp can be released from different cells have been discussed in a recent review article (33).

Hsp molecules associated with the cell membrane can bind microbial products and modulate Toll-like receptor (TLR) signaling (34). Specifically, LPS, a bacterial cell wall constituent that induces a strong inflammatory response during gram-negative sepsis, initiates the expression of Hsp molecules on the cell surface of M ϕ and PMN through TLR-4 (35). The appearance of Hsp associated with the external cell membranes of M ϕ and PMN has also been observed with bacterial infections, for example in experimental listeria infections in mice (17, 31, 36) or in severe sepsis in patients (28).

Hsp molecules on the cell surface can elicit a robust immune response because these molecules contain several highly conserved epitope sequences with strong immunogenic properties (20, 37). Moreover, due to the high degree of phylogenetic conservation (38), the immune response elicited by Hsp molecules of microbial origin is similar to that induced by endogenously produced Hsp that is expressed on the surface of host cells under severe distress (20, 39). In either case, Hsp molecules undergoing processing by antigen-presenting cells become available for recognition by conventional T cells. However, Hsp can also directly activate specialized nonconventional T cell subsets, NK cells, and antigen-presenting cells (40). A detailed appraisal of the immunostimulatory properties of Hps has been summarized in two excellent recent review articles (39, 41).

TABLE 1. HEAT SHOCK PROTEINS AND THEIR ROLES IN HOST PROTECTION

Hsp Family	Molecular Weight	Possible Functional Roles	Prokaryotic Equivalent
Hsp10	10 kD		GroES
Hsp27	20–30 kD		GrpE
Hsp40	40 kD		DnaJ
Hsp60	60 kD	Recognition of inflamed M ϕ by $\gamma\delta$ T cells	GroEL
Hsp70 (Hsp72)	70 kD	Protection during heat stress Recognition of inflamed PMN by $\gamma\delta$ T cells Recognition of cancer cells by NK cells	DnaK
Hsp90, Grp94	90 kD	Recognition of cancer cells by NK cells	HtpG
Hsp104, Hsp110	100 kD	Protection from extreme temperature	ClpB, ClpA, ClpX

Definition of abbreviations: Hsp, heat shock protein; NK cells, natural killer cells; PMN, polymorphonuclear neutrophils.

$\gamma\delta$ T LYMPHOCYTES AND NK CELLS RECOGNIZE HSP

T cells that bear T cell receptors (TCR) composed of γ and δ polypeptide chains are referred to as $\gamma\delta$ T cells. This T cell subset has been implicated in the regulation of the host response to microbial infections and other inflammatory challenges (42–46). The regulatory function of $\gamma\delta$ T cells is mediated by production of cytokines such as IFN- γ , IL-10, and TNF- α , as well as by direct cytotoxic actions toward target cells (43, 47). $\gamma\delta$ T cells accumulate at sites of inflammation in response to bacterial, viral, and parasitic infections (42, 45, 47). Studies in mice lacking functional $\gamma\delta$ T cells have revealed that bacterial infections culminate in abnormally exaggerated and protracted inflammatory responses that result in increased mortality (48–50). These studies indicate that a main function of $\gamma\delta$ T cells is to protect host tissues from injury secondary to inflammatory responses that follow infections. $\gamma\delta$ T cells have also been shown to be involved in the

systemic inflammation that is induced by thermal injury or surgical trauma; and it is thought that $\gamma\delta$ T cells have an important role in providing chemokines that attract monocytes and M ϕ to inflammatory focus in burn patients (51, 52). Accumulation of $\gamma\delta$ T cells thus seems to be essential to limit acute lung injury that occurs during the course of peritoneal sepsis, for example by the ligation and puncture of the cecum of mice subjected to experimental sepsis (7, 53). Sepsis induced by cecal ligation and puncture (CLP) in $\gamma\delta$ T cell-deficient mice is characterized by diminished production of proinflammatory cytokines and increased mortality (54). On the other hand, no differences in survival, bacterial clearance, or cytokine production after CLP have been found in another study comparing wild-type and δ TCR knockout mice (55). The authors explain these findings by differences in the CLP model they used compared with that used by previous studies.

As with conventional $\alpha\beta$ T cells, $\gamma\delta$ T cells can also recognize antigen in the context of MHC molecules (56). However, the majority of $\gamma\delta$ T cells recognize antigens presented by multiple surface molecules, including the classical MHC gene products and stress-induced MHC class I molecules (reviewed in Ref. 57). These variable patterns of antigen recognition allow $\gamma\delta$ T cells to rapidly and efficiently respond to invading pathogens (56). However, due to the limited germline-encoded diversity of the $\gamma\delta$ TCR (57), the response of $\gamma\delta$ T cells is less specific than that of $\alpha\beta$ T cells. This can explain why $\gamma\delta$ T cells can respond so strongly to conservative antigens such as Hsp molecules. In fact, peptides derived from bacterial Hsp molecules are well-characterized ligands of the TCR of $\gamma\delta$ T cells (58). Several bacterial or parasitic infections activate specific $\gamma\delta$ T cell subsets that are capable of responding to Hsp60 and Hsp70. These $\gamma\delta$ T cell subpopulations have been shown to have an essential role in the protection of the host against infections, for example in experimental *Listeria monocytogenes* (59), *Mycobacteria tuberculosis* (60), or *Plasmodium malariae* (61) infections. Thus, when the immune surveillance system detects Hsp molecules on the surface of host cells, it recognizes these cells as pathogen-afflicted and induces a cytotoxic immune response that results in the elimination of the affected host cells. In addition to cells that are infected with intracellular pathogens, this cytotoxic immune response can also trigger the elimination of stressed inflammatory cells and of certain cancer cells (62).

Thus, $\gamma\delta$ T cells can direct their cytotoxic response toward M ϕ and PMN that are altered through their involvement in inflammatory responses. Therefore, $\gamma\delta$ T cells are critical for the resolution of inflammatory responses and for the recovery of patients from infections. This role of $\gamma\delta$ T cells has been reviewed in an excellent article by Born and colleagues (42). The notion that $\gamma\delta$ T cells are critical for that role is supported by studies of Carding and Egan, who have demonstrated that robust expression of Hsp60 on the cell surface of M ϕ during experimental listeriosis in mice correlates with significantly increased susceptibility of M ϕ to attack by $\gamma\delta$ T cells (17, 31) and that $\gamma\delta$ T cells recognize inflamed M ϕ by Hsp60 molecules that are expressed on the cell surface of M ϕ (36). Although the exact molecular nature of the interactions of $\gamma\delta$ TCR with Hsp60 is still poorly studied, several investigators have found that the pretreatment with Hsp60-specific blocking antibodies can inhibit the interactions between $\gamma\delta$ T cells and their target cells (62). A very similar sequence of events is involved in the recognition and killing of PMN that express Hsp70 by $\gamma\delta$ T cells (7). In PMN, Hsp70 molecules on the cell surface serve $\gamma\delta$ T cells that recognize this evolutionary conserved molecule to eliminate activated PMN (Figure 1). Multiple patterns of antigen recognition and activation employed by $\gamma\delta$ T cells (47, 56, 57) enable fast and vigorous responses to various pathogens. While conventional $\alpha\beta$ T cells require 5 to

7 days to manifest their cytotoxic activity (42, 43), $\gamma\delta$ T cells need only minutes to engage autologous PMN that express Hsp70 on their cell surface (7). This interaction requires direct cell-to-cell contact between $\gamma\delta$ T cells and PMN. Interestingly, increased expression of Hsp70 in PMN has been reported in critically ill patients who sustained trauma, endotoxemia, or sepsis (28, 63), suggesting that recognition of Hsp70 on the cell surface of PMN could be involved in the clinical outcome of these patients. However, it remains to be seen if Hsp molecules and $\gamma\delta$ T cells play a unique role in clearing M ϕ and PMN from inflamed tissues and whether additional mechanisms are involved in this process.

CONCLUSIONS

Therapeutic approaches that prevent the recruitment of phagocytes to inflamed sites may reduce host tissue damage in chronic and acute inflammation. Treatments that hasten the clearance of inflammatory cells from inflamed tissues may yield similar results. During infections, however, the latter approach seems preferable, as it could be timed to encourage the resolution of inflammation after the phagocytes have been given the opportunity to clear microbial invaders from host tissues. The work from this and

Figure 1. Schematic depiction of heat shock protein (Hsp)70-mediated killing of polymorphonuclear neutrophils (PMN) by $\gamma\delta$ T lymphocytes. Under normal conditions Hsp70 molecules of PMN are located in the cytoplasm, where Hsp70 is not recognized by $\gamma\delta$ T cells with Hsp70-specific T cell receptors. Under stress conditions (e.g., during inflammation), PMN express increased levels of Hsp70 molecules that translocate to the cell membrane, where they are recognized by Hsp70-specific $\gamma\delta$ T cells, serving these cells as markers that signal the elimination of the PMN bearing Hsp70.

other laboratories suggests that $\gamma\delta$ T cells have an important function in protecting host tissues from damage by inflammatory cells (7, 50, 53, 54). This concept is strongly supported by findings with mice that are deficient in $\gamma\delta$ T cells. These animals show abnormally strong inflammatory responses to infectious insults, which results in extensive tissue necrosis, delayed resolution of inflammatory infiltrates, and an increased overall mortality (48, 49). These findings, together with our previous work, suggest that $\gamma\delta$ T cells may be suitable therapeutic targets to accelerate the clearance of phagocytes from inflamed tissues such as the lungs in attempts to limit tissue damage (7). Future treatments that stimulate the recruitment of $\gamma\delta$ T cells to the lungs or that enhance their ability to recognize and eliminate target cells seem feasible. More work is needed to develop such treatments.

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