HSP60 and the regulation of inflammation: Physiological and pathological

Irun R. Cohen, Francisco J. Quintana, Gabriel Nussbaum, Michal Cohen, Alexandra Zanin-Zhorov and Ofer Lider

Department of Immunology, The Weizmann Institute of Science, Rehovot 76100, Israel

Introduction

This chapter positions HSP60 at the center of inflammation and body maintenance. We shall discuss the following topics:
- Inflammation: Physiological
- Inflammation: Pathological
- HSP60: Autoimmune target
- HSP60: Regulator signal
- HSP60: Innate ligand
- HSP60 model
- Signal fidelity and HSP60

Inflammation: Physiological

Inflammation has come to have a bad name. We talk about inflammatory diseases – diseases apparently caused by the inflammatory process. The pharmaceutical industry abets inflammation’s ill repute and works hard to develop “anti-inflammatory” drugs, which are widely prescribed by physicians and even sold over the counter to the public.

But inflammation has not always been disparaged. The bio-medical scientists who developed the concept of inflammation through the first half of the 20th Century were aware of the beneficial aspects of inflammation [1]. In his book General Pathology [2], Lord Florey defines inflammation by citing Ebert: “Inflammation is a process which begins following a sub-lethal injury and ends with complete healing” [3].

Defined so, inflammation is physiological. From the moment of birth, the body must be maintained in the face of constant exposure to sub-lethal injury; the response to injury is inflammation and repair. The physiological system responsible for regulating inflammation is the immune system. The cytokines, chemokines,
adhesion molecules, and other molecules produced by the immune system’s adaptive and innate agents are required for angiogenesis, wound healing, tissue remodeling and regeneration, connective tissue formation, phagocytosis, apoptosis, and other processes needed for body maintenance. Even recognition of specific antigens is involved in the regulation of inflammation. A telling example is the phenomenon of neuroprotection: It appears that the preservation and recovery of function following trauma to the central nervous system is enhanced by activated autoimmune T-cells that recognize myelin antigens [4]. The point is that the adaptive arm of the immune system also takes part in the physiology of inflammation: antibodies, B-cells and T-cells. We shall discuss below how T-cells that recognize heat shock protein 60 (HSP60) aid the regulation of inflammation. HSP60, as a ligand for innate Toll-like receptors (TLR), helps connect innate and adaptive immunity into one integrated system. Defense against infectious agents is just one aspect of the immune maintenance of a healthy body; here too, both the innate and the adaptive arms of the immune system play critical roles [5].

To maintain the body, the immune system has to diagnose the need for inflammation at any particular site and at all times, and to respond dynamically with the exact mix of inflammatory molecules, in the degree needed to repair the damage. The inflammatory response needs to be turned on, fine tuned, and turned off dynamically as the healing process progresses [6]. The physiological regulation of inflammation by the immune system involves a dynamic dialog between the immune cells and the damaged tissue. The immune system responds to molecules from the tissue that signals the state of the tissue. As we shall discuss below, the expression of HSP60 is a reliable signal. The immune system, in turn, produces molecules (cytokines, chemokines, angiogenic factors, growth factors, apoptotic factors, and so forth) that induce changes in the target tissue that, properly orchestrated, lead to healing.

**Inflammation: Pathological**

If the inflammatory process is not properly regulated, or not terminated, or activated at the wrong place, at the wrong time, or to an inappropriate degree, then the inflammatory process itself can become the cause of significant damage [7]. Indeed, infectious agents bent on damaging the host, usually do so by triggering inappropriate inflammation through their toxins; the host is made sick by his or her own inflammatory reaction to pathogenic stimuli that trigger TNF-α, IFN-γ and other strong pro-inflammatory mediators [8]. Autoimmune diseases are the classic example of inappropriate inflammation. Chronic inflammation plays a role in diseases such as atherosclerosis, which bear autoimmune stigmata [9]. Allergies too are the expression of inappropriate inflammation [10]. Even agents of chemical or biological warfare have been designed to activate pathological inflammation [11].