Ofer Lider

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Regulation Of T-cell Activation, Behavior, And Communication With Other Cells In Sites Of Inflammation

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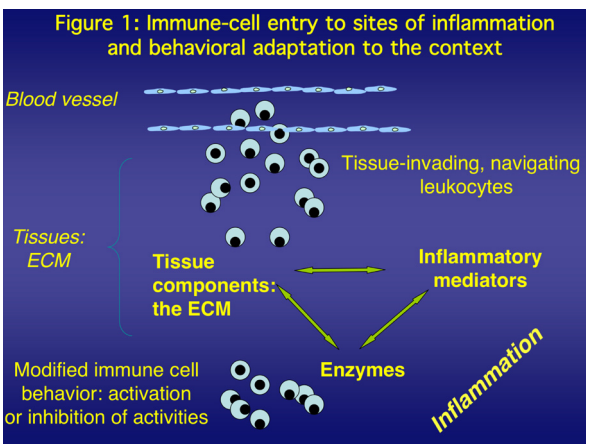
Tissue injury caused by infection, disease (for example, autoimmune reactions and cancer), or a wound evokes inflammatory events that can eventually restore the tissue to a normal state. Inflammation is commonly characterized by the migration of blood borne immune cells from the vascular circulatory system into the extracellular matrix (ECM), which is composed of macromolecules, such as, collagen, fibronectin, and heparan sulfate proteoglycans. The ECM functions both as a structural scaffold to support cell adhesion and tissue integrity, and as a reservoir for a myriad of inflammatory mediators, including cytokines, heat shock proteins (HSP), and chemokines. As we now know, such mediators, presented in the context of ECM, can provide intrinsic signals to co-ordinate immune cells functions, such as, activation, adhesion, migration, molecule synthesis, and phenotype changes. During inflammation, the composition of the ECM can be dynamically modified by the immune cells' degradative enzymes (Figure 1), the secretion of which can be, in turn, regulated by cytokines, which themselves can be enzymatically cleaved, thus yielding bioactive cytokine products. We are studying how these multi-directional and dynamic modifications of the ECM, and its associated mediators, generate signals that can regulate immune-cell functions and movement through the ECM.



For example, we have found that human HSP60, which is secreted into the inflammatory context, can signal the inhibition of T-cell activation, via toll-like receptors, and affect their functioning in tissues (e.g. ECM) *in vitro* and *in vivo* (Figure 2 shows how HSP60 transmits these signals to T cells).

We are also studying how T cells orient their locomotion, *in vitro*, according to gradients of heat ranging from the inflammatory site to the inner compartments of the adjacent blood capillaries. Such (enhancing or inhibitory) signals, and the sequence in which they are encountered, may determine the activatory capacities of immune cells, the mediators they produce, the receptors they express, and effector functions needed for a specific inflammatory reaction.

While studying how inflammation is controlled, we have recently found a set of enzymatically-generated breakdown products of ECM components and pro-inflammatory mediators that can decrease, *in vitro* and *in vivo*, the intensity of inflammation by down-regulating T-cell activation and subsequent functions. These naturally-occurring small molecular weight products of inflammation are the center of our intention in trying to find cure for ongoing, devastating autoimmune diseases.

Taken together, understanding how immune cells adapt their behavior to their extravascular environment, its physical state (intact or enzyme-treated), and ECM-associated mediators, while migrating to or being in sites of inflammation, is our long-term goal.

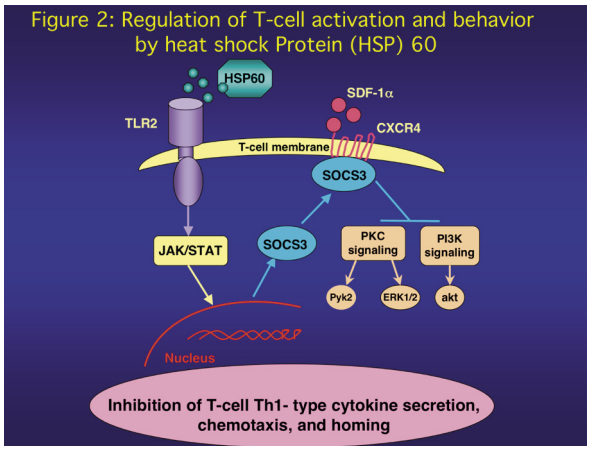


Figure 2: Regulation of T-cell activation and behavior by heat shock Protein (HSP) 60

Selected Publications

Franitza, S., Kollet, O., Brill B., Vaday, G. G., Petit, I., Lapidot, T., Alon, R., and Lider, O. (2002) TGFβ1 enhances SDF-1α-induced chemotaxis and homing of naïve T cells by up-regulating CXCR4 expression and downstream cytoskeletal effector molecules. *Eur. J. Immunol.* 32, 193-202.

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Zanin-Zhorov, A., Hershkoviz, R., Hecht, I., Cahalon, L., and Lider, O. (2003) Fibronectin-associated Fas ligand rapidly induces o.pposing and time-dependent effects on the activation and apoptosis of T cells. *J. Immunol.* 171, 5882-5889.

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Shenkman, B., Brill, A., Brill, G., Lider, O., Savion, N., and Varon, D. (2004) RANTES non-competitively inhibits stimulatory effect of SDF-1α. *J. Thromb. Haemost.* 2, 154-160.

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