

Talia Belogus
Alexander Brill
Liora Cahalon
Sol Efroni
Sharon Ganor
Iris Hecht
Rami Hershkovich
L. T. Herschkovitz
Laura Netzer

Ilya Sotnikov
Alexandra Zanin

Regulation of immune cell interactions with extracellular matrix during inflammation

Department of Immunology

Tel. 972 8 934 3657 Fax. 972 8 934 3657
E-mail: ofer.lider@weizmann.ac.il

Upon their extravasation from the vascular system into inflamed tissues, leukocytes, such as T lymphocytes and monocytes, must maneuver through a complex insoluble network of molecules termed the extracellular matrix (ECM). Leukocytes navigate toward their target sites by adhering to ECM glycoproteins and secreting degradative enzymes, while constantly orienting themselves in response to specific signals in their surroundings. Cytokines and chemokines are key biological mediators that provide such signals for cell navigation. While the individual effects of various cytokines have been well characterized, it is becoming increasingly evident that the mixture of cytokines encountered in the ECM provides important combinatorial signals that influence cell behavior. Herein, we present an overview of previous and ongoing studies that have examined how leukocytes integrate signals from different combinations of cytokines they encounter either simultaneously or sequentially within the ECM, to dynamically alter their navigational activities. For example, we found that TNF- α acts as an adhesion-strengthening and stop signal for T cells migrating toward SDF-1 α , while TGF- β downregulates TNF- α -induced matrix metalloproteinase (MMP)-9 secretion by monocytes.

These findings implicate the importance of how one cytokine, such as TNF- α , can transmit diverse signals to different subsets of leukocytes, depending on its combination with other cytokines, its concentration, and its time and sequence of exposure. The combinatorial effects of multiple cytokines thus affect leukocytes in a step-by-step manner, whereby cells react to cytokine signals in their immediate vicinity by altering their adhesiveness, directional movement, and remodeling of the ECM. However, cytokines and chemokines are not the only factors that affect the inflammatory capacities of immune cells; T cells and monocytes can adapt their activation phenotype to the amount of damage caused to their underlying ECM by ECM-specific enzymes, such as elastase or MMP. Thus, how immune cells react to their signal-rich and complexed microenvironment during migration is the focus of our research.

Selected Publications

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