Mira Barda-Saad et al., J Clin Cell Immunol 2016, 7:3(Suppl)
http://dx.doi.org/10.4172/2155-9899.C1.027

Signaling cascades regulating natural killer cell activation threshold

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Natural killer (NK) cells represent a powerful weapon of immune defense against viral infections and tumor growth via the cytotoxicity of target cells and the production of cytokines. NK cell function is regulated by a balance between activating and inhibitory signals. Cancer cells or viruses often perturb this balance by expressing ligands for activating NK cell receptors and by down-regulating ligands for the inhibitory receptors, i.e., MHC class I molecules, resulting in target cell killing. Engagement of inhibitory receptors, including the killer cell immunoglobulin-like receptor (KIR), antagonizes activating pathways through the recruitment and activation of the SH2-containing protein tyrosine phosphatase-1 (SHP-1) to the NK immunological synapse (NKIS). To date, only the signaling molecule VAV1 was clearly demonstrated as a direct substrate of SHP-1 in human NK cells. Since SHP-1 activity is the major mechanism that prevents NK cell autoimmune response, it is of great importance to determine whether additional substrates of SHP-1 exist and whether additional molecular mechanisms down-regulate NK cell activation. Moreover, the mechanisms that control SHP-1 activity remain to be unraveled. In the present study, we demonstrate that in response to KIR receptor engagement, SHP-1 and the E3 ubiquitin ligases Cbls negatively regulate the linker for the activation of T cells (LAT) and phospholipase Cγ (PLCγ) 1/2. LAT dephosphorylation by SHP-1 abrogated PLCγ 1/2 recruitment to NKIS and decreased calcium flux and degranulation, thus abolishing NK cell cytotoxicity. Furthermore, LAT ubiquitylation via c-Cbl and Cbl-b following NK cell inhibition leads to its degradation and to the down-regulation of NK cell activation. Using a cutting-edge microscope system, we follow this cellular signaling cascade from the moment of encounter through target-cell killing. Our data suggest that LAT phosphorylation triggers its ubiquitylation, implying a collateral inhibitory mechanism in which a pool of phosphorylated LAT that escapes SHP-1 dephosphorylation is targeted to proteasomal degradation. These mechanisms serve as a key checkpoint in tuning NK cell activation threshold and the immune response.

Biography

Mira Barda-Saad is a returning Scientist from the National Cancer Institute at NIH in Maryland, Senior Lecturer at the Mina and Everard Goodman Faculty of Life Sciences. She is currently examining the molecular signaling mechanisms controlling immune cell response with the primary goal of relating this knowledge to pathophysiological conditions of the immune system. She believes that understanding the dynamic behavior of signaling and cytoskeletal molecules that control immune cell activation is essential for identification of targets relevant for the treatment of cancer, autoimmune diseases and immunodeficiencies.

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