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Cross-talk between CD8+ T and NK cells: Fine-tuning of anti-tumor immune response

Anil Shanker[1,3], **Shawn J Goodwin**[1], **Lino Costa**[2], **Alexander Terekhov**[2], **Menaka C Thounaojam**[1], **William H Hofmeister**[2] and **Roman V Uzhachenko**[1]
[1]Meharry Medical College, USA
[2]University of Tennessee Space Institute, USA
[3]Vanderbilt University, USA

Local tumor antigen-specific T cell-NK cell collaboration is indispensable for the elimination of tumor cells, including antigen-deficient tumor escape variants before metastasis. While mechanistic details are available for the innate instruction of the T cell responses, little is known for the adaptive control of NK cell activity. We observed in a mouse model of mastocytoma expressing a self tumor antigen P1A that effector CD8+ T cells provided a necessary "help" to dormant NK cells in eliciting their antitumor effector function. Bioluminescence imaging of mastocytoma tumors following adoptive transfer of P1A-specific T cells in RAG-/- and RAG-/-γc-/- mice showed that NK cell anti-tumor activity requires cytolytic T cells, whereas T cells can function independent of NK cells. In 2D and 3D co-culture systems, we observed that PMA/ionomycin-stimulated CD8+ T cells form multiple contacts with naive NK lymphocytes. Data show that NK cells interacting with activated CD8+ T cells show an up-regulation of CD25 and CD69 expression mediated by intercellular contacts, and activation of NKG2D receptors and Stat2, Stat6, Jak1, Jak3, Tyk2, and PTEN signaling molecules with a decrease in the phosphorylation of Stat1, PKB/Akt, SAPK/JNK, p38. On the other hand, interacting NK cells down-regulate CD25 molecule expression on CD8+ T cells and promote differentiation of central-memory CD44+CD62L+ T cells. CD8+ T cells display an elevation in the phosphorylation of Stat1 and down-regulation of Stat5 with stimulated PKB/Akt, Lck, mTOR, and p42/p44. Moreover, significant changes in the cytosolic and mitochondrial Ca2+, production of mitochondrial ROS, mitochondrial membrane potential, mitochondrial permeability transition pore, and synthesis of nitric oxide and non-protein thiols (mostly, reduced glutathion) were observed in a reciprocal T cell-NK cell interaction. These results highlight the importance of mitochondrial activity in the re-modeling of activation signaling and memory differentiation of interacting CD8 T cells and NK cells. These results will help refine cancer immunotherapeutic strategies.

Biography

Anil Shanker is an Associate Professor in the Department of Biochemistry and Cancer Biology at Meharry Medical College. He is also a member of Vanderbilt-Ingram Comprehensive Cancer Center at Vanderbilt University. Dr. Shanker obtained his PhD from Banaras Hindu University in 1999. He performed his postdoctoral studies at the CNRS/INSERM Center of Immunology, Marseille, France and the National Cancer Institute, Frederick, Maryland. His pioneering work with solid tumor models demonstrated that activated CD8 T cells provided a necessary "help" to dormant NK cells in eliciting their antitumor function. His laboratory is currently focused on understanding mechanisms of functional cross-talk between T cells and NK cells in tumor models. He is also dissecting the mechanisms of immunomodulation by the proteasome inhibitor bortezomib and Notch ligand DLL1 in adoptive T cell/NK cell transfer settings in an effort to design novel combinatorial immune strategies in cancer patients. He has over 35 research publications to his credit in cancer and immunology journals.

ashanker@mmc.edu