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Meeting Abstract

NKG2D, unconventional T cells, and the regulation of carcinogenesis

Adrian Hayday[1*], **Jessica Strid**[1], **David Vermijlen**[1] **and Michael Girardi**[2]

[1]*King's College School of Medicine at Guy's Hospital, London, United Kingdom*
[2]*Yale University School of Medicine, New Haven, CT, USA*
[*]*Presenting author*

Abstract

The observation that solid tumors may harbor billions of tumor-infiltrating lymphocytes qualitatively distinct from those in the normal parenchyma shows that the immune system responds to tumors. The pressing issue is whether responses occur early enough to limit the outgrowth of transformed cells, and whether their aggregate effector outcome is uniformly useful. Indeed, results exist in support of the respective views that the impact of T cells on tumors is beneficial, neutral and even "tumor-promoting". Many such studies focus on conventional, antigen-specific T cells, whereas our approach has been to build on the observation that unconventional γδ T cells are a natural component of the resistance of mice to chemical carcinogenesis. γδ T cells do not recognize processed antigens presented by polymorphic MHC, but may be activated *in vivo* by "nominal antigens". Thus they may act equivalently in essentially all individuals, with clinical applicability. We will show that the anti-tumor activity of γδ T cells may in part be attributable to TRAIL expression. Among molecules activating γδ cells are MHC-like molecules (Rae-1/MICA) that bind the receptor, NKG2D. We will present data that MICA is regulated post-transcriptionally by growth factors. From mice in which we can vary NKG2D ligand expression, we will describe the events that follow Rae-1 upregulation in an epithelium, and consider their implications for immunosurveillance. We shall also consider that by sustained NKG2D ligand expression, tumors may benefit from a physiologic (as opposed to tumor-specific) immuno-evasion mechanism to prevent chronic cytolysis. Finally, we shall consider the results of a preliminary clinical trial designed to overcome immuno-evasion by promoting TRAIL expression by γδ T cells in Stage 4 prostate and breast cancer.