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Mechanisms of tumor-induced myeloid-derived suppressor cell development

Scott I. Abrams
Department of Immunology, Roswell Park Cancer Institute, USA

The accumulation of bone marrow-derived myeloid subpopulations, termed myeloid-derived suppressor cells (MDSC), has arisen as a major barrier to effective immune surveillance or immunotherapy. Despite the fact that much is now known about how MDSC mediate tumor progression, much less is known regarding the molecular events that promote their development. Thus, our laboratory has focused on how MDSC develop in the first place. We have been testing the central hypothesis that MDSC develop as a consequence of tumor-induced downregulation of interferon regulatory factor-8 (IRF8), a key myeloid developmental transcription factor. The importance of IRF8 in myeloid biology was originally unveiled in IRF8-deficient mice which develop myeloproliferative phenotypes. Indeed, our studies demonstrated that IRF8 levels are severely diminished in MDSC reflecting both implantable and autochthonous mouse mammary tumor models. To determine causality, we established genetic gain- and loss-of-function approaches using IRF8 transgenic and knockout mice, respectively. First, the overexpression of IRF-8 led to a significant decline in tumor-induced MDSC accumulation. Second, IRF8 overexpression abrogated the pro-tumorigenic behavior of MDSC and restored their cytokine phenotype to a type-1 pattern associated with adaptive immunity. Third, IRF8-deficiency defined myeloid populations that were highly homologous to MDSC generated in tumor-bearing mice, based on strong similarities in phenotype, gene expression patterns and suppression of T cell activation. Taken collectively, our data suggest that IRF8 is an MDSC-defining transcription factor, with potentially important clinical implications.

Biography

Dr. Abrams earned his Ph.D. degree from Indiana University and then completed a postdoctoral fellowship at Washington University. He is currently an Associate Professor at Roswell Park Cancer Institute. Prior to joining Roswell, Dr. Abrams served as an Investigator at the National Cancer Institute, NIH. He received several NIH Federal Technology Transfer Awards for the identification of human T cell peptide epitopes reflecting ras codon 12 mutations. Patents for these discoveries are issued both in the USA and Europe. He serves as a reviewer on study sections and has authored or co-authored nearly 90 articles, reviews and book chapters.

Scott.Abrams@RoswellPark.org