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Granulocytic myeloid-derived suppressor cell development via G-CSF-dependent mechanisms

Myeloid-derived suppressor cells (MDSCs) constitute a heterogeneous population of dysfunctional myeloid cells that suppress adaptive immunity. While the mechanisms by which MDSCs mediate immunosuppression are well-characterized, details on how they develop remain less understood. Indeed, it is known that chronic inflammatory mediators generated during pathologic processes, such as neoplasia, play significant roles in MDSC biology. Given that MDSC accumulation results from aberrant myelopoiesis and that a major subset is granulocytic, we tested the hypothesis that granulocyte-colony stimulating factor (G-CSF) promotes MDSC development. Using both implantable and autochthonous mouse tumor models, we observed abundant amounts of G-CSF in vivo, which correlated with robust granulocytic MDSC responses. Both loss- and gain-of-function approaches were then established to determine a causal role of tumor-derived G-CSF in MDSC generation. Inhibiting G-CSF production in vivo led to a significant decline in granulocytic MDSCs and, importantly, tumor growth. Conversely, over-expressing G-CSF in G-CSF-negative tumors augmented granulocytic MDSC accumulation and tumor growth. Lastly, administration of recombinant G-CSF protein to naive mice elicited immunosuppressive, pro-tumorigenic granulocytic-like MDSCs. Overall, we demonstrate that tumor-derived G-CSF enhances neoplastic growth through granulocytic MDSC-dependent mechanisms. These findings provide new insights into MDSC subset development, as well as potential biomarkers or therapeutic targets.

Biography

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, 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.

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