Inflammatory cross talk signals in myeloid-derived suppressor cells (MDSC) accumulating in experimental model of pancreatic cancer

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Pancreatic tumors (PT) create inflammatory environment that induces MDSC accumulating in patients. Our collaborators and we have demonstrated dual molecular mechanism of immunosuppressive action of MDSC. It includes: (1) inducing immunological tolerance to tumor antigens in anti-tumor cytotoxic T cells (CTL) and (2) rendering tumor cells unresponsive to tumor-specific CTL. Both types of unresponsiveness result from generation of peroxynitrite (PON) by intratumoral MDSC that nitrates tyrosine residues in T cells or tumor MHC molecules presenting antigenic epitopes to CTLs. We hypothesized that inflammatory molecules C5a, TLR2, calgranulin (S100A9), related to production of reactive oxidative/nitrative species, are involved in a cross talk signaling by MDSC. In our experiments, C57BL/6.hMUC1 transgenic mice with growing subcutaneous PT PancO2.hMUC1 exhibited a significant accumulation of MDSC with a phenotype CD11b+Gr1+ vs. non-tumor-bearing control mice. Most of MDSC expressed inflammatory markers S100A9 and CD88 (C5a receptor). Recombinant C5a significantly increased the mean fluorescence intensity for S100A9 and TLR2 on the surface of CD11b+, Gr1+, CD88+ MDSC after 6-hour incubation. This suggests that pro-inflammatory C5a and known TLR2 ligands (bacterial products or hyaluronan and versican commonly over-accumulated within the PT microenvironment) may represent potential contributors to increasing the generation of PON by intratumoral and circulating MDSC. Monitoring of PON-induced nitrotyrosines within the PT, tumor microenvironment and in circulation is needed to determine whether nitrotyrosine quantification might represent a biomarker of tumor escape from CTL. Further, we hypothesize that pharmacological control of PON generation should accompany immunotherapeutic strategies in cancer patients exhibiting biomarkers of significant MDSC activity.

Biography

Vladimir Pisarev received PhD and DSc from the Research Center for Medical Genetics (RSMG), Moscow, Russia. After completion of a 3-year study at St Jude Children’s Research Hospital, Memphis, TN in 1998 he joined University of Nebraska Medical Center (UNMC), Omaha, NE, as a faculty member for 11 years. Currently he is a professor/leading scientist at the RSMG and adjunct assistant professor at the UNMC. During last 10 years he contributed to 22 papers published in reputed journals including Nature Medicine (2007), J. Clinical Investigation (2011), Int. J. of Cancer (2010), Clin. Cancer Res. resulted in more than 620 citations.