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Cancer Cell-derived IL-6 Promotes MDSC, TAM, PD-1 Expression in Peripheral Blood Mononuclear Cells

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Monocytes, myeloid derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) have emerged as key immune modulators in various tumor models and human malignancies that suppress innate and adaptive immunity to support tumorigenesis. Programmed Cell Death Protein 1 (PD-1), which is up-regulated on T cells upon activation and remains high on exhausted T cells, also plays critical roles in immunosuppression. The increased presence of MDSCs, TAMs and PD-1 in the tumor is associated with progression of disease and poor prognosis in several cancer types. However, the mechanism remains unclear. We used conditioned media (CM) from head and neck cancer (HNC) and lung cancer cell lines to treat peripheral blood mononuclear cells (PBMCs) and found that the CM treatment increased the population of MDSCs ($Lin^-/CD11b^+/CD33^+/HLA\text{-}DR^-$) and TAMs ($CD11b^+/CD68^+/CD163^+$) in PBMCs. We assessed the expression of inflammatory cytokines in cancer cells associated with PBMC PD-1 and its ligands PD-L1 and PD-L2, Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4), Lymphocyte-Activation Gene 3 (LAG-3), T-Cell Immunoglobulin and Mucin-Domain Containing-3 (TIM-3), and cytokines. We found that the CM from all cancer cell lines significantly stimulated expression of IL-1β, PD-1, and CTLA-4 in PBMCs. Most importantly, we discovered that IL-6, but not IL-4, was significantly elevated in cancer cell CMs and played a major role in promoting the immunosuppressive phenotype of PBMCs. In this study, we provide evidence that cancer cell-derived IL-6 increases the population of MDSCs, TAMs, PD-1- and PD-L1-expressing immune cells, thereby establishing an immunosuppressive tumor microenvironment for progression.

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Biography

Ge Jin, Ph.D., is an Associate Professor in the Department of Biological Sciences, Case Western Reserve University School of Dental Medicine, USA. Dr. Jin'sresearch interest focuses on the mechanism underlying cancer cell-derived cytokines and/or metabolites and immune response and the role of HIV-infection in the development and progression of non-AIDS-defining cancers.