Tumor-Associated Macrophages Promote Tumor Development Through Remodeling of Its Extracellular Matrix

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Abstract

Tumor associated macrophages (TAM) play a pivotal role in mounting pro-tumoral effects, such as supporting proliferation and immune suppression. The extracellular matrix (ECM) is a mesh of proteins and glycans which provides physical support but also biochemical signals to all cells.

Here we characterize the influence of TAM on tumor ECM structure and composition, and the consequent pro-tumoral effect of this ECM on tumor progression.

We utilized a murine model of colorectal cancer (CRC) based on the endoscopy-guided orthotopic implantation of CRC cells into the colonic lamina propria of WT mice or *Ccr2*$^{-/-}$ mice, the latter are TAM-deficient due to failure in recruiting monocytes. Advanced second harmonics generation and scanning electron microscopy imaging revealed altered ECM-organization in the *Ccr2*$^{-/-}$ tumors, manifested by reduced content, linearization and cross-linking of collagen fibers, all are critical for tumor development. Moreover, using mass spectrometry we characterized significant and profound changes in ECM composition in TAM-deficient tumors. Among 314 differentially expressed proteins between WT and *Ccr2*$^{-/-}$ tumors, 42 are ECM proteins.

Using Affymetrix microarray we defined the specific repertoire of ECM remodeling enzymes and effector molecules expressed by sorted CRC-TAM subsets and correlated this signature with the changes in ECM composition in the absent of TAM.

Subsequently, these changes of tumor ECM by TAM were shown to promote cancer progression. In-vitro incubation of MC38 cell with ECM specifically from WT tumor resulted in significantly increased proliferation of MC38 cells, compared to ECM from normal colon or *Ccr2*$^{-/-}$ tumors. Finally, addition of ECM fragments isolated from WT CRC tumors during the orthotopic transplantation of MC38 CRC cells significantly accelerated tumor development, compared with ECM fragments from normal colons or *Ccr2*$^{-/-}$ tumors.

Collectively, our integrated biophysical-immunologic approach revealed that TAM play a substantial role promoting tumor development by the remodeling of its ECM structure and composition.