

Presentation:

TLR2-mediated Tumorigenesis

Speaker:

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Abstract:

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Introduction: Carcinoma cells release many factors including growth factors, cytokines, chemokines, and enzymes that regulate tumor growth, angiogenesis, invasion, and/or metastasis(1,2). Inflammatory populations, long been known to its infiltration into the tumor cells and already suggested its important roles for metastatogenesis and tumorigenesis, respond to these stimuli from tumor cells and activated(1-3). This complicated architecture of tumor is called tumor microenvironment. Activated inflammatory cells produce numerous cytokines which recruit and activate more myeloid cells, such as neutrophils, eosinophils, mast cells, macrophages and dendritic cells(4). Some inflammatory cells generate massive amounts of reactive oxygen and nitrogen species, *e.g.*, ROS and RNS, which possess bactericidal and proinflammatory activity, but can also cause oxidative DNA-damage and mutagenesis as well as general tissue damage(5). Macrophages, major component of this inflammatory populations, are involved in clearance of damaged tissues and dead cells, but once clearance has been completed, the inflammation mediated by macrophages should be resolved to allow epithelial and mesenchymal cells to restore normal tissue architecture. However, repeated exposure to secreted factors by carcinoma cells can promote the persistent activation of inflammatory cells, elevated ROS production and oxidative stress, that can further aid for tumor progression, promotion and metastasis. Despite the evident link between secreted factors by tumor cells and activation of inflammatory response on metastatogenesis and tumorigenesis, the mechanistic understanding is incomplete.

Results: Bone marrow-derived macrophages (BMDMs), incubated with conditioned medium from lung carcinoma cell lines (LCM) for 20-24 hrs, secreted pronounced IL-6, and IL-1 β , IL-6, and TNF α mRNA levels were enhanced. LCM-mediated activation was totally abrogated in BMDMs from *Tlr2*- and its major adaptor protein *Myd88*-deficient mice (*Tlr2*^{-/-} and *Myd88*^{-/-}, respectively). None of the other TLR signaling deficiencies had a significant effect on the response. TLR2 was also required for activation of MAP kinases by LCM. Importantly, TLR2 was also required for induction of IL-1 β , TNF α , MIP1 α and MCP1 mRNAs by subcutaneous injection of lung carcinoma cells. The results using radiation chimeras reconstituted with *Tlr2*^{-/-} bone marrow and inoculated with lung carcinoma cells via the tail vein showed decreased growth of lung metastases and substantially prolonged survival compared to chimeras reconstituted with WT bone marrow. Furthermore, injection of LCM but not control medium accelerated the growth of lung and liver metastases following tail vein injection of LLC cells. This enhancement was not seen in WT mice reconstituted with *Tlr2*^{-/-} bone marrow.

Conclusions: We showed that secreted compounds from carcinoma cells can activate inflammatory/innate immune system mainly via TLR2, albeit not all. We further showed that TLR2-mediated signaling plays important roles in tumorigenesis and metastatogenesis.

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