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Synaptic actin cytoskeleton remodeling: A novel mechanism for tumor cell escape from natural killer cell mediated death

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Natural killers cells (NKs) are effectors of the innate immune system able to kill cancer and pathogen infected cells without pre stimulation through the directed secretion of lytic granule contents. This process requires the formation of a well defined structure termed the immunological synapse (IS) between immune and cancer cells. Previous studies reported that the formation and activity of the IS largely rely on sequential rearrangement of actin filaments (AFs) of NKs. Our results provide evidence that the actin cytoskeleton of NK resistant tumor cells experiences an extensive remodeling at the IS and this process is associated with tumor cell escape from NK mediated cell lysis. Live cell imaging analyses revealed that AFs accumulate in resistant breast tumor cells in a region close to the IS within a few seconds after contact with NKs. The disruption of AFs with Latrunculin B or Cytochalasin D increased conjugate formation and enhanced tumor cell susceptibility to NK mediated cell death. The analysis of a range of epithelial and mesenchymal breast cancer cell lines revealed a striking correlation between the cell mesenchymal status and the ability to remodel the actin cytoskeleton upon NK attack. Also, mesenchymal cells exhibited significantly higher level of resistance to NK mediated cell lysis as compared to epithelial cells. Together our data suggest that actin remodeling is a novel strategy used by breast tumor cells to escape from NK mediated cell death. The precise functions of the prominent and fast accumulation of AFs observed in tumor cells as well as the underlying molecular mechanism are under investigation.

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Irradiated autologous multicellular vaccine isolated from fresh carcinoma induces multiple-target antitumor immunity

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Introduction: X-irradiated autologous tumor cells with adjuvant have been proved as an effective vaccine which induces reduction of tumor recurrence in some cancer patients but the mechanism remained to be further demonstrated. In a murine model we investigated the composition, efficacy and mechanism of irradiated autologous multicellular vaccine isolated from fresh carcinoma without any manipulations.

Material & Method: Single-cell suspensions isolated from tumor tissues were cultured for 24 hours to acquire adherent cells, whose contents were analyzed by flow cytometry. X-irradiated autologous multicellular vaccine (AMCV) or PBS were then injected into mice of protective CT26 and LLC models. Adoptive transfer experiments, depletion of immune cell subsets, ^{51}chromium-release assay, IHC of tumor sections and flow cytometry of spleen and tumor cells were carried out to demonstrate different immune mechanisms.

Results & Discussion: AMCV, including tumor cells, epithelial cells, myeloid-derived suppressor cells (MDSCs), provoked protective anti-tumor activity, which was dependent on $CD8^+$ T cells. Compared with PBS group, AMCV not only increased the percentages of $CD8^+IFN\text{-}\gamma^+$ and $CD4^+IFN\text{-}\gamma^+$ T-cells in spleen and tumor, but also decreased the percentages of MDSCs in spleen. The ^{51}Cr-release assay showed that spleen lymphocytes from mice immunized by AMCV exhibited a higher cytotoxicity against tumor cells, mixed cells derived from carcinoma and endothelial cells (also confirmed in IHC of tumor tissues with CD31).

Conclusions: AMCV was able to elicit anti-tumor immunity through multiple target including killing tumor cells and inhibiting angiogenesis, which might be a new strategy for cancer therapy in patients.

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