

## MEK1 WITHIN EXTRACELLULAR VESICLES INHIBITS TUMOR GROWTH BY PROMOTING ANTI-TUMOR IMMUNITY

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**Background** All cells have the capability to produce and release extracellular vesicles (ECVs), small vesicles that have similar topology to the cell and can deliver diverse cargo to mediate cell-cell communication. ECVs derive from the late endosomal pathway and contain bioactive cargo that can include lipids, nucleic acids (both RNA and DNA), and proteins. Once released into the extracellular space, ECVs can bind to and enter other cells, resulting in the physical transfer of bioactive cargo between cells, leading to functional changes in the target cell. Cancer cells secrete more ECVs than non-transformed cells. Tumor-derived (TD) ECVs can affect numerous cell types, including other cancer cells in an autocrine/paracrine manner and non-cancer host cells exerting both pro- and anti-tumor effects on immunity.

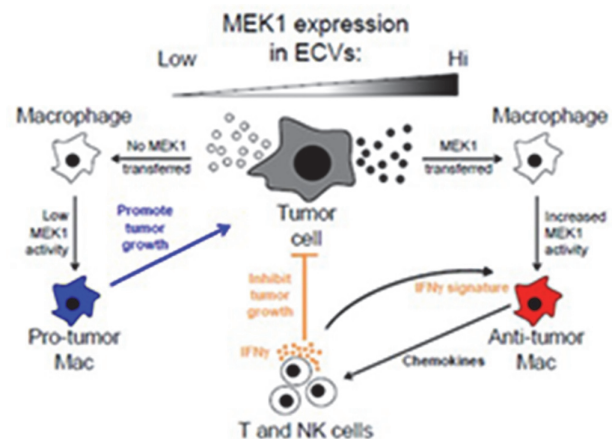
**Methods** To identify ECV proteins that could modulate immune responses, we have used a model of regressor and progressor cell lines that undergo immune rejection or progressive growth, respectively. We isolated ECVs from these cultured cell lines and performed proteomic analysis of the ECVs to identify unique proteins in ECVs secreted by regressor versus progressor cell lines. Having identified MEK1 as a unique protein in regressor-derived ECVs, we developed a model system to test the effect of MEK1-containing ECVs on tumor immunity.

**Results** We found that the signaling molecule MAP2K1 (MEK1) was enriched in ECVs secreted by regressor versus to progressor cells. ECVs engineered to have levels of MEK1 similar to regressor ECVs could inhibit tumor growth. In labeling experiments, ECVs were found to be taken up by tumor macrophages, delivering MEK1 into the cytoplasm, resulting in upregulation of certain genes such as chemokines. In tumors expressing MEK1 in ECVs, the microenvironment was enriched in cytolytic lymphocytes, resulting in induction of genes in the interferon gamma (IFN $\gamma$ ) pathway. Blocking IFN $\gamma$ , MEK1 inhibition, or lack of adaptive immunity prevented the effect of MEK1-containing ECVs. Our results support a mechanism by which MEK1 protein within certain ECVs is delivered to tumor macrophages to promote adaptive immune responses against the tumor via IFN $\gamma$  (figure 1).

**Conclusions** We conclude that MEK1 activity within exosomes and macrophages promote tumor immunity. These results suggest that the delivery of MEK1 to tumor-associated macrophages, either by ECVs, nanoparticles, or some other means, could be a useful strategy to treat cancer. On the other hand, the use of systemic MEK1 inhibitors in patients could reduce anti-tumor immunity. Therefore, targeting MEK1 inhibition to tumor cells could spare its putative immune suppressive effects.

**Acknowledgements** We acknowledge funding and conceptual support from The Hartwell Foundation.

**Ethics Approval** Animal studies were approved by the UCSD IACUC under protocol S06201.



**Abstract 984 Figure 1** Model of how MEK1-ECVs activate tumor immunity  
Tumor cells secreting ECVs that contain high levels of MEK1 can deliver MEK1 to macrophages, resulting in production of chemokines and recruitment of IFN $\gamma$ -producing lymphocytes, leading to tumor growth inhibition

<http://dx.doi.org/10.1136/jitc-2022-SITC2022.0984>