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Immunomodulation by tumor-derived exosomes

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Pancreatic cancer has a dismal prognosis, particularly when diagnosed at a stage prohibiting surgery. Immunotherapy might serve as an adjuvant therapy, which possibly could be supported by tumor exosomes.
However, though dendritic cell-derived exosomes induce, tumor cell-derived exosomes might suppress an immune response. To see whether immunosuppression by tumor exosomes is a general feature and what might be the underlying mechanisms, I explored whether and how tumor exosomes modulate an immune response with exsosomes from the rat pancreatic adenocarcinoma BSp73ASML (ASML), that support premetastatic niche preparation. ASML-exosomes bind to and are taken up by leukocytes *in vitro* and *in vivo*. Up-take by makrophages (CD11b+) exceeds that by T- and B-lymphocytes. Leukocytes respond to ASML-exosome up-take with reduced proliferation. Mitigated proliferative activity which is compensated by activated dendritic cells, is likely a consequence of reduced upregulation of the adhesion molecule CD44v6 which leads to impaired lck , ZAP70 and ERK1,2 phosphorylation. Instead, ASML-exosomes do not support regulatory T-cells or myeloid-derived suppressor cell expansion. Slightly increased apoptosis susceptibility relies on impaired activation of anti-apoptotic signals without alterations of receptor or mitochondrial caspase activation. IgM secretion of B-cells is unaffected and natural killer cells and cytotoxic lymphocyte activity are strengthened.
Exosomes interfere with leukocyte migration only transiently due to internalization of the migration-promoting receptors CD44, CD49d and CD62L during exosome up-take.

Notalbly, exosome-induced modulation of immune cells most likely relies on exosome up-take rather than binding, pointing towards an important contribution of transferred exosomal miRNA. As ASML-exosomes, which are taken up by all leukocyte subpopulations, have a minor impact on leukocyte activation that can be overridden by mitogens or dendritc cells, but support leukocyte effector functions, ASML-exosomes could well serve as a helpful tool in an anti-cancer immunotherapy. I expect that the features elaborated for ASML-exosomes also account for human pancreatic cancer exsosomes. Though an in vitro pre-check will be required, there is hope that tumor exsosomes isolated from patients' serum, could serve as an adjuvant in cancer immunotherapy.