Extracellular vesicles, immune responses and cancer

U932 - Immunity and Cancer

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Cells release in their environment membrane-enclosed vesicles collectively called “Extracellular Vesicles” (EVs), which are thought to act as intercellular messengers. Exosomes are a type of EV formed inside endocytic compartments, the multivesicular bodies (MVBs) and secreted in vitro upon fusion of these MVBs with the plasma membrane.

Our group analyses the roles of exosomes and other EVs secreted by immune cells (especially dendritic cells) and tumor cells in the immune responses established during tumor progression, with a view to evaluate the therapeutic potential of exosomes and/or EVs in cancer.

Fifteen years ago, we had initiated proteomic analyses of the composition of exosomes secreted by dendritic cells. We have shown that these EVs are distinct from EVs isolated from apoptotic cells, and thus are the result of an active process of secretion by live cells (Théry et al, J Cell Biol 1999, J Immunol 2011). Furthermore, we showed that exosomes secreted by dendritic cells bear antigen and MHC-peptide complexes and thus participate in induction of immune responses (Théry et al, Nature immunol 2002), especially when secreted by mature DCs (Segura et al, Blood 2005, J Immunol 2007). We also showed that forcing secretion of an antigen on their exosomes by tumors promoted induction of anti-tumor immune responses (Zeelenberg et al, Cancer Res 2008). Our results have been used to design a phase II clinical trial, at Institut Gustave Roussy and Institut Curie, using
We have also analysed the role in tumor progression of one of the major components of tumor cell- and mouse dendritic cell-derived EVs, called MFGE8/lactadherin. We observed that MFGE8 promotes VEGF-mediated angiogenesis (Silvestre, Théry et al, *Nature Med* 2005), bladder tumor progression via an effect on the host immune system (Sugano et al, *Oncogene* 2011), and survival and migration of ovarian cancer cells (Tibaldi et al, *Plos One* 2013). MFGE8 thus represents a potential target for novel anti-tumor therapies.

In the last 5 years, we have focused our research on the molecular mechanisms of biogenesis.
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and secretion of the different types of EVs, with a goal to find specific tools to affect their selective secretion, and thus understand their respective roles in tumor progression, and their potential use as targets or biomarkers in cancer. We have initially identified RAB27 small GTPases as required for exosome secretion by tumor cells, and used it to show an in vivo pro-tumoral role of exosome secretion by a murine tumor, although inhibition of exosome secretion by another tumor did not affect its progression.

Our cell biology studies have now evidenced the heterogeneity of the EVs secreted by dendritic and tumor cells, and we are currently focusing on unravelling their respective composition, including their differences and similarities with enveloped viruses, their immune functions, and the best ways to isolate and/or affect specifically secretion of the different EV subtypes.

Key publications

Year of publication 2019

Pérez PS1, Romaniuk MA1, Duette GA1, Zhao Z2, Huang Y2, Martin-Jaular L3, Witwer KW2,4, Théry C3, Ostrowski M1. (2019 Nov 6)
Extracellular vesicles and chronic inflammation during HIV infection.

Théry C1, Gho YS2, Quesenberry P3. (2019 Sep 11)
Journal of extracellular vesicles: the seven year itch!

Witwer KW1, Théry C2. (2019 Aug 1)
Extracellular vesicles or exosomes? On primacy, precision, and popularity influencing a choice of nomenclature.

Mathilde Mathieu, Lorena Martin-Jaular, Grégory Lavieu, Clotilde Théry (2019 Jan 4)
Specificities of secretion and uptake of exosomes and other extracellular vesicles for cell-to-cell communication.
Nature cell biology : 9-17 : DOI : 10.1038/s41556-018-0250-9
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Year of publication 2018

Clotilde Théry, Kenneth W Witwer, Elena Aikawa, Maria Jose Alcaraz, Gregory Lavieu, ... Lorena Martin-Jaular, ... Mathilde Mathieu, ... Mercedes Tkach,...., Ewa K Zuba-Surma (2018 Nov 23)


Year of publication 2017

Mercedes Tkach, Joanna Kowal, Andres E Zucchetti, Lotte Enserink, Mabel Jouve, Danielle Lankar, Michael Saitakis, Lorena Martin-Jaular, Clotilde Théry (2017 Sep 20)

Qualitative differences in T-cell activation by dendritic cell-derived extracellular vesicle subtypes.

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