Grenoble Alliance for Integrated Structural & Cell Biology

GRAL MASTER 2 RESEARCH SCHOLARSHIP - Program 2017 - 2018

INTERNSHIP PROPOSAL

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Research project title: CK2 dysregulation in breast cancer: Impact on cancer-derived exosomes.

5 Keywords to describe the project: Exosomes; metastasis, Protein kinase CK2, EMT, drug resistance

Description of the project (aims, experimental techniques, recommended background):

Exosomes which are micro-vesicles secreted from cells participate in intracellular communication [1]. Tumor-secreted exosomes are now emerging as critical messengers in tumor progression and metastasis. In particular, they have been implicated in the transfer of oncogenic features resulting in a phenocopy of the tumor and promoting resistance to chemotherapy. The multifunctional Protein kinase CK2 is overexpressed in metastatic breast cancer [2]. Unexpectedly, we found that in a subtype of breast cancer samples, a downregulation of its regulatory β subunit was associated with the acquisition of traits of epithelial-to-mesenchymal transition (EMT)[3]. The tumor promoting factor TGFβ triggers EMT and confers on epithelial cells, stem-like properties associated with resistance to conventional therapeutics. Recently, it has been shown that the activation of the cAMP pathway can reverse this TGFβ-induced EMT program [4]. Surprisingly, we found that EMT induced by CK2β downregulation was not reversible upon activation of the cAMP pathway suggesting additional genetic alterations. Our project aims to perform a comparative analysis of exosomes secreted by mammary epithelial cells (MCF10A) in which EMT has been induced either by TGFβ or depletion of CK2β. Bioactive molecules present in the exosomes (receptors, transcription factors, enzymes, extracellular matrix proteins) will be identified by M/S in collaboration with EDyP (CEA Grenoble). Nucleic acids (DNA, mRNA, miRNA) will be characterized by RT-qPCR.

1. Becker, A., et al., *Extracellular Vesicles in Cancer: Cell-to-Cell Mediators of Metastasis.* Cancer Cell, 2016. **30**(6): p. 836-848.
2. Giusiano, S., et al., *Protein kinase CK2alpha subunit over-expression correlates with metastatic risk in breast carcinomas: quantitative immunohistochemistry in tissue microarrays.* Eur J Cancer, 2011. **47**(5): p. 792-801.
3. Deshiere, A., et al., *Unbalanced expression of CK2 kinase subunits is sufficient to drive epithelial-to-mesenchymal transition by Snail1 induction.* Oncogene, 2013. **32**(11): p. 1373-83.
4. Pattabiraman, D.R., et al., *Activation of PKA leads to mesenchymal-to-epithelial transition and loss of tumor-initiating ability.* Science, 2016. **351**(6277): p. aad3680.

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Relevant publications of the team:

1. Giusiano, S., C. Cochet, O. Filhol, E. Duchemin-Pelletier, V. Secq, P. Bonnier, X. Carcopino, L. Boubli, D. Birnbaum, S. Garcia, J. Iovanna and C. Charpin (2011). "Protein kinase CK2alpha subunit over-expression correlates with metastatic risk in breast carcinomas: quantitative immunohistochemistry in tissue microarrays." Eur J Cancer 47(5): 792-801.

2. Deshiere, A., E. Duchemin-Pelletier, E. Spreux, D. Ciais, F. Combes, Y. Vandenbrouck, Y. Coute, I. Mikaelian, S. Giusiano, C. Charpin, C. Cochet and O. Filhol (2013). "Unbalanced expression of CK2 kinase subunits is sufficient to drive epithelial-to-mesenchymal transition by Snail1 induction." Oncogene 32(11): 1373-1383.

3. Burute, M., M. Prioux, S.Truchet, G.Blin, G.Letort, Q. Tseng, T. Bessy, J. Young, O. Filhol and M. Théry (2016). “Polarity Reversal Primes Cell Scattering during Epithelial to Mesenchymal Transition.” Dev Cell. In press