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PROJECT 2 (optional)

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Title: *Nucleosome count, genome plasticity and Epithelial-to-Mesenchymal-Transition (EMT) in cancer*

Curriculum: Basic and Applied Immunology and Oncology

Link to OSR/UniSR personal page:

<http://research.hsr.it/en/divisions/genetics-and-cell-biology/in-vivo-chromatin-and-transcription.html>

Project description (Number of characters, including spaces: 2.000 - 3.000):

Nucleosome count: Cell biology textbooks support the idea that all DNA is organized in nucleosomes, save for promoters and enhancers, where no or few nucleosomes are detectable. We challenged this idea and found that cells exploit nucleosome modulation by 30%, either up or down, [10.1371/journal.pbio.1001086, 10.1111/joim.12286] to respond to environmental cues. We proposed that nucleosome number regulation might represent a novel layer of epigenetic regulation.

Chromatin plasticity allows safe responses to environmental cues and, most importantly, in development. The unlimited potential to differentiate or not in pluripotent Embryonic Stem Cells (ESCs) is linked to an open chromatin state that is more accessible and dynamic relative to differentiated cells. ***We recently found that ESCs contain 50% of the nucleosomes*** as compared to differentiated cells [10.3389/fphys.2014.00330 and Cartoon]. This finding points to nucleosomes modulation as an additional hallmark of pluripotency, in addition to, and besides histone modifications.

Epithelial-mesenchymal transition (EMT) is a basic developmental process [10.1016/j.cell.2016.11.037] by which epithelial cells lose their cell-polarity and cell-cell adhesion, gain migratory and invasive properties and become similar to multipotent stromal cells that can further differentiate into a variety of cell types and have ESCs-like properties. Besides embryogenesis, EMT confers the same features to cancer cells that can exit the cancer mass, migrate to distant tissues and form metastasis.

We have recently found that cancer cells contain 1.5-fold more nucleosomes when compared with the normal counterpart [10.1093/nar/gkaa613]. When nucleosome reduction is applied, cancer cells show a distinct EMT transcriptional signature and more pronounced metastatic phenotypes appear, in vitro and in vivo (extravasation and parenchyma invasion of distal organs).

Our hypothesis posits that cancer cells actively modulate their nucleosome content to gain a phenotype that will facilitate metastasis spreading. Since little is known on chromatin structure in EMT, we will help the

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student answer one of the following open questions (or sub-questions) by providing cutting-edge technical tools and support:

1. What are the i) molecular changes in chromatin organization during EMT, ii) mechanisms regulating nucleosome abundance and iii) their impacts on transcription profiles.
2. How nucleosome-modulation, adhesion and invasion parameters are connected in vitro?
3. Can we reverse the “EMT phenotype” by up-modulating nucleosome number in vitro?
4. Can we rescue the cancer phenotype in metastatic cells in vivo by up-regulating nucleosomes?
5. What are the molecular steps regulating the dynamics of nucleosome loss during EMT in vivo?

Skills to be acquired by the student:

Basic cell and molecular biology techniques, ATAC-seq, RNA seq, Mass/spec, both in bulk and at single cell level, In vivo cancer engraftment, tumor growth by bioluminescence quantification, Immunostaining and ImmunoHistoChemistry, In vivo fluorescence microscopy.

References (max. 3)

10.1371/journal.pbio.1001086, 10.1111/joim.12286; 10.3389/fphys.2014.00330; 10.1093/nar/gkaa613