**PROJECT**

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| **Supervisor:** | Rosa Bernardi |
| Title: | Unraveling transposable elements regulation in cancer |
| *Curriculum*: | BAIO |
| Link to the personal page of the University or relevant hospital site website: | https://research.hsr.it/en/divisions/experimental-oncology/mechanisms-of-non-oncogene-addiction-in-cancer/rosa-bernardi.html |

**Description of the Project (max 3,000 characters including spaces)**

**Background/gap of knowledge**

The human genome comprises a large amount of repetitive DNA that was incorporated throughout evolution and plays at large unknown functions[1]. In this context, repetitive elements that derive from the domestication of ancient retroviruses are especially dangerous as some retain the capacity to retrotranspose, therefore they are epigenetically repressed to safeguard the genome[1]. However, the detailed molecular mechanisms of their inactivation remain to be clearly defined: several epigenetic modulators have been implicated in this process, but it is currently unknown if their activity is coordinated towards enduring repression or they exert context-specific functions[1]. In disease, the regulation of repetitive elements appears more complex. Interestingly, recent studies suggest that a general derepression of retrotransposons triggers efficient tumor-suppressive mechanisms in cancer[2], but a better understanding of their regulation is necessary to harness these processes for novel therapies.

**Rationale and hypothesis**

We will investigate the molecular mechanisms of repetitive DNA inhibition in cancer, with a specific focus on transposable elements of retroviral origin. We will test the hypothesis that a protein that evolved to fight viral infections[3] has been coopted during evolution to suppress both exogenous viruses as well as endogenous DNA of viral origin. Of note, this protein is overexpressed in certain tumors including breast and kidney cancer[4-7] and can be targeted with an FDA-approved compound. Therefore, we aim not only to improve our understanding of the molecular mechanisms of transposable elements regulation, but also to provide a new therapeutic tool to exploit the tumor suppressive consequences of their reactivation.

**Objectives and specific aims**

In this project, we will comprehensively map the genomic location and regulation of transposable elements in cell lines representative of breast and kidney cancer compared to their normal counterparts via transcriptome and epigenome analyses. Chromatin occupancy of epigenetic regulators will be mapped via Cut&Tag sequencing and different epigenetic modulators will be targeted via genetic and pharmacological means to reveal the regulatory landscape of repetitive elements. RNA sequencing datasets will be analyzed with specific bioinformatics tools designed to identify repetitive elements and the regulation of individual transposable elements will be analyzed based on their genomic position and evolutionary age. This project will be conducted in collaboration with the Computational Genomics Laboratory at the International School for Advanced Studies (SISSA) in Trieste, which has specific expertise on the analysis of repetitive elements.

**Expected outcomes**

With this project we aim to provide the first comprehensive map of the basal expression of repetitive elements in cancer cells, identify their regulatory mechanisms and study their deregulation upon epigenetic modulation.

**Skills that the student should acquire** (max. 600 characters including spaces):

The candidate will acquire wet lab and computational experience, including growth and manipulation of tumor cells in 2D/3D, RNA-, ChIP-, Cut&Tag and DNA methylation sequencing, write scripts and perform full bioinformatics analysis. At least one computational language and advanced computational analysis of repetitive DNA will be learnt in collaboration with the Computational Genomics Laboratory at the International School for Advanced Studies in Trieste. Also, the student will learn to design experiments, discuss results and published literature, present at meetings and write manuscripts.

**References** (max. 15)

1. Almeida MV, Vernaz G, Putman ALK, Miska EA. Taming transposable elements in vertebrates: from epigenetic silencing to domestication. 2022 Trends Genet 38:529-553.
2. Liang Y, Qu X, Shah NM, Wang T. Towards targeting transposable elements for cancer therapy. 2024 Nat Rev Cancer 24:123-140.
3. Patra U, Müller S. A Tale of Usurpation and Subversion: SUMO-Dependent Integrity of Promyelocytic Leukemia Nuclear Bodies at the Crossroad of Infection and Immunity. 2021 Front Cell Dev Biol 9: 696234.
4. Ponente M, Campanini L, Cuttano R, et al. Bernardi R PML promotes metastasis of triple-negative breast cancer through transcriptional regulation of HIF1A target genes. 2017 Jci Insight 2:e87380.

5. Fracassi C, Ugge' M, Abdelhalim M, et al. Bernardi R PML modulates epigenetic composition of chromatin to regulate expression of pro-metastatic genes in triple-negative breast cancer. 2023 Nucleic Acids Res 51:11024-39.
6. Simoni M, Menegazzi C, Fracassi C, et al. Bernardi R PML restrains p53 activity and cellular senescence in clear cell renal cell carcinoma. 2024 EMBO Mol Med 16:1324-1351.
7. Fracassi C, Simoni M, Uggè M,et al. PML is a constitutive component of chromatin domains enriched in repetitive elements and duplicated gene clusters in cancer cells. 2024 *Heliyon* 10:e36499.