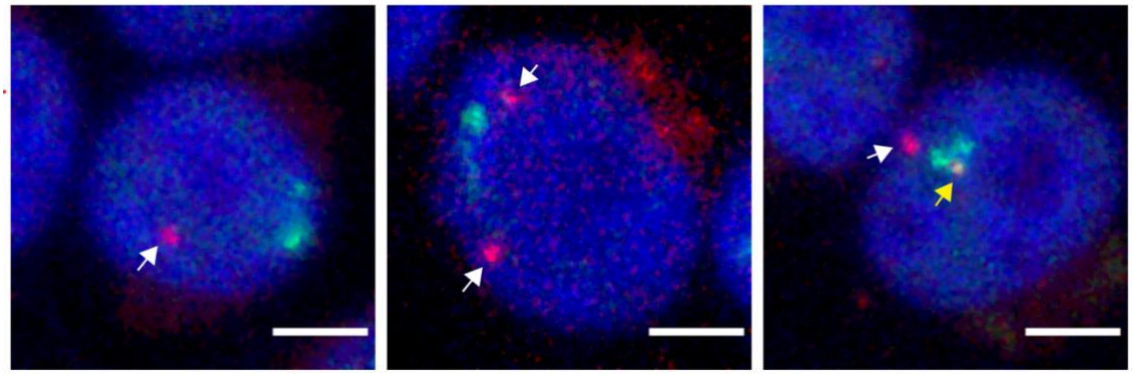
UNIVERSITY OF NAPLES FEDERICO II

DOCTORATE IN
MOLECULAR MEDICINE AND MEDICAL BIOTECHNOLOGY

XXXVI CYCLE

Alessandra Spaziano

"Understanding the reactivation of genes on the human inactive X chromosome in somatic cells"



2020-2023

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"Understanding the reactivation of genes on the human inactive X chromosome in somatic cells"

Tutor
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Candidate
Alessandra Spaziano

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Abstract

In mammals, X chromosome inactivation (XCI) silences one of the two X chromosomes in females (XX), to equalize gene expression with males (XY). The master regulator XCI is the lncRNA XIST, which coats the inactive X chromosome (Xi) and recruits other silencing factors to stabilize the inactivation. Studies in mice have shown that Xist coating is required for XCI initiation but becomes dispensable upon an initial developmental window. Recently, the loss of Xist/XIST or its de-localization from the Xi have, however, been associated with gene reactivation challenging the idea that Xist/XIST is not required for maintenance of Xi gene silencing.

The project aims to dissect X Chromosome Reactivation (XCR) mechanisms and their relevance to the sex bias in autoimmune diseases. In the first part, I engineered an experimental system to investigate the role of specific Transcription Factors (TFs) in the stochastic reactivation of Xi genes in somatic cells upon exit from mitosis. In the second part of the thesis, I investigated the (de-)localization of XIST in human T lymphocytes, a somatic cell type whose function underlies the sex bias in human autoimmune diseases. I showed that XIST is delocalized in naive T cells and partially re-localizes upon activation. I also showed that X-linked genes involved in autoimmune diseases present a bi-allelic signal, thus suggesting they escape XCI in T cells potentially leading to a sex-gene dosage unbalance. Finally, we devised a non-empirical way of evaluating XIST localization/delocalization and its association with Xi gene reactivation by high-throughput image analysis.