SCIENTIFIC SEMINAR

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Functional consequences of ALIX methylation by CARM1 on the completion of cytokinesis and the biogenesis of extracellular vesicles in triple-negative breast cancer cells

Triple negative breast cancer (TNBC) is characterized by higher rates of relapse, greater metastatic potential, and shorter survival compared to the other breast cancer subgroups. The aim of our laboratory is to better understand the molecular pathology of TNBC to identify new therapeutic targets to prevent tumor relapse and dissemination. We are evaluating the therapeutic potential of targeting enzymes mediating post-translational modifications that are overexpressed/activated in TNBC compared to normal breast tissues. After focusing on kinases, we are currently concentrating on the family of protein arginine methyltransferases (PRMT1-9) as therapeutic targets and analyzing their functions in TNBC (1-3). PRMTs catalyze the transfer of one or two methyl group(s) onto arginine to a wide range of cytosolic and nuclear substrates. By doing so, they regulate gene expression, pre-mRNA splicing, and DNA damage response. Multi-omics analyses of a Curie cohort composed of the different breast cancer subtypes revealed that some PRMTs are overexpressed in TNBC compared to normal breast tissues (1-3). We then demonstrated that PRMT1 and PRMT5 represent attractive therapeutic targets for TNBC (1-3). Recently, we have focused on PRMT4, also called CARM1 (4), which is also overexpressed in TNBC compared to normal tissues. To gain insight into its functions, we have characterized the CARM1 interactome in TNBC cell lines. Mass-spectrometry analysis identified ALIX, an Endosomal Sorting Complex Required for Transport (ESCRT) accessory protein, as a main endogenous CARM1 partner. We found that endogenous ALIX is methylated on several arginine within its proline-rich domain (PRD) in a TNBC cell line, and that CARM1 methylates these residues in vitro. The PRD of ALIX serves as a platform for protein-protein interactions which participate to the various cellular ALIX functions such as cytokinesis, plasma membrane damage repair, virus budding, multivesicular body formation, and extracellular vesicle biogenesis. We hypothesize that arginine methylation will interfere with, or promote protein-protein interactions, consequently regulating ALIX functions. Therefore, we are currently addressing the impact of ALIX methylation on its cellular functions.

(1) Suresh et al. (2022) PRMT1 Regulates EGFR and Wnt Signaling Pathways and Is a Promising Target for Combinatorial Treatment of Breast Cancer. Cancers, 14, 306

(2) Vinet et al. (2019) PRMT5: a novel therapeutic target for triple-negative breast cancers. Cancer Med., 8, 2414-2428

(3) Suresh et al. (2022) Expression, localization, and prognosis-association of MEP50 in breast cancer. Cancers, 14, 4766

(4) Suresh et al. (2021) CARM1/PRMT4: Making its mark beyond its function as a transcriptional coactivator. Trends Cell Biol., 31, 402-417

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