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Role of proteins involved in epithelial integrity and polarity, regulated by (de)phosphorylation by Syk or PTPN13, in mammary tumour invasion

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Introduction

The spleen tyrosine kinase (Syk) and tyrosine-protein phosphatase non-receptor type 13 (PTPN13) were described in hematopoietic cells with pro-oncogenic effects. Our team and others observed, however, that Syk and PTPN13 are also expressed in non-hematopoietic cells and established their role as tumor suppressors in mammary epithelial cells. To better understand their negative role in breast cancer, our team recently demonstrated a role of these proteins in cell junction stabilization (Hamyeh et al., *Theranostics*, 2020; Kassouf et al., *Cancers*, 2019). However, the downstream signaling effectors of Syk and PTPN13 remain largely unknown.

Material and Methods

Using phosphoproteomics and interactomics approaches, we identified Rho guanine nucleotide exchange factor 7 (ARHGEF7) and Par-3 family cell polarity regulator (PARD3) as common putative effectors of Syk and PTPN13. In this study, we aim to investigate whether these proteins are direct partners or substrates of Syk and PTPN13. Their function, consequences of their (de)phosphorylation and role in epithelial integrity in 2D/3D models are being studied. In addition, we will investigate these proteins of interest in genetically-engineered mouse models in order to unravel their function *in vivo*. Based on the obtained results, clinical studies will later on be performed on breast cancer biopsies.

Results and Discussions

We showed that PARD3 and ARHGEF7 co-immunoprecipitate with Syk and PTPN13. Immunofluorescence analysis on MCF7 cells revealed the colocalization of Syk and PTPN13 with PARD3 and ARHGEF7 at cell-cell junctions. Notably, enhanced Syk expression and activation increased PARD3 recruitment at cell-cell junctions. Moreover, we developed various assays allowing us to explore PARD3 and ARHGEF7 functions and extended our studies to an additional breast cancer cell line, MCF10DCIS, clinically relevant for cancer research and drug development.

Conclusion

This study will characterize new signaling effectors through which Syk and PTPN13 exert their anti-proliferative and anti-invasive effects in epithelial cells, which may ultimately aid to identify novel biomarkers and therapeutic targets.