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Mechanism of SIGIRR$^{\Delta E8}$-mediated ER retention and its implications for colorectal tumor progression

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Statement of the Problem: Colorectal cancer (CRC) is second most common cancer in Europe, with 450,000 new cases each year. A critical step in the pathogenesis of CRC is the inactivation of tumor suppressor genes. We have previously shown that the single immunoglobulin IL-1 receptor related molecule (SIGIRR) functions as a tumor suppressor in animal models of CRC. Recently, we have found that SIGIRR is frequently inactivated in human CRC by the increased expression of a novel SIGIRR isoform (SIGIRR$^{\Delta E8}$), which is generated by an alternative splicing. SIGIRR$^{\Delta E8}$ functions as a dominant negative mutant that inactivates the full-length SIGIRR protein by trapping it in the ER, *via* interaction with ER resident protein - ribophorin 1 (RPN1).

Aim: The aim of this study was to determine the mechanism of SIGIRR$^{\Delta E8}$-mediated ER retention.

Methodology & Theoretical Orientation: A major difference between full-length and SIGIRR$^{\Delta E8}$ is the unique C- terminus generated by the frameshift resulted from exon 8 skipping. The unique peptide contains several arginine residues that conform to the arginine-based ER retention signal motif. By mutating these residues, we sought to determine whether the arginine motif is bona fide ER retention signal.

Findings: Using confocal microscopy, we analyzed localization of overexpressed full-length, SIGIRR$^{\Delta E8}$ and SIGIRR$^{\Delta E8}$ ER retention signal mutants. The immunostaining analysis revealed weaker ER retention and stronger cell membrane localization of ER mutants compared to the SIGIRR$^{\Delta E8}$.

Conclusion & Significance: Removal of the putative arginine-based ER retention signal motif by point mutations leads to the restoration of membrane expression of SIGIRR$^{\Delta E8}$. Our hypothesis predicts that loss of the ER retention signal would also abolish the dominant negative function of SIGIRR$^{\Delta E8}$ as it could no longer trap full-length SIGIRR in the cytoplasm. Further studies are required to evaluate overall impact of loss of ER retention and its implication for CRC tumor promotion.

Biography

Malgorzata Bodaszewska Lubas is currently a Scientific Assistant in the Immunology Department at the Faculty of Biochemistry, Biophysics and Biotechnology of Jagiellonian University, Kracow, Poland. She is involved in the project seeking to elucidate the mechanism of epigenetic-driven inactivation of tumor suppressor SIGIRR. She has Master's degree in Medical Analysis and a PhD degree in Microbiology from Jagiellonian University. Her research interest lies in the field of Microbiology (especially lactic acid bacteria, bacteriocins, gut microbes) and Medical Diagnostic. Her area of interest includes nutrition, impressionism and traveling.

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