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European Endocrinology and DIABETES CONGRESS

August 05, 2021 | Webinar

A Promising Druggable target in Breast Cancer Progression: Oxer1 and Rack1-associated pathway

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Background: BC is a heterogeneous disease due to variable histological subtypes and differences in response to therapy and clinical outcome. In BC, RACK1 was reported as putative prognostic marker and drug target due to its critical role in cancer cell migration and invasion. RACK1 increased expression negatively correlates with overall survival by promoting BC progression. Important binding sites on RACK1 promoter were found through in silico analysis, including c-Rel sites and a Glucocorticoid Responsive Element. Hence, RACK1 expression is controlled by a complex glucocorticoids-androgens balance and due to the hormonal nature of most BC types, androgen signaling in BC and its role in regulating RACK1 transcription became of pivotal interest. In this regard, an important role is now emerging for OXER1, a membrane androgen receptor (mARs) involved in activating PI3K/Akt/NF-κB and FAK signaling pathways to promote survival, cell adhesion and migration. Methods: MCF7 and MDA-MB-231 treated with testosterone, testosterone-BSA-FITC, or nandrolone were analyzed to assess whether RACK1 transcriptional regulation was AR- or mAR-dependent, involving PI3K/Akt/NF-κB pathway. To this purpose luciferase reporter assay, qPCR, immunoblotting, cell proliferation, colony formation assay, cytofluorometry and scratch-wound healing assay were performed. Nandrolone-mediated OXER1-initiated effects were confirmed by in silico molecular docking and immunofluorescence. Finally, we validated our panel with patient-based transcriptomic data. Results: Our data confirmed RACK1 involvement in BC progression and provide evidence that nandrolone exerts negative effects on BC cell proliferation and migration by antagonizing PI3K/Akt/NF-κB pathway, ultimately down-regulating RACK1. Nandrolone impairs this signaling pathway through its binding to OXER1, whose increased expression is higher in tumors tissue compared to non-cancerous ones and correlated with ER and PR status in patients. Conclusions: Our data support the idea that androgen derivatives tailored to antagonize OXER1 activation pathway may represent a promising and rational agents for the personalized treatment of TNBC.

Biography

Erica Buoso is an Assistant Professor of Pharmacology and Pharmacotherapy at the University of Pavia. She is currently working on a project that aims to elucidate Oxoeicosanid Receptor 1 (OXER1)-mediated scaffold and ribosomal protein RACK1 (Receptor for Activated C Kinase 1) hormone-dependent transcriptional regulation and their role in breast cancer migration and proliferation. She also joined an international collaboration with Prof. Emanuela Corsini of the University of Milan to study PKCβ and its anchoring protein RACK1, in immune cell activation, and their implication in immunosenescence and immunotoxicity. Therefore, RACK1 may represent an interesting target of steroid-active compounds, and its evaluation may offer the opportunity to screen the immunotoxic potential of hormone-active substances.

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