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Immunological implications of Endocrine Disrupting Chemicals (EDCs): RACK1 as a bridge between the Endocrine and the immune systems

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Background: RACK1 (Receptor for Activated C Kinase 1) has a central role in the immune system after the strong correlation demonstrated between its expression and immune cells activation via PKC. This has been shown to result in the modulation of pro-inflammatory cytokines TNF-α and IL-8 in vitro, in vivo and ex vivo. Because of the presence of a hormone-related regulatory element for androgens and glucocorticoids in RACK1 gene promoter that mediates its transcriptional regulation, we hypothesized that hormone-active substances can affect the immune response via RACK1 modulation. EDCs (Endocrine Disrupting Chemicals) have been shown to induce immune alterations by exerting inflammation-enhancing and immunosuppressive actions and a role for EDCs in the increased incidence of cancers, autoimmune diseases, and allergies in most industrialized countries has been hypothesized. Therefore, the aim of our study is to assess how EDCs interfere with the immune response by modulating RACK1 expression and to elucidate the mechanisms behind their immunological implications. Methods: To investigate EDCs ability to modulate RACK1 expression, human promyelocytic THP-1 cells were treated with increasing concentrations of anti-androgen p,p'DDT, p,p'DDE, Vinclozolin (VCZ), Atrazine (ATZ) and Cypermethrin (CYP), estrogen-active compounds 17β-estradiol, 17β-estradiol-BSA, diethylstilbestrol (DES), zearalenone (ZEA) and ethynyl-estradiol (EE) and, finally, Perfluorooctanesulfonic acid (PFOS), Diethylphthalate (DEP), bisphenols A, AF and S (BPA, BPAF, BPS), flutamide, BAY 11-7082 (NF-κB inhibitor) and agonist G1. Luciferase reporter assay, qPCR, Western blot analysis, specific sandwich ELISA and flow cytometric analysis were performed. Results: p,p'DDT, p,p'DDE, VCZ, ATZ, CYP (all AR antagonists), PFOS and DEP (GR agonists) induced a significant decrease in RACK1 transcriptional activity, RACK1 expression, LPS-induced IL-8 and TNF-α production and CD86 expression. On the other hand, 17β-estradiol, DES, ZEA and EE (through GPER activation) increased RACK1 transcriptional activity and its expression, which paralleled an increase in LPSinduced IL-8, TNF-α production, and CD86 expression all dependent on RACK1/PKCβII activation. Flutamide completely prevented DES-induced RACK1 transcriptional activity and protein expression, confirming a role for AR in RACK1 transcription regulation. Finally, while BPS displayed up regulating effects on RACK1 production and consequent cytokine release, BPA and BPAF initially down regulated RACK1 but mifepristone, flutamide and BAY 11-7082 unmasked up regulating effects and shed light on their mechanism of action. Conclusions: The complex effect resulting from the activity as antagonist or agonist of hormone-active substances shows how RACK1 modulation and its PKC-mediated downstream effects in the immune context are of important interest. Therefore, RACK1 represents a bridge between the immune and the endocrine systems, indicating its relevance as target of steroid-active substances and EDCs. This offers the possibility to exploit RACK1 as a tool to screen EDCs for their immunotoxic potential.

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.