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IMMUNOLOGICAL IMPLICATIONS OF ENDOCRINE DISRUPTING CHEMICALS (EDCS): EMERGING ROLE OF RACK1 AS EDCS SCREENING TOOL

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Background: Cancers, autoimmune diseases and allergies arose in most industrialized countries, and a role of endocrine disrupting chemicals (EDCs) has been hypothesized. EDCs have been linked with immune alterations due to inflammation-enhancing and immunosuppressive properties. Therefore, elucidating how EDCs interfere with the immune response is becoming of pivotal interest. Since we demonstrated a tight correlation between RACK1 expression and immune cells activation via PKC, RACK1 was investigated as an EDC target. Indeed, a hormone-related regulatory element for glucocorticoids and androgens was found in rack1 gene promoter to mediate its transcriptional regulation, resulting in modulation of cytokine production. Methods: To investigate EDCs ability to modulate RACK1 expression, human promyelocytic THP1 cells were treated with increasing concentrations of p,p'DDT (weak AR antagonist), p,p'DDE (strong AR antagonist), nandrolone (AR agonist), estrogen-active compounds 17β-estradiol, 17β-estradiol-BSA, diethylstilbestrol (DES), zearalenone (ZEA), flutamide and agonist G1. Luciferase reporter assay, qPCR, Western blot analysis and specific sandwich ELISA and flow cytometric analysis were performed. Results: p,p'DDT and p,p'DDE induced a significant decrease in RACK1 transcriptional activity, RACK1 expression, LPS-induced IL-8 and TNF-α production and CD86 expression. Consistent with its stronger AR antagonistic effect, p,p'DDE exerts a stronger repressor effect than p,p'DDT. On the other hand, 17β-estradiol, DES, and ZEA (through GPER activation) increased RACK1 transcriptional activity and its expression, which paralleled an increase in LPS-induced 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. Conclusions: A complex effect results from the activity as agonist or antagonist of estrogens, androgens or glucocorticoids indicating that RACK1 could be a relevant target of steroid-active compounds and EDCs. Hence, RACK1 represents a bridge between the endocrine system and the innate immune system, offering the opportunity to use RACK1 as a possible screening tool for immunotoxic potential of hormone-active substances.

Biography

Mirco Masi is a PhD student at University School for Advanced Studies IUSS in Pavia. He is currently working on a project that aims to understand the involvement of scaffold and ribosomal protein RACK1 (Receptor for Activated C Kinase 1) in breast cancer migration and proliferation. As a collaborator, he joined an international project to study RACK1 role in immune system activation and cytokines release via PKCβII in toxicology context, with a specific focus on the effects of different types of Endocrine Disrupting Chemicals (EDCs) on RACK1 expression and their immunologic implications.

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