

EDCs function in tumor microenvironment

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Endocrine disruptors (EDCs) can display estrogenic and androgenic effects, and their exposure has been linked to increased cancer risk. EDCs have been shown to directly affect cancer cell regulation and progression, but their influence on tumour microenvironment is still not completely elucidated. In this context, the signalling hub protein RACK1 (Receptor for Activated C Kinase 1) could represent a nexus between cancer and the immune system due to its roles in cancer progression and innate immune activation. Since RACK1 is a relevant EDCs target that responds to steroid-active compounds, it could be considered a molecular bridge between the endocrine-regulated tumour microenvironment and the innate immune system.

Keywords: cancer ; endocrine disruptors ; tumour microenvironment ; signal transduction ; RACK1 ; immune system ; EMT ; ER ; cytokine release ; inflammation

1. Introduction

Steroid hormones can interact with specific receptors, orchestrating a vast set of physiological functions, including growth, development, reproduction, energy imbalance, metabolism, immunity and behaviour ^[1]. These hormones derive from cholesterol and can be divided into corticosteroids (glucocorticoids and mineralocorticoids) and sex steroids (androgens, oestrogens, and progestogens). Steroid hormones are present in body fluids and act at nanomolar concentrations to ensure a continual dialogue between the endocrine system and the other two main communication systems of the body, the nervous system and the immune system. Any alteration of the endocrine system may also affect these other two systems ^[1]. In this regard, certain man-made and natural chemicals, known as endocrine-disrupting chemicals (EDCs), have been reported to affect the endocrine system functions, interfering with hormone action, thereby increasing the risk of adverse health outcomes ^[2] including reproductive impairment ^{[3][4][5]}, cognitive deficits ^{[6][7][8]}, metabolic diseases and disorders ^{[9][10]} and various tumours, mainly breast (BC) and prostate cancer (PC) ^{[11][12][13][14]}.

Human exposure to EDCs can occur via ingestion (food, dust and water), via inhalation (gases and particles in the air) and through the skin. EDCs can be found in food contact materials, cosmetics, consumer goods (including furnishings, cleaning products), toys, as well as in drinking water. Moreover, EDCs can act on similar or different pathways displaying cumulative or synergistic effects. These effects can be observed in different temporal windows (i.e., pre- and postnatal life, puberty and adulthood), with adverse effects in both the short- and long-term ^[15]. Hence, the deleterious effects of EDCs represent a health issue due to their potency, constant and universal human exposure ^[16].

EDCs are known to display hormonal features, including oestrogen and androgen activities, and they have been correlated with increased tumour risk considering their effects on cancer progression ^{[11][12][13][14]}. The tumour microenvironment plays an important role in establishing the cancer phenotype by interacting with the immune system. The role of EDCs in modulating the tumour microenvironment has not been elucidated, but is of pivotal interest. In this regard, the scaffold protein Receptor for Activated C Kinase 1 (RACK1) is an EDC target in the immune context ^{[17][18][19][20]} and an important molecular player for cancer progression (reviewed in ^[21]). Therefore, EDCs-mediated RACK1 regulation in both contexts could be central to understand the role of endocrine-mediated microenvironment regulation and to link innate immune activation with cancer progression through RACK1.

2. Tumour Microenvironment (TME) and EDCs

2.1. Tumour Microenvironment as Promoter of Cancer Progression

The tumour mass consists of a heterogeneous population of cancer cells together with different resident and infiltrating host cells, secreted factors and extracellular matrix proteins, collectively known as the tumour microenvironment (TME) ^[22]. The dynamic interactions of cancer cells with their microenvironment consisting of stromal cells including stromal fibroblasts, endothelial cells and immune cells like microglia, macrophages and lymphocytes and the non-cellular

components of extracellular matrix (ECM) such as collagen, fibronectin and laminin [23][24] are essential to promote cancer cell progression and metastasis [25]. Indeed, this intercellular crosstalk consists of a composite network of soluble factors (e.g., ECM remodelling enzymes, growth factors, cytokines, chemokines and inflammatory mediators), ECM, cell components and new emerging entities, such as exosomes, cell-free DNA (cfDNA), circulating tumour cells (CTCs) and apoptotic bodies [26][27]. The reciprocal cell–cell and cell–ECM interactions and the tumour cell hijacking of non-malignant cells force stromal cells to lose their function and acquire new phenotypes that promote the development and invasion of tumour cells [25], making the role of TME pivotal in favouring carcinogenesis and loss of tissue integrity [28][29]. Since tumour development is highly influenced by microenvironment dynamics, understanding how the different TME components potentially affect cancer progression is of central interest.

Among all tumour cells interactors in TME—which also include multifunctional pericytes involved in angiogenesis and tumorigenesis [30][31], tumour endothelial cells that support primary tumour growth [32] and cancer-associated fibroblast (CAFs) that produce ECM proteins for immunosuppression, recruit immunosuppressive cells and support tumour cells proliferation [33][34][35]—tumour-associated macrophages (TAMs) play a pivotal role as cellular components of the immune system. TAMs are key TME elements capable of affecting cancer cell behaviour [36] through migration-stimulating factors that favour tumour cell motility, metastatisation [37] and enhance cancer cell stemness by promoting Epithelial-Mesenchymal transition (EMT) [38][39]. In addition, modification of ECM composition and organisation (mostly performed by CAFs [40][41]) can also influence and promote tumour phenotype and metastasis formation when stiffness/rigidity, tension and molecular density are altered [42].

2.2. Immune System in TME and Its Tumour-Associated Macrophages

An important role in TME regulation is held by the host immune system, which has been reported to be involved in controlling development and progression of the tumour [43]. Indeed, during tumour development, cancer cells become resistant to the innate immune response and impair the adaptative response [44][45][46]. Cytotoxic CD8⁺ memory T cells, a common type of T lymphocytes in the TME, are capable of killing tumour cells [47] through the recognition of tumour-specific antigens and the consequent triggered, tri-phasic pathway immune response [48]. CD8⁺ T cells in the TME are supported by CD4⁺ T helper 1 cells (Th1), that release interleukin-2 (IL-2) and interferon-gamma (IFN- γ) [46] and Th2 cells-producing IL-4, IL-5 and IL-13 to support B cell response [49]. However, other immune cell populations can favour cancer progression by altering TME. In this regard, Th17 cells at TME level release IL-17A, IL-17F, IL-21 and IL-22 with antimicrobial action that favours tissue inflammation and promote tumour growth [48][49]. B lymphocytes in TME have been shown to play pivotal roles in regulating cancer cell proliferation and survival, induce chemoresistance and immune escape, and have also been linked to cancer-induced immunosuppression by initiating TGF- β -dependent conversion of FoxP3⁺ cells that contribute to tumour metastatisation [50][51]. CAFs have been reported to favour cancer cell proliferation by supporting metastatic site growth [52][53] and secreting fibroblast secreted protein-1 (FSP1) and other cytokines involved in initiating metastatisation in different cancer types, including BC [53][54].

A pivotal role in determining the importance of TME in cancer development and progression is held by TAMs, which support cancer cell invasion and clonal expansion by favouring tissue remodelling (e.g., Epidermal Growth Factor, EGF; matrix metalloproteinase-2 and 9, MMP2, MMP9; Membrane type 1-matrix metalloproteinase, MT1-MMP) and pro-inflammatory molecules (e.g., IL-1 β , TNF- α and C-X-C motif chemokine ligand 10 (CXCL10)) [55]. Moreover, TAMs immune functions can facilitate tumour cell proliferation, migration and survival through cancer cell-induced release of specific growth factors and cytokines [56], while expression of vascular cell adhesion molecule 1 (V-CAM1) allows TAMs proliferation upon differentiation into inflammatory monocytes [57].

2.3. EDCs as Landscape Shapers in BC- and PC-Associated TME

It is noteworthy that EDCs can affect oestrogen signalling cascades by promoting a crosstalk between BC cells and fibroblasts, which have been shown, for example, to increase aromatase expression or secrete several growth factors able to trigger rapid oestrogen-related pathways in cancer cells [58], ultimately contributing to cancer cell progression, invasion and metastasis formation. Indeed, EDCs in stromal cells are capable of mediating cellular differentiation and survival mechanisms [59][60][61], although their effect on ER α -, ER β -, and GPER-related functions and expression in the stromal components still needs to be demonstrated.

BPS has been shown to exert oestrogenic activity on stromal and stem cells in BC context [62][63] and to enhance lipid accumulation through an ER-mediated mechanism [63], while BPA is capable of promoting cell survival after DNA damage [64] and driving adipocyte differentiation through its ERR- γ activity [64][65]. Moreover, DDT and its metabolite DDE have been reported to induce an oestrogenic microenvironment in breast adipose tissue, which may support cancer phenotype establishment. In this regard, oestrogen-mediated signalling was observed to display an important impact on ECM matrix

composition [66]. Breast tumourigenesis and malignancy is tightly linked with differential collagen crosslinking and clustered integrin-mediated formation of focal adhesion, resulting in increased tumour stiffness [67]. In turn, integrin clustering and consequent increased tumour rigidity have been shown to promote cancer growth by enhancing growth factor signalling and focal adhesion assembly [68]. Interestingly, BPA has been reported to increase collagen fibre content and cell proliferation [69], suggesting that EDCs can influence matrix remodelling in a pro-tumorigenic manner. Indeed, high collagen content has been associated with increased carcinogenesis and oestrogenic signalling was observed to modulate collagen, integrin, MMP2 and MMP9 expression in BC context [70][71][72], supporting the hypothesis that environmental EDCs exposure may play a mechano-transductive role in oncogenic ECM remodelling and cell-ECM crosstalk, especially in TME context [73].

Regarding PC, EDC exposure has been reported to possibly reprogram or transform adult prostate progenitor cells favouring their tumour-initiating capacity through ER signalling pathways. In this regard, BPA has been shown to display carcinogenic potential by inducing PC cell proliferation, differentiation defects of the adult epithelium, thus predisposing to prostate dysplasia. Moreover, BPA has also been observed to induce epigenetic mechanisms leading to PC cell reprogram. These considerations highlight the potential to provide evidence for an effect of EDCs exposure on human prostate [74]. However, literature data lack studies on PC-related TME involvement and the possible role of EDCs in this context.

In light of the effects of different classes of EDCs on BC and PC development and progression discussed in the previous section, investigating EDCs role in TME functional alteration may allow a deeper understanding of EDCs effects not only on the tumour stromal component (i.e., fibroblasts) and their consequent involvement in cancer initiation and progress [75], but also on the immune system cells that are present within the TME and that could play an important role in establishing tumour development and progression. In this regard, accumulating evidence suggests that EDCs can affect the immune system and induce functional alteration in the immune response—both innate and adaptive [76][77]—potentially resulting in adverse reactions, immunosuppression, autoimmunity and enhanced immunostimulation [78]. Notably, TNF α , a pleiotropic cytokine involved in body's inflammatory response, is mainly produced by monocytes and macrophages after phthalates exposure [79]. In addition, EDCs can modulate production and release of several pro-inflammatory interleukins, including IL-1 β , IL-6 and IL-8 [79]. Moreover, enhanced DEHP-induced chemokine production [80] and increased BPA-mediated monocyte chemotactic protein (MCP-1 also known as CCL2) were observed [81]. EDCs have also been reported to hamper neutrophils function (e.g., DDT-induced decreased chemotaxis, phagocytosis adhesion and oxygen-dependent killing) as well as affect maturation of dendritic cells (DCs). In this regard, BPA decreases DCs endocytic ability [82] and increases release of IL-5, IL-10 and IL-13 upon TNF α [83]. Furthermore, DEHP and BPAF can suppress ERK1/2 and NF- κ B activation in DCs, affecting their maturation [82]. In lymphocytes context, DDT decreases NF- κ B expression, ultimately leading to reduced IL-2 production [84].

EDCs can display their effect on the immune system through several mechanisms that mainly involve estrogenic receptors ER, ERRs, PPAR γ and GPER, thyroid receptors and AhR [85]. In this regard, phthalates and BPA have been shown to induce alteration of cytokines levels through ER-mediated signalling. Moreover, BPA alters ER and ERRs expression in a dose and sex-specific manner. Indeed, BPA was observed to influence T-cell function through ERR α expression modulation, suggesting that EDCs may exert their immunomodulatory activities by targeting ERRs [86]. In addition, BPA acts as antagonist for PPAR γ , an adipocyte-specific receptor involved in adipogenesis with typically anti-inflammatory effects, indicating that EDCs can promote a pro-inflammatory phenotype in immune cells [86].

3. RACK1 as a Possible Target of EDCs

Literature data here presented strongly suggest a tight correlation between EDCs exposure and their involvement in cancer development and progression and, on the other hand, in alterations of the immune system through their activity on TME and cellular signalling cascades. In this regard, the identification of RACK1 as a possible EDC target in the immune context and, at the same time, its importance in tumour progression may indicate that RACK1 could play a dual role in BC- and PC-associated TME establishment and in modification of the immune response, particularly related to xeno-oestrogenic EDCs.

Oestrogenic EDCs (e.g., BPA, DES, ZEA) can promote the proliferation and migration of hormone-responsive and triple-negative BC cells where RACK1 appears to be involved due to its role in favouring proliferation and Epithelial-Mesenchymal Transition (EMT). Oestrogenic EDCs can display cancer-promoting effects by inducing alterations in the immune system, including an increased release of pro-inflammatory cytokines and ECM-remodelling factors.

Altogether, these observations highlight the importance of a deeper understanding of EDCs immunomodulatory effect in TME context, based on the consideration that alteration of released cytokine pattern and other immune-related features can affect cancer development and progression. In this regard, investigating molecular EDC targets in both contexts is of pivotal interest for a better characterisation of the crosstalk between the different TME components able to influence reciprocally.

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