EDCs function in tumor microenvironment

Subjects: Oncology & Oncogenics
Submitted by: Erica Buoso

Definition

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.

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, metastasisation [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 metastasisation [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 metastasisation 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-1β, 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 ERα-, ERβ-, 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 [61] 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, TNFα, 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-1β, 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 wells 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 TNFα[83]. Furthermore, DEHP and BPAF can suppress ERK1/2 and NF-κB activation in DCs, affecting their maturation [82]. In lymphocytes context, DDT decreases NF-κB 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, PPARγ 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 ERRα expression modulation, suggesting that EDCs may exert their immunomodulatory activities by targeting ERRs [86]. In addition, BPA acts as antagonist for PPARγ, 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.

References

1. Whirledge, S.; Cidlowski, J.A. Chapter 5—Steroid Hormone Action. Yen and Jaffe's Reproductive Endocrinology (Eighth Edition), Physiology, Pathophysiology, and Clinical Management; Eds: Strauss, J.; Barbieri R. Elsevier 2018; pp. 115–131.e4.
2. La Merrill, M.A.; Vandenberg, L.N.; Smith, J.R.; Goodson, W.; Browne, P.; Patisaul, H.B.; Guyton, K.Z.; Kortenkamp, A.; Cogliano, V.J.; Woodruff, T.; et al. Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. Nat. Rev. Endocrinol. 2020, 16, 45–57, doi:10.1038/s41574-019-0273-8.
3. Axelstad, M.; Hass, U.; Scholze, M.; Christiansen, S.; Kortenkamp, A.; Boberg, J. EDC IMPACT: Reduced sperm counts in rats exposed to human relevant mixtures of endocrine disrupters. Endocr. Connect. 2018, 7, 139–148, doi:10.1530/ec-17-0307.
4. Johansson, H.K.L.; Svingen, T.; Fowler, P.A.; Vinggaard, A.M.; Boberg, J. Environmental influences on ovarian dysgenesis—Developmental windows sensitive to chemical exposures. Nat. Rev. Endocrinol. 2017, 13, 400–414, doi:10.1038/nrendo.2017.36.
5. Skakkebaek, N.E. A Brief Review of the Link between Environment and Male Reproductive Health: Lessons from Studies of Testicular Germ Cell Cancer. Horm. Res. Paediatr. 2016, 86, 240–246, doi:10.1159/000443400.
6. Amano, I.; Takatsuru, Y.; Khairinisa, M.A.; Kokubo, M.; Haijima, A.; Koibuchi, N. Effects of Mild Perinatal Hypothyroidism on Cognitive Function of Adult Male Offspring. Endocrinology 2018, 159, 1910–1921, doi:10.1210/en.2017-03125.
7. Ghassabian, A.; Trasande, L. Disruption in Thyroid Signaling Pathway: A Mechanism for the Effect of Endocrine-Disrupting Chemicals on Child Neurodevelopment. Front. Endocrinol. 2018, 9, 204, doi:10.3389/fendo.2018.00204.
8. Jefferson, W.N.; Kinyamu, H.K.; Wang, T.; Miranda, A.; Padilla-Banks, E.; Suen, A.A.; Williams, C.J. Widespread enhancer activation via ERα mediates estrogen response in vivo during uterine development. Nucleic Acids Res. 2018, 46, 5487–5503, doi:10.1093/nar/gky260.
9. Alonso-Magdalena, P.; Vieira, E.; Soriano, S.; Menes, L.; Burks, D.; Quesada, I.; Nadal, A. Bisphenol A Exposure during Pregnancy Disrupts Glucose Homeostasis in Mothers and Adult Male Offspring. Environ. Health Perspect. 2010, 118,

1243–1250, doi:10.1289/ehp.1001993.
10. Cano-Sancho, G.; Salmon, A.G.; La Merrill, M.A. Association between Exposure to p,p ′-DDT and Its Metabolite p,p ′-DDE with Obesity: Integrated Systematic Review and Meta-Analysis. Environ. Health Perspect. 2017, 125, 096002, doi:10.1289/ehp527.
11. Heindel, J.J.; Skalla, L.A.; Joubert, B.R.; Dilworth, C.H.; Gray, K.A. Review of developmental origins of health and disease publications in environmental epidemiology. Reprod. Toxicol. 2017, 68, 34–48, doi:10.1016/j.reprotox.2016.11.011.
12. Sifakis, S.; Androutsopoulos, V.P.; Tsatsakis, A.M.; Spandidos, D.A. Human exposure to endocrine disrupting chemicals: Effects on the male and female reproductive systems. Environ. Toxicol. Pharmacol. 2017, 51, 56–70, doi:10.1016/j.etap.2017.02.024.
13. Giulivo, M.; De Alda, M.L.; Capri, E.; Barcelo, D. Human exposure to endocrine disrupting compounds: Their role in reproductive systems, metabolic syndrome and breast cancer. A review. Environ. Res. 2016, 151, 251–264, doi:10.1016/j.envres.2016.07.011.
14. Scsukova, S.; Rollerova, E.; Mlynarcikova, A.B. Impact of endocrine disrupting chemicals on onset and development of female reproductive disorders and hormone-related cancer. Reprod. Biol. 2016, 16, 243–254, doi:10.1016/j.repbio.2016.09.001.
15. Lucaccioni, L.; Trevisani, V.; Marrozzini, L.; Bertoncelli, N.; Predieri, B.; Lugli, L.; Berardi, A.; Iughetti, L. Endocrine-Disrupting Chemicals and Their Effects during Female Puberty: A Review of Current Evidence. Int. J. Mol. Sci. 2020, 21, 2078, doi:10.3390/ijms21062078.
16. Corsini, E.; Ruffo, F.; Racchi, M. Steroid hormones, endocrine disrupting compounds and immunotoxicology. Curr. Opin. Toxicol. 2018, 10, 69–73, doi:10.1016/j.cotox.2018.01.006.
17. Buoso, E.; Galasso, M.; Serafini, M.M.; Ronfani, M.; Lanni, C.; Corsini, E.; Racchi, M. Transcriptional regulation of RACK1 and modulation of its expression: Role of steroid hormones and significance in health and aging. Cell. Signal. 2017, 35, 264–271, doi:10.1016/j.cellsig.2017.02.010.
18. Buoso, E.; Galasso, M.; Ronfani, M.; Papale, A.; Galbiati, V.; Eberini, I.; Marinovich, M.; Racchi, M.; Corsini, E. The scaffold protein RACK1 is a target of endocrine disrupting chemicals (EDCs) with important implication in immunity. Toxicol. Appl. Pharmacol. 2017, 325, 37–47, doi:10.1016/j.taap.2017.04.011.
19. Buoso, E.; Masi, M.; Galbiati, V.; Maddalon, A.; Iulini, M.; Kenda, M.; Dolenc, M.S.; Marinovich, M.; Racchi, M.; Corsini, E. Effect of estrogen-active compounds on the expression of RACK1 and immunological implications. Arch. Toxicol. 2020, 94, 2081–2095, doi:10.1007/s00204-020-02756-9.
20. Racchi, M.; Buoso, E.; Ronfani, M.; Serafini, M.M.; Galasso, M.; Lanni, C.; Corsini, E. Role of Hormones in the Regulation of RACK1 Expression as a Signaling Checkpoint in Immunosenescence. Int. J. Mol. Sci. 2017, 18, 1453, doi:10.3390/ijms18071453.
21. Buoso, E.; Masi, M.; Long, A.; Chiappini, C.; Travelli, C.; Govoni, S.; Racchi, M. Ribosomes as a nexus between translation and cancer progression: Focus on ribosomal Receptor for Activated C Kinase 1 (RACK1) in breast cancer. Br. J. Pharmacol. 2020, doi:10.1111/bph.15218.
22. Arneth, B. Tumor Microenvironment. Medicina 2019, 56, 15, doi:10.3390/medicina56010015.
23. Jahanban-Esfahlan, R.; Seidi, K.; Banimohamad-Shotorbani, B.; Jahanban-Esfahlan, A.; Yousefi, B. Combination of nanotechnology with vascular targeting agents for effective cancer therapy. J. Cell. Physiol. 2018, 233, 2982–2992, doi:10.1002/jcp.26051.
24. Jahanban-Esfahlan, R.; Seidi, K.; Zarghami, N. Tumor vascular infarction: Prospects and challenges. Int. J. Hematol. 2017, 105, 244–256, doi:10.1007/s12185-016-2171-3.
25. Baghban, R.; Roshangar, L.; Jahanban-Esfahlan, R.; Seidi, K.; Ebrahimi-Kalan, A.; Jaymand, M.; Kolahian, S.; Javaheri, T.; Zare, P. Tumor microenvironment complexity and therapeutic implications at a glance. Cell Commun. Signal. 2020, 18, 1–19, doi:10.1186/s12964-020-0530-4.
26. Denisenko, T.V.; Budkevich, I.N.; Zhivotovsky, B. Cell death-based treatment of lung adenocarcinoma. Cell Death Dis. 2018, 9, 1–14, doi:10.1038/s41419-017-0063-y.
27. Balkwill, F.R.; Capasso, M.; Hagemann, T. The tumor microenvironment at a glance. J. Cell Sci. 2012, 125, 5591–5596, doi:10.1242/jcs.116392.
28. Jahanban-Esfahlan, R.; Seidi, K.; Manjili, M.H.; Jahanban-Esfahlan, A.; Javaheri, T.; Zare, P. Tumor Cell Dormancy: Threat or Opportunity in the Fight against Cancer. Cancers 2019, 11, 1207, doi:10.3390/cancers11081207.
29. Seidi, K.; Neubauer, H.A.; Moriggl, R.; Jahanban-Esfahlan, R.; Javaheri, T. Tumor target amplification: Implications for nano drug delivery systems. J. Control. Release 2018, 275, 142–161, doi:10.1016/j.jconrel.2018.02.020.
30. Kloc, M.; Kubiak, J.Z.; Li, X.C.; Ghobrial, R.M. Pericytes, Microvasular Dysfunction, and Chronic Rejection. Transplantation 2015, 99, 658–667, doi:10.1097/tp.0000000000000648.
31. Baluk, P.; Morikawa, S.; Haskell, A.; Mancuso, M.; McDonald, D.M. Abnormalities of Basement Membrane on Blood Vessels and Endothelial Sprouts in Tumors. Am. J. Pathol. 2003, 163, 1801–1815, doi:10.1016/s0002-9440(10)63540-7.
32. Dudley, A.C. Tumor Endothelial Cells. Cold Spring Harb. Perspect. Med. 2011, 2, a006536,

doi:10.1101/cshperspect.a006536.
33. Monteran, L.; Erez, N. The Dark Side of Fibroblasts: Cancer-Associated Fibroblasts as Mediators of Immunosuppression in the Tumor Microenvironment. Front. Immunol. 2019, 10, 1835, doi:10.3389/fimmu.2019.01835.
34. Liu, T.; Han, C.; Wang, S.; Fang, P.; Ma, Z.; Xu, L.; Yin, R. Cancer-associated fibroblasts: An emerging target of anti-cancer immunotherapy. J. Hematol. Oncol. 2019, 12, 1–15, doi:10.1186/s13045-019-0770-1.
35. Zhou, W.; Xu, G.; Wang, Y.; Xu, Z.; Liu, X.; Xu, X.; Ren, G.; Tian, K. Oxidative stress induced autophagy in cancer associated fibroblast enhances proliferation and metabolism of colorectal cancer cells. Cell Cycle 2017, 16, 73–81, doi:10.1080/15384101.2016.1252882.
36. Zhang, R.; Qi, F.; Zhao, F.; Li, G.; Shao, S.; Zhang, X.; Yuan, L.; Feng, Y. Cancer-associated fibroblasts enhance tumor-associated macrophages enrichment and suppress NK cells function in colorectal cancer. Cell Death Dis. 2019, 10, 1–14, doi:10.1038/s41419-019-1435-2.
37. Solinas, G.; Schiarea, S.; Liguori, M.; Fabbri, M.; Pesce, S.; Zammataro, L.; Pasqualini, F.; Nebuloni, M.; Chiabrando, C.; Mantovani, A.; et al. Tumor-Conditioned Macrophages Secrete Migration-Stimulating Factor: A New Marker for M2-Polarization, Influencing Tumor Cell Motility. J. Immunol. 2010, 185, 642–652, doi:10.4049/jimmunol.1000413.
38. Wei, C.; Yang, C.; Wang, S.; Shi, D.; Zhang, C.; Lin, X.; Liu, Q.; Dou, R.; Xiong, B. Crosstalk between cancer cells and tumor associated macrophages is required for mesenchymal circulating tumor cell-mediated colorectal cancer metastasis. Mol. Cancer 2019, 18, 1–23, doi:10.1186/s12943-019-0976-4.
39. Chen, Y.; Tan, W.; Wang, C. Tumor-associated macrophage-derived cytokines enhance cancer stem-like characteristics through epithelial–mesenchymal transition. OncoTargets Ther. 2018, 11, 3817–3826, doi:10.2147/ott.s168317.
40. Liu, T.; Zhou, L.; Li, D.; Andl, T.; Zhang, Y. Cancer-Associated Fibroblasts Build and Secure the Tumor Microenvironment. Front. Cell Dev. Biol. 2019, 7, 60, doi:10.3389/fcell.2019.00060.
41. Walker, C.; Mojares, E.; Hernández, A.E.D.R. Role of Extracellular Matrix in Development and Cancer Progression. Int. J. Mol. Sci. 2018, 19, 3028, doi:10.3390/ijms19103028.
42. Lu, P.; Weaver, V.M.; Werb, Z. The extracellular matrix: A dynamic niche in cancer progression. J. Cell Biol. 2012, 196, 395–406, doi:10.1083/jcb.201102147.
43. Watnick, R.S. The Role of the Tumor Microenvironment in Regulating Angiogenesis. Cold Spring Harb. Perspect. Med. 2012, 2, a006676, doi:10.1101/cshperspect.a006676.
44. Angell, H.; Galon, J. From the immune contexture to the Immunoscore: The role of prognostic and predictive immune markers in cancer. Curr. Opin. Immunol. 2013, 25, 261–267, doi:10.1016/j.coi.2013.03.004.
45. Dong, H.; Strome, S.E.; Salomao, D.R.; Tamura, H.; Hirano, F.; Flies, D.B.; Roche, P.C.; Lu, J.; Zhu, G.; Tamada, K.; et al. Tumor-associated B7-H1 promotes T-cell apoptosis: A potential mechanism of immune evasion. Nat. Med. 2002, 8, 793–800, doi:10.1038/nm730.
46. Wang, T.; Niu, G.; Kortylewski, M.; Burdelya, L.; Shain, K.H.; Zhang, S.; Bhattacharya, R.; Gabrilovich, D.I.; Heller, R.; Coppola, D.; et al. Regulation of the innate and adaptive immune responses by Stat-3 signaling in tumor cells. Nat. Med. 2004, 10, 48–54, doi:10.1038/nm976.
47. Hivroz, C.; Chemin, K.; Tourret, M.; Bohineust, A. Crosstalk between T Lymphocytes and Dendritic Cells. Crit. Rev. Immunol. 2012, 32, 139–155, doi:10.1615/critrevimmunol.v32.i2.30.
48. Klebanoff, C.A.; Gattinoni, L.; Restifo, N.P. CD8+ T-cell memory in tumor immunology and immunotherapy. Immunol. Rev. 2006, 211, 214–224, doi:10.1111/j.0105-2896.2006.00391.x.
49. Lv, L.; Pan, K.; Li, X.-D.; She, K.-L.; Zhao, J.-J.; Wang, W.; Chen, J.-G.; Chen, Y.-B.; Yun, J.-P.; Xia, J.-C. The Accumulation and Prognosis Value of Tumor Infiltrating IL-17 Producing Cells in Esophageal Squamous Cell Carcinoma. PLoS ONE 2011, 6, e18219, doi:10.1371/journal.pone.0018219.
50. Schioppa, T.; Moore, R.; Thompson, R.G.; Rosser, E.C.; Kulbe, H.; Nedospasov, S.; Mauri, C.; Coussens, L.M.; Balkwill, F.R. B regulatory cells and the tumor-promoting actions of TNF- during squamous carcinogenesis. Proc. Natl. Acad. Sci. USA 2011, 108, 10662–10667, doi:10.1073/pnas.1100994108.
51. Olkhanud, P.B.; Damdinsuren, B.; Bodogai, M.; Gress, R.E.; Sen, R.; Wejksza, K.; Malchinkhuu, E.; Wersto, R.P.; Biragyn, A. Tumor-Evoked Regulatory B Cells Promote Breast Cancer Metastasis by Converting Resting CD4+ T Cells to T-Regulatory Cells. Cancer Res. 2011, 71, 3505–3515, doi:10.1158/0008-5472.can-10-4316.
52. Li, B.; Wang, J.H.-C. Fibroblasts and myofibroblasts in wound healing: Force generation and measurement. J. Tissue Viability 2011, 20, 108–120, doi:10.1016/j.jtv.2009.11.004.
53. Xing, F. Cancer associated fibroblasts (CAFs) in tumor microenvironment. Front. Biosci. 2010, 15, 166–179, doi:10.2741/3613.
54. Spaeth, E.L.; Dembinski, J.L.; Sasser, A.K.; Watson, K.; Klopp, A.; Hall, B.; Andreeff, M.; Marini, F. Mesenchymal Stem Cell Transition to Tumor-Associated Fibroblasts Contributes to Fibrovascular Network Expansion and Tumor Progression. PLoS ONE 2009, 4, e4992, doi:10.1371/journal.pone.0004992.
55. Birbrair, A.; Zhang, T.; Wang, Z.-M.; Messi, M.L.; Olson, J.D.; Mintz, A.; Delbono, O. Type-2 pericytes participate in normal and tumoral angiogenesis. Am. J. Physiol. Physiol. 2014, 307, C25–C38, doi:10.1152/ajpcell.00084.2014.
56. Wang, S.-C.; Hong, J.-H.; Hsueh, C.; Chiang, C.-S. Tumor-secreted SDF-1 promotes glioma invasiveness and TAM

tropism toward hypoxia in a murine astrocytoma model. Lab. Investig. 2012, 92, 151–162, doi:10.1038/labinvest.2011.128.
57. Franklin, R.A.; Liao, W.; Sarkar, A.; Kim, M.V.; Bivona, M.R.; Liu, K.; Pamer, E.G.; Li, M.O. The cellular and molecular origin of tumor-associated macrophages. Sci. 2014, 344, 921–925, doi:10.1126/science.1252510.
58. Fisher, D.T.; Appenheimer, M.M.; Evans, S.S. The two faces of IL-6 in the tumor microenvironment. Semin. Immunol. 2014, 26, 38–47, doi:10.1016/j.smim.2014.01.008.
59. Strong, A.L.; Burow, M.E.; Gimble, J.M.; Bunnell, B.A. Concise Review: The Obesity Cancer Paradigm: Exploration of the Interactions and Crosstalk with Adipose Stem Cells. STEM CELLS 2015, 33, 318–326, doi:10.1002/stem.1857.
60. Ohlstein, J.F.; Strong, A.L.; McLachlan, J.A.; Gimble, J.M.; Burow, M.E.; Bunnell, B.A. Bisphenol A enhances adipogenic differentiation of human adipose stromal/stem cells. J. Mol. Endocrinol. 2014, 53, 345–353, doi:10.1530/jme-14-0052.
61. Gassman, N.R.; Coşkun, E.; Stefanick, N.F.; Horton, J.K.; Jaruga, P.; Dizdaroglu, M.; Wilson, S.H. Bisphenol A Promotes Cell Survival Following Oxidative DNA Damage in Mouse Fibroblasts. PLoS ONE 2015, 10, e0118819, doi:10.1371/journal.pone.0118819.
62. Rochester, J.R.; Bolden, A.L. Bisphenol S and F: A Systematic Review and Comparison of the Hormonal Activity of Bisphenol A Substitutes. Environ. Health Perspect. 2015, 123, 643–650, doi:10.1289/ehp.1408989.
63. Kuruto-Niwa, R.; Nozawa, R.; Miyakoshi, T.; Shiozawa, T.; Terao, Y. Estrogenic activity of alkylphenols, bisphenol S, and their chlorinated derivatives using a GFP expression system. Environ. Toxicol. Pharmacol. 2005, 19, 121–130, doi:10.1016/j.etap.2004.05.009.
64. Liu, X.; Matsushima, A.; Okada, H.; Tokunaga, T.; Isozaki, K.; Shimohigashi, Y. Receptor binding characteristics of the endocrine disruptor bisphenol A for the human nuclear estrogen-related receptor γ. Chief and corroborative hydrogen bonds of the bisphenol A phenol-hydroxyl group with Arg316 and Glu275 residues. FEBS J. 2007, 274, 6340–6351, doi:10.1111/j.1742-4658.2007.06152.x.
65. Kubo, M.; Ijichi, N.; Ikeda, K.; Horie-Inoue, K.; Takeda, S.; Inoue, S. Modulation of adipogenesis-related gene expression by estrogen-related receptor γ during adipocytic differentiation. Biochim. Biophys. Acta 2009, 1789, 71–77, doi:10.1016/j.bbagrm.2008.08.012.
66. Zoubouliss, C.C.; Chen, W.-C.; Thornton, M.J.; Qin, K.; Rosenfield, R. Sexual Hormones in Human Skin. Horm. Metab. Res. 2007, 39, 85–95, doi:10.1055/s-2007-961807.
67. Levental, K.R.; Yu, H.; Kass, L.; Lakins, J.N.; Egeblad, M.; Erler, J.T.; Fong, S.F.; Csiszar, K.; Giaccia, A.; Weninger, W.; et al. Matrix Crosslinking Forces Tumor Progression by Enhancing Integrin Signaling. Cell 2009, 139, 891–906, doi:10.1016/j.cell.2009.10.027.
68. Paszek, M.J.; Zahir, N.; Johnson, K.R.; Lakins, J.N.; Rozenberg, G.I.; Gefen, A.; Reinhart-King, C.A.; Margulies, S.S.; Dembo, M.; Boettiger, D.; et al. Tensional homeostasis and the malignant phenotype. Cancer Cell 2005, 8, 241–254, doi:10.1016/j.ccr.2005.08.010.
69. Ibrahim, M.A.A.; Elbakry, R.H.; Bayomy, N.A. Effect of bisphenol A on morphology, apoptosis and proliferation in the resting mammary gland of the adult albino rat. Int. J. Exp. Pathol. 2016, 97, 27–36, doi:10.1111/iep.12164.
70. Leśniewska, M.; Miltyk, W.; Światecka, J.; Tomaszewska, M.; Kuzmicki, M.; Palka, J.; Wolczyński, S. Estrogen receptor beta participate in the regulation of metabolizm of extracellular matrix in estrogen alpha negative breast cancer. Folia Histochem. et Cytobiol. 2010, 47, 107–112, doi:10.2478/v10042-009-0047-6.
71. Kousidou, O.C.; Berdiaki, A.; Kletsas, D.; Zafiropoulos, A.; Theocharis, A.D.; Tzanakakis, G.N.; Karamanos, N.K. Estradiol-estrogen receptor: A key interplay of the expression of syndecan-2 and metalloproteinase-9 in breast cancer cells. Mol. Oncol. 2008, 2, 223–232, doi:10.1016/j.molonc.2008.06.002.
72. Nilsson, U.W.; Garvin, S.; Dabrosin, C. MMP-2 and MMP-9 activity is regulated by estradiol and tamoxifen in cultured human breast cancer cells. Breast Cancer Res. Treat. 2006, 102, 253–261, doi:10.1007/s10549-006-9335-4.
73. Burks, H.; Pashos, N.; Martin, E.; McLachlan, J.; Bunnell, B.; Burow, M. Endocrine disruptors and the tumor microenvironment: A new paradigm in breast cancer biology. Mol. Cell. Endocrinol. 2017, 457, 13–19, doi:10.1016/j.mce.2016.12.010.
74. Hu, W.-Y.; Shi, G.-B.; Hu, D.-P.; Nelles, J.L.; Prins, G.S. Actions of estrogens and endocrine disrupting chemicals on human prostate stem/progenitor cells and prostate cancer risk. Mol. Cell. Endocrinol. 2012, 354, 63–73, doi:10.1016/j.mce.2011.08.032.
75. Aghajanova, L.; Giudice, L.C. Effect of bisphenol A on human endometrial stromal fibroblasts in vitro. Reprod. Biomed. Online 2010, 22, 249–256, doi:10.1016/j.rbmo.2010.12.007.
76. Csaba, G. Effect of endocrine disruptor phytoestrogens on the immune system: Present and future. Acta Microbiol. Immunol. Hung. 2018, 65, 1–14, doi:10.1556/030.65.2018.018.
77. Malaisé, Y.; Ménard, S.; Cartier, C.; Lencina, C.; Sommer, C.; Gaultier, E.; Houdeau, E.; Guzylack-Piriou, L. Consequences of bisphenol a perinatal exposure on immune responses and gut barrier function in mice. Arch. Toxicol. 2017, 92, 347–358, doi:10.1007/s00204-017-2038-2.
78. Anwer, F.; Chaurasia, S.; Khan, A.A. Hormonally active agents in the environment: A state-of-the-art review. Rev. Environ. Health 2016, 31, 415–433, doi:10.1515/reveh-2016-0014.
79. Xie, Y.; Schafer, R.; Barnett, J. The Immunomodulatory Effects of the Herbicide Propanil on Murine Macrophage

Interleukin-6 and Tumor Necrosis Factor-α Production. Toxicol. Appl. Pharmacol. 1997, 145, 184–191, doi:10.1006/taap.1997.8179.
80. Nishioka, J., Iwahara, C., Kawasaki, M., Yoshizaki, F., Nakayama, H., Takamori, K., Ogawa, H., Iwabuchi, K. Di-(2-ethylhexyl) phthalate induces production of inflammatory molecules in human macrophages. Inflamm. Res. 2012, 61, 69–78, doi:10.1007/s00011-011-0390-x.
81. Sugita-Konishi, Y.; Shimura, S.; Nishikawa, T.; Sunaga, F.; Naito, H.; Suzuki, Y. Effect of Bisphenol A on non-specific immunodefenses against non-pathogenic Escherichia coli. Toxicol. Lett. 2003, 136, 217–227, doi:10.1016/s0378-4274(02)00388-0.
82. Švajger, U.; Dolenc, M.S.; Jeras, M. In vitro impact of bisphenols BPA, BPF, BPAF and 17β-estradiol (E2) on human monocyte-derived dendritic cell generation, maturation and function. Int. Immunopharmacol. 2016, 34, 146–154, doi:10.1016/j.intimp.2016.02.030.
83. Guo, H.; Liu, T.; Uemura, Y.; Jiao, S.; Wang, D.; Lin, Z.; Narita, Y.; Suzuki, M.; Hirosawa, N.; Ichihara, Y.; et al. Bisphenol A in combination with TNF-α selectively induces Th2 cell-promoting dendritic cells in vitro with an estrogen-like activity. Cell. Mol. Immunol. 2010, 7, 227–234, doi:10.1038/cmi.2010.14.
84. Ndebele, K.; Tchounwou, P.B.; McMurray, R.W. Coumestrol, Bisphenol-A, DDT, and TCDD Modulation of Interleukin-2 Expression in Activated CD+4 Jurkat T Cells. Int. J. Environ. Res. Public Health 2004, 1, 3–11, doi:10.3390/ijerph2004010003.
85. Nowak, K.; Jabłońska, E.; Ratajczak-Wrona, W. Immunomodulatory effects of synthetic endocrine disrupting chemicals on the development and functions of human immune cells. Environ. Int. 2019, 125, 350–364, doi:10.1016/j.envint.2019.01.078.
86. Bansal, A.; Henao-Mejia, J.; Simmons, R.A. Immune System: An Emerging Player in Mediating Effects of Endocrine Disruptors on Metabolic Health. Endocrinology 2017, 159, 32–45, doi:10.1210/en.2017-00882.

Keywords

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