Review Article

PPARδ as a Metabolic Initiator of Mammary Neoplasia and Immune Tolerance

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PPARδ is a ligand-activated nuclear receptor that regulates the transcription of genes associated with proliferation, metabolism, inflammation, and immunity. Within this transcription factor family, PPARδ is unique in that it initiates oncogenesis in a metabolic and tissue-specific context, especially in mammary epithelium, and can regulate autoimmunity in some tissues. This review discusses its role in these processes and how it ultimately impacts breast cancer.

1. Introduction

The PPAR nuclear receptor family consists of the PPARα, PPARγ, and PPARδ/β isotypes, which function as heterodimeric partners with RXR with specificity dictated by high-affinity binding of PPAR ligands and coactivators [1]. Similar to other nuclear receptors, PPARs contain an N-terminal transactivation domain, a DNA-binding domain, a ligand-binding domain, and a C-terminal ligand-dependent transactivation region [2]. PPARs bind to a DR-1 response element (PPRE) with the consensus sequence AGG(T/A)CA that is recognized specifically by the PPAR heterodimeric partner [3]. Ligand-activated PPARs interact with coactivators CEBPA/B and NCOA3 and in the unliganded state with corepressor NCOR2 [4–7]. Of the three isotypes, PPARδ plays a dominant role in regulating fatty acid β-oxidation, glucose utilization, cholesterol transport, and energy balance [8–10] but also modulates the cell cycle, apoptosis, angiogenesis, inflammation, and cell lineage specification [11–14]. These multifaceted functions indicate that PPARδ has a critical homeostatic role in normal physiology and that its aberrant expression can impact the initiation and promotion of oncogenesis. This review discusses recent advances pertaining to the involvement of PPARδ in these processes primarily as they relate to mammary tumorigenesis.

2. PPARδ and Tumorigenesis

The role of PPARδ in tumorigenesis has been investigated for almost two decades, and whether it exerts an oncogenic or antioncogenic role depends in large part on the targeted tissue and the gene targeting strategy utilized [14–16]. In the context of the mammary gland, however, most animal models confirm that PPARδ exerts an oncogenic effect. This can be envisioned to result in part from competition between the tumor promoting effects of PPARδ and the tumor suppressor effects of PPARγ. PPARγ agonists reduce mammary carcinogenesis [17–19], which correlates with induction of PTEN [20, 21] and BRCA1 [22] tumor suppressor activity, as well as reduction of inflammation via the Cox2/Ptgs2 pathway [23]. Conversely, PPARγ haploinsufficiency [23] or expression of a dominant-negative Pax8-PPARγ transgene [24] and direct or indirect inhibition of PPARγ [21, 25] enhance DMBA mammary carcinogenesis. In MMTV-Pax8-PPARγ mice, the increased rate of carcinogenesis correlates with enhanced Wnt, Ras/Erk, and PDK1/Akt signaling, reduced PTEN expression, and a more stem cell-like phenotype [24]. The respective Yin/Yang functions of PPARδ and PPARγ are consistent with the ability of PPARδ to enhance survival through the PI3K and PDK1 pathways in response to wound healing [26, 27], as well as with the proliferative and
Figure 1: Interactions between inflammation, metabolism, and mTOR signaling in the mammary gland of MMTV-PPARδ mice. PPARδ activates PPRE-containing genes associated with metabolism (Olah, Ptgs2, Pla2, and Pld), invasion (Mmp12, Klk6), and inflammation (S100a8/9, Saa1/2/3). Arachidonic acid (AA) is a substrate for Ptds2 and is a constituent of phosphatidylcholine (PC) required for prostaglandin synthesis. Lysophosphatidylcholine (LPC) is generated from PC by phospholipase A2 (Pla2), and lysophosphatidic acid (LPA) and phosphatidic acid (PA) are generated by phospholipase D (Pld). LPA stimulates mTOR through a G protein-coupled receptor, and PA directly activates mTOR. The mTOR inhibitor RAD001 (everolimus) inhibits tumorigenesis in this animal model. The net result is an increase in inflammation, extracellular matrix remodeling, immune suppression, and neoplasia. Adapted from [31].

The angiogenic response of breast cancer and endothelial cells to conditional activation of PPARδ [28]. The induction of PDK1 signaling by the PPARδ agonist GW501516 in DMBA-treated wild-type mice [19], the increased expression of PPARδ in GW501516-treated MMTV-PDK1 mice [29], and reduction of mammary tumorogenesis in MMTV-Cox2 mice crossed into a PPARδ null background [30] further support its oncogenic potential. This outcome was ultimately proven by the generation of MMTV-PPARδ mice, which developed infiltrating mammary adenocarcinomas and whose progression was accelerated by, but not dependent on, agonist stimulation [31]. From a clinical perspective, this result is concordant with the increased expression of PPARδ in invasive breast cancer [12, 32] and by manifestation of a PPARδ signaling network that predicts poor survival in this disease [33].

A signature feature of MMTV-PPARδ mice is the development of ER+/PR+/ErbB2− tumors resembling the luminal B subtype of breast cancer [31], which is denoted by lower ER expression, higher Ki-67 staining, and a higher histologic grade [34]. Since ER mRNA is relatively low in these mice in comparison to immunohistochemical staining, it suggests that PPARδ may affect ER stability posttranslationally, for example, phosphorylation of ER Ser167 by mTOR/S6K [35], a pathway activated in this mouse model (Figure 1). The development of ER+ tumors in MMTV-PPARδ mice is similar to what was observed in DMBA-treated MMTV-Pax8-PPARγ mice [24] and DMBA-treated wild-type mice administered the irreversible PPARγ inhibitor, GW9662 [25]. These findings support the notion that PPARγ and PPARδ, either by direct competition [36], cofactor competition [37], and/or ligand-dependent activation [38] have opposing actions that affect expansion of the ER+ lineage tumor subtype. Interestingly, ER+ tumors also arose in MMTV-NCOA3 mice [39, 40], but not in other MMTV-driven transgenic models [41], suggesting that it is the PPARδ coactivator complex itself, rather than the MMTV promoter that drives expansion of the ER+ lineage. This conclusion is also supported by the similarities between MMTV-NCOA3 and MMTV-PPARδ mice for activation of the mTOR signaling axis [39, 40], suggesting its importance in ER+ luminal tumor specification.

Another intriguing feature of MMTV-PPARδ mice is the association between the onset of neoplasia and the upregulation of Plac1 [31], a microvillous membrane protein expressed primarily in trophoblasts, but not in most somatic tissues [42] (Figure 1). Plac1 is reexpressed in several malignancies [43–45], and reduction of Plac1 in breast cancer cells inhibits proliferation and invasion [43]. These findings suggest that Plac1 may serve as a diagnostic biomarker as shown by the more favorable prognosis of colorectal cancer patients expressing Plac1 autoantibodies [46]. Analysis of a limited set of paired breast cancer specimens indicates that Plac1 expression is elevated in the majority of biopsies, but not in adjacent normal tissue (Isaacs and Glazer, unpublished results), which is consistent with the presence of circulating Plac1 RNA in
the majority of breast cancer subjects [43, 44]. The high level of expression of Plac1 in MMTV-PPARδ mice also suggests that Plac1 may be under the transcriptional control of PPARδ as demonstrated by its dependence on the PPARδ coactivators CEBPA and CEBPB [47] and the presence of PPREs in the promoter regions of mouse and human Plac1 (http://www.genecards.org/cgi-bin/carddisp.pl?gene=PLAC1 &keywords=plac1).

3. PPARδ and Inflammation

One of the earliest recognized functions of PPARδ was its antiapoptotic, chemotactic, and inflammatory actions mediated through the Akt and Rho pathways in response to wound healing in keratinocytes [26, 27, 48]. This was the first indication that PPARδ might be a contributing factor to inflammatory disorders, such as psoriasis [49], and tumorigenesis. It had been previously shown that inflammatory molecules, such as eicosanoids, could serve as endogenous PPARδ ligands [50–52]. In colon tumorigenesis and colitis, Ptgs2 and prostaglandin synthase is dependent on PPARδ [53, 54], whereas inhibition of tumorigenesis by NSAIDs results from induction of the endogenous PPARδ antagonist, 13-S-hydroxyoctadecadienoic acid [55]. Of note is that a similar Ptgs2/prostaglandin phenotype is expressed in MMTV-13-S-hydroxyoctadecadienoic acid [55]. Of note is that as immunosuppressive action, CD4+ T cells may control adaptive immunity [79] to prevent diabetes. This suggests that PPARδ may play a similar role in tumorigenesis, but with a decidedly different outcome. As discussed in Section 2, PPARδ regulates the inflammatory Saa1/2/3 and S100a8/9 gene family [68], which facilitates fatty acid transport and potentiate EGFR- and ErbB2-mediated proliferation [69, 70] and invasion [71]. Lastly, PPARδ and fatty acid oxidation are required to maintain asymmetric stem cell division [72], an area that may be linked to ER+ tumor specification and one unexplored thus far in mammary tumorigenesis.

5. PPARs and Immune Tolerance

One of the primary mechanisms associated with cancer progression is the coopting of immune tolerance to produce an immunologically permissive tumor microenvironment [73]. This can occur through several mechanisms associated with adaptive immunity, including expansion of tumor infiltrating regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSC), and tumor-associated macrophages (TAM) [74, 75] (Figure 2). Tregs contribute to immune escape by activation of the programmed cell death protein-1 (PD-1) receptor through immune and tumor cell expression of its ligand, PD-L1 (not shown), which results in suppression of effector T cell function mediated by CD4+ helper T cells and CD8+ cytotoxic T cells. MDSC also differentiate into TAM with similar T cell inhibitory properties [76], a process driven by inflammatory Th2 cytokines, which ultimately leads to tumor progression. Although there are numerous studies of these pathways in immune tolerance, the role of PPARδ in this process has not been examined in mammary tumor models. Nevertheless, a clue as to its functional role in adaptive immunity may be gleaned from studies in diabetic obese mice. In liver and adipose tissue, PPARδ is required to maintain insulin sensitivity via Th2 cytokines, which promote M2 macrophage polarization [77, 78] that have the characteristics of TAMs, and promotes tolerance to “self” recognition [79] to prevent diabetes. This suggests that PPARδ may play a similar role in tumorigenesis, but with a decidedly different outcome. As discussed in Section 2, PPARδ regulates the inflammatory Saal/2/3 and S100a8/9 pathways, which are linked to tumor-bearing mice are associated with MDSC expansion [80] and metastasis [81]. Immune tolerance mediated by Tregs, MDSC, and TAM are dependent on PGE2 synthesis, reactive oxygen species generated by NADPH oxidase (NOXI), and tryptophan depletion by indoleamine 2,3 dioxygenase (IDO) [74] (Figure 2), all of which are under the transcriptional control of PPARδ, MDSC and Treg infiltration of mammary tumors is dependent on PGE2 synthesis and IDO activation [82], and inhibition of CD8+ T cell activation via the PD-1/PD-L1 axis is dependent on mTOR activation [83], a pathway that is activated in MMTV-PPARδ mice [31]. Since the transcriptions of ARGI, IDO2, inducible nitric oxide synthetase (NOS2), Ptgs2, Ptger4, and NOXI are all regulated by the coactivators CEBPA/B, which also function in this capacity with PPARδ, this suggests a mechanism whereby PPARδ may control adaptive immunity.

4. PPARδ and Metabolism

PPARδ is one of the primary regulators of intermediary metabolism, including fatty acid synthesis and β-oxidation, particularly in adipose and muscle tissue [13, 64]. In MMTV-PPARδ mice, PPARδ functions as an integrator of metabolism and tumorigenesis via the biosynthesis of lysophosphatidic acid (LPA), a metabolite that promotes mammary tumorigenesis [65, 66], and phosphatidic acid (PA), a metabolite that directly activates mTOR [67] (Figure 1). The LPA/PA signaling pathway is also coupled to expression of Pdk4, a PPARδ-regulated inhibitor of pyruvate oxidation that increases unsaturated fatty acid, arachidonic acid, LPA, and PA biosynthesis in MMTV-PDK1 mice [29, 31] and is in accordance with the capacity of long chain unsaturated fatty acids to serve as endogenous PPARδ ligands [50–52]. Additionally, PPARδ upregulates the fatty acid-binding protein (FABP) gene family [68], which facilitate fatty acid transport and potentiate EGFR- and ErbB2-mediated proliferation [69, 70] and invasion [71]. Lastly, PPARδ and fatty acid oxidation are required to maintain asymmetric stem cell division [72], an area that may be linked to ER+ tumor specification and one unexplored thus far in mammary tumorigenesis.

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metabolically within the tumor microenvironment. This conclusion is also consistent with our recent finding that Plac1, which is overexpressed in MMTV-PPARδ mice, mediates immune tolerance in murine breast cancer cells by upregulating the expression of chemokines necessary for MDSC-mediated activation of Tregs (H. Yuan and R. I. Glazer, unpublished results). Thus, there is compelling evidence, although circumstantial in some instances, which suggests that PPARδ through its ability to regulate metabolic and inflammatory gene expression acts as a rheostat to control autoimmunity in normal tissues and immune tolerance during tumorigenesis.

6. Conclusions

Both genetic and pharmacological manipulation of PPARδ expression provide strong evidence for its role in regulating metabolism, inflammation, and immunity in a concerted fashion to ultimately impact mammary tumorigenesis. This conclusion suggests possible novel targets for drug development that may control this process and complement current approaches to develop immunotherapies for the treatment of cancer.

Competing Interests

The author declares that there are no competing interests.

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References

[1] C. Grommes, G. E. Landreth, and M. T. Heneka, "Antineoplastic effects of peroxisome proliferator-activated receptor γ agonists," Lancet Oncology, vol. 5, no. 7, pp. 419–429, 2004.

[2] J. M. Olefsky and A. R. Saltiel, "PPARγ and the treatment of insulin resistance," Trends in Endocrinology and Metabolism, vol. 11, no. 9, pp. 362–368, 2000.

[3] J. Berger and J. A. Wagner, "Physiological and therapeutic roles of peroxisome proliferator-activated receptors," Diabetes Technology and Therapeutics, vol. 4, no. 2, pp. 163–174, 2002.

[4] J. Direnzo, M. Söderström, R. Kurokawa et al., "Peroxisome proliferator-activated receptors and retinoic acid receptors differentially control the interactions of retinoid X receptor heterodimers with ligands, coactivators, and corepressors," Molecular and Cellular Biology, vol. 17, no. 4, pp. 2166–2176, 1997.

[5] R. M. Lavinsky, K. Jepsen, T. Heinzel et al., "Diverse signaling pathways modulate nuclear receptor recruitment of N-CoR and SMRT complexes," Proceedings of the National Academy of Sciences of the United States of America, vol. 95, no. 6, pp. 2920–2925, 1998.

[6] R. T. Nolte, G. B. Wiseley, S. Westin et al., "Ligand binding and co-activator assembly of the peroxisome proliferator-activated receptor-γ," Nature, vol. 395, no. 6698, pp. 137–143, 1998.

[7] Y. Yin, H. Yuan, C. Wang et al., "3-Phosphoinositide-dependent protein kinase-1 activates the peroxisome proliferator-activated receptor- and promotes adipocyte differentiation," Molecular Endocrinology, vol. 20, no. 2, pp. 268–278, 2006.

[8] J. P. Berger, T. E. Akiyama, and P. T. Meinke, "PPARs: therapeutic targets for metabolic disease," Trends in Pharmacological Sciences, vol. 26, no. 5, pp. 244–251, 2005.

[9] R. M. Evans, G. D. Barish, and Y.-X. Wang, "PPARs and the complex journey to obesity," Nature Medicine, vol. 10, no. 4, pp. 355–361, 2004.

[10] M. Lehrke and M. A. Lazar, "The many faces of PPARγ," Cell, vol. 123, no. 6, pp. 993–999, 2005.

[11] L. Michalik, B. Desvergne, and W. Wahli, "Peroxisome proliferator-activated receptors and cancers: complex stories," Nature Reviews Cancer, vol. 4, no. 1, pp. 61–70, 2004.

[12] R. I. Glazer, H. Yuan, Z. Xie, and Y. Yin, "PPARγ and PPARδ as modulators of neoplasia and cell fate," PPAR Research, vol. 2008, Article ID 247379, 8 pages, 2008.

[13] K.-D. Wagner and N. Wagner, "Peroxisome proliferator-activated receptor beta/delta (PPARβ/δ) acts as regulator of metabolism linked to multiple cellular functions," Pharmacology and Therapeutics, vol. 125, no. 3, pp. 423–435, 2010.
human cancer patients," *International Journal of Cancer*, vol. 122, no. 9, pp. 2038–2043, 2008.

[46] F.-F. Liu, X.-Y. Dong, X.-W. Pang et al., “The specific immune response to tumor antigen CPI and its correlation with improved survival in colon cancer patients,” *Gastroenterology*, vol. 134, no. 4, pp. 998–1006, 2008.

[47] L. Brunelli, K. A. Cieslik, J. L. Alcorn, M. Vatta, and A. Baldini, “Peroxisome proliferator-activated receptor-δ upregulates 14-3-3ε in human endothelial cells via CCAAT/enhancer binding protein-β,” *Circulation Research*, vol. 100, no. 5, pp. e59–e71, 2007.

[48] N. S. Tan, G. Icre, A. Montagner, B. Bordier-ten-Heggheler, W. Wahl, and L. Michalik, “The nuclear hormone receptor peroxisome proliferator-activated receptor β/δ potentiates cell chemotaxis, polarization, and migration,” *Molecular and Cellular Biology*, vol. 27, no. 20, pp. 7161–7175, 2007.

[49] M. Romanowska, L. Reilly, C. N. A. Palmer, M. C. U. Gustafsson, and J. Forster, “Activation of PPARβ/δ causes a psoriasis-like skin disease in vivo,” *PLoS ONE*, vol. 5, no. 3, Article ID e9701, 2010.

[50] S. A. Jones et al., “Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors α and γ,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 94, no. 9, pp. 4318–4323, 1997.

[51] B. M. Forman, J. Chen, and R. M. Evans, “Hypolipidemic drugs, polyunsaturated fatty acids, and eicosanoids are ligands for peroxisome proliferator-activated receptors α and δ,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 94, no. 9, pp. 4312–4317, 1997.

[52] H. E. Xu, M. H. Lambert, V. G. Montana et al., “Molecular recognition of fatty acids by peroxisome proliferator-activated receptors,” *Molecular Cell*, vol. 3, no. 3, pp. 397–403, 1999.

[53] R. A. Gupta, J. Tan, W. F. Krause et al., “Prostaglandin-mediated activation of peroxisome proliferator-activated receptor δ in colorectal cancer,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 24, pp. 13275–13280, 2000.

[54] D. Wang, L. Fu, W. Ning et al., “Peroxisome proliferator-activated receptor δ promotes colon inflammation and tumor growth,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 111, no. 19, pp. 7084–7089, 2014.

[55] I. Shureiqi, W. Jiang, X. Zuo et al., “The 15-lipoxygenase-1 product 13-S-hydroxyoctadecadienoic acid down-regulates PPAR-δ to induce apoptosis in colorectal cancer cells,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 17, pp. 9968–9973, 2003.

[56] C. H. Liu, S.-H. Chang, K. Narko et al., “Overexpression of cyclooxygenase-2 is sufficient to induce tumorigenesis in transgenic mice,” *Journal of Biological Chemistry*, vol. 276, no. 21, pp. 18563–18569, 2001.

[57] S. Han, J. D. Ritzenthaler, B. Wingerd, and J. Roman, “Activation of peroxisome proliferator-activated receptor β/δ (PPARβ/δ) increases the expression of prostaglandin E2 receptor subtype EP4: the roles of phosphorylidylinositol 3-kinase and CCAAT/enhancer-binding protein β,” *The Journal of Biological Chemistry*, vol. 280, no. 39, pp. 33240–33249, 2005.

[58] L. Xu, C. Han, K. Lim, and T. Wu, “Cross-talk between peroxisome proliferator-activated receptor δ and cytosolic phospholipase A2α/cyclooxygenase-2/prostaglandin E2 signaling pathways in human hepatocellular carcinoma cells,” *Cancer Research*, vol. 66, no. 24, pp. 11859–11868, 2006.

[59] J. Eswaran, D. Cyamam, P. Mudvari et al., “Transcriptomic landscape of breast cancers through mRNA sequencing,” *Scientific Reports*, vol. 2, article 264, 2012.

[60] B. L. Pierce, R. Ballard-Barbash, L. Bernstein et al., “Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients,” *Journal of Clinical Oncology*, vol. 27, no. 21, pp. 3437–3444, 2009.

[61] C. Gebhardt, J. Németh, P. Angel, and J. Hess, “S100A8 and S100A9 in inflammation and cancer,” *Biochemical Pharmacology*, vol. 72, no. 11, pp. 1622–1631, 2006.

[62] S. Ghavami, S. Chitayat, M. Hashemi et al., “S100A8/A9: a Janus-faced molecule in cancer therapy and tumorgenesis,” *European Journal of Pharmacology*, vol. 625, no. 1–3, pp. 73–83, 2009.

[63] C. B. Pollock, O. Rodriguez, P. L. Martin et al., “Induction of metastatic gastric cancer by peroxisome proliferator-activated receptor activation,” *PPAR Research*, vol. 2010, Article ID 571783, 12 pages, 2010.

[64] G. D. Barish, V. A. Narkin, and R. M. Evans, “PPARδ: a dagger in the heart of the metabolic syndrome,” *Journal of Clinical Investigation*, vol. 116, no. 3, pp. 590–597, 2006.

[65] J. Jonkers and W. H. Moolenaar, “Mammary tumorigenesis through LPA receptor signaling,” *Cancer Cell*, vol. 15, no. 6, pp. 457–459, 2009.

[66] N. Panupinthu, H. Y. Lee, and G. B. Mills, “Lysophosphatidic acid production and action: critical new players in breast cancer initiation and progression,” *British Journal of Cancer*, vol. 102, no. 6, pp. 941–946, 2010.

[67] D. A. Foster, “Phosphatidic acid signaling to mTOR: signals for the survival of human cancer cells,” *Biochimica et Biophysica Acta (BBA)—Molecular and Cell Biology of Lipids*, vol. 1791, no. 9, pp. 949–955, 2009.

[68] J. Storch and A. E. Thumser, “Tissue-specific functions in the fatty acid-binding protein family,” *The Journal of Biological Chemistry*, vol. 285, no. 43, pp. 32679–32683, 2010.

[69] P. Kannan-Thulasiraman, D. D. Seachrist, G. H. Mahabeleshwar, M. K. Jain, and N. Noy, “Fatty acid-binding protein 5 and PPARβ/δ are critical mediators of epidermal growth factor receptor-induced carcinoma cell growth,” *Journal of Biological Chemistry*, vol. 286, no. 41, pp. 19106–19115, 2011.

[70] L. Levi, G. Lobo, M. K. Doud et al., “Genetic ablation of the fatty acid-binding protein FABPs suppresses HER2-induced mammary tumorigenesis,” *Cancer Research*, vol. 73, no. 15, pp. 4770–4780, 2013.

[71] K. M. Niemi, H. A. Kenny, C. V. Penicka et al., “Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth,” *Nature Medicine*, vol. 17, no. 11, pp. 1498–1503, 2011.

[72] K. Ito, A. Carracedo, D. Weiss et al., “A PML-PPAR-δ pathway for fatty acid oxidation regulates hematopoietic stem cell maintenance,” *Nature Medicine*, vol. 18, no. 9, pp. 1350–1358, 2012.

[73] L. M. Coussens, L. Zitvogel, and A. K. Palucka, “Neutralizing tumor-promoting chronic inflammation: a magic bullet?” *Science*, vol. 339, no. 6177, pp. 286–291, 2013.

[74] D. I. Gabrilovich and S. Nagaraj, “Myeloid-derived suppressor cells as regulators of the immune system,” *Nature Reviews Immunology*, vol. 9, no. 3, pp. 162–174, 2009.

[75] D. M. Pardoll, “The blockade of immune checkpoints in cancer immunotherapy,” *Nature Reviews Cancer*, vol. 12, no. 4, pp. 252–264, 2012.

[76] A. Sica and V. Bronte, “Altered macrophage differentiation and immune dysfunction in tumor development,” *The Journal of Clinical Investigation*, vol. 117, no. 5, pp. 1155–1166, 2007.
K. Kang, S. M. Reilly, V. Karabacak et al., “Adipocyte-derived Th2 cytokines and myeloid PPARδ regulate macrophage polarization and insulin sensitivity,” *Cell Metabolism*, vol. 7, no. 6, pp. 485–495, 2008.

J. I. Odegaard, R. R. Ricardo-Gonzalez, A. Red Eagle et al., “Alternative M2 activation of Kupffer cells by PPARδ ameliorates obesity-induced insulin resistance,” *Cell Metabolism*, vol. 7, no. 6, pp. 496–507, 2008.

L. Mukundan, J. I. Odegaard, C. R. Morel et al., “PPAR-δ senses and orchestrates clearance of apoptotic cells to promote tolerance,” *Nature Medicine*, vol. 15, no. 11, pp. 1266–1272, 2009.

P. Cheng, C. A. Corzo, N. Lutetteke et al., “Inhibition of dendritic cell differentiation and accumulation of myeloid-derived suppressor cells in cancer is regulated by S100A9 protein,” *Journal of Experimental Medicine*, vol. 205, no. 10, pp. 2235–2249, 2008.

S. Hiratsuka, A. Watanabe, Y. Sakurai et al., “The S100A8-serum amyloid A3-TLR4 paracrine cascade establishes a pre-metastatic phase,” *Nature Cell Biology*, vol. 10, no. 11, pp. 1349–1355, 2008.

P. Sinha, V. K. Clements, A. M. Fulton, and S. Ostrand-Rosenberg, “Prostaglandin E2 promotes tumor progression by inducing myeloid-derived suppressor cells,” *Cancer Research*, vol. 67, no. 9, pp. 4507–4513, 2007.

C.-H. Chang, J. Qiu, D. O’Sullivan et al., “Metabolic competition in the tumor microenvironment is a driver of cancer progression,” *Cell*, vol. 162, no. 6, pp. 1229–1241, 2015.

A. J. Muller and P. A. Scherle, “Targeting the mechanisms of tumoral immune tolerance with small-molecule inhibitors,” *Nature Reviews Cancer*, vol. 6, no. 8, pp. 613–625, 2006.