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 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 Ptgs2 and is a constituent of phosphatidylcholine (PC) required for prostaglandin synthesis. Lysophosphatidylcholine (LPC) is generated from PC by phospholipase A2 (Pla2), and lysophosphatic 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].
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 synthesis are 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-Ptgs2 mice [56], but not in PPARδ-null mice [30]. These findings suggest a feed-forward mechanism, whereby transactivation of the prostaglandin E2 receptor, Ptger4, by PPARδ [57], coupled with the generation of arachidonic acid by phospholipase A2 [58] and the biosynthesis of prostaglandin E2 (PGE2) via Pges2, elicits a self-sustaining inflammatory response.

In addition to activation of the prostaglandin axis, PPARδ increases expression of the acute phase proteins Saa1, Saa2, S100a8, and S100a9, as well as several members of the kallikrein gene family [31], all of which are elevated in ER+ breast cancer [59, 60] and whose promoter regions contain PPREs. S100a8 and S100a9 are ligands for Ager (advanced glycation end-product receptor), another PPAR-dependent gene that mediates acute and chronic inflammation, tumor development, and metastasis in several types of cancer and proliferative disorders [61, 62], including gastric carcinogenesis [63] and psoriasis [49]. Thus, there is strong evidence to implicate PPARδ in driving multiple inflammatory pathways implicated in tumorigenesis.

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.

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 Saal2/3 and S100a8/9 pathways, which are implicated in 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 ARG1, 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.
metabolically within the tumor microenvironment. This conclusion is also consistent with our recent finding that Plac1, which is overexpressed in MMTV-PPAR\(\delta\) 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 PPAR\(\delta\) 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 PPAR\(\delta\) 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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