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Molecular Pathways: Dietary regulation of stemness and tumor initiation by the PPAR-δ pathway

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Abstract

Peroxisome Proliferator-Activated Receptor delta (PPAR-δ) is a nuclear receptor transcription factor that regulates gene expression during development and disease states such as cancer. However, the precise role of PPAR-δ during tumorigenesis is not well understood. Recent data suggest that PPAR-δ may have context specific oncogenic and tumor suppressive roles depending on the tissue, cell-type, or diet-induced physiology in question. For example in the intestine, pro-obesity diets, like a high fat diet (HFD), are associated with increased colorectal cancer incidence. Interestingly, many of the effects of a HFD in the stem and progenitor cell compartment are driven by a robust PPAR-δ program and contribute to the early steps of intestinal tumorigenesis. Importantly, the PPAR-δ pathway or its downstream mediators may serve as therapeutic intervention points or biomarkers in colon cancer that particularly arise in obese patients. Although potent PPAR-δ agonists and antagonists exist, their clinical utility may be enhanced by uncovering how PPAR-δ mediates tumorigenesis in diverse tissues and cell-types as well as in response to diet.

BACKGROUND

Peroxisome Proliferator-Activated Receptor delta (PPAR-δ) belongs to the Peroxisome Proliferator-Activated Receptor (PPAR) subfamily of nuclear receptor transcription factors that is comprised of three members (alpha, beta/delta and gamma) (1). PPARs are critical regulators of metabolism and exhibit tissue and cell-type specific expression patterns and functions that can be altered by physiological cues. Although PPAR isoforms have highly homologous structures and have overlapping functions, distinct selective ligands have been identified to activate each family member exclusively. PPAR-α is the first member of the family that was cloned and characterized in mouse liver where it regulates lipid homeostasis.
and reduces triacylglycerol levels. PPAR-γ has been extensively studied in adipose tissue where it controls adipogenesis, lipid metabolism and enhances glucose metabolism (1). In particular, PPAR-δ is highly expressed in the intestinal crypts, keratinocytes and oxidative skeletal muscle fibers (2) and is a master regulator of lipid metabolism (3). For example, PPAR-δ mediated metabolic regulation prevents against diet-induced obesity, metabolic syndrome and enhances skeletal muscle endurance and function (4, 5). Furthermore, dietary interventions such as fasting (3) and inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ) (6) augment PPAR-δ signaling. Thus, PPAR-δ couples diverse dietary, nutritional, or physiological inputs to organismal metabolism (7–9).

While long chain fatty acids and their derivatives were initially recognized as endogenous activators of PPAR-δ pathway, the actual nature of the physiological ligands of PPAR-δ remains elusive. In the past decade, in addition to fatty acids, derivatives of arachidonic acid (10), lipoperoxidation products (11) and all-trans-retinoic acid (ATRA) (12) have been proposed to activate the PPAR-δ pathway. Although a general consensus is lacking, two major models have been postulated regarding how nuclear PPAR-δ senses its ligand(s). In the first model, it is proposed that the ligands are delivered from the cytoplasm to the nucleus by fatty acid binding proteins (FABPs) (13, 14), and in a second model it is suggested that the ligands are products of active nuclear lipid metabolism (15). Importantly, several very potent and selective small molecule PPAR-δ agonists including GW501516, GW0742 (16), and MBX-8025 (17) have been developed and widely used experimentally to decipher the biological significance of PPAR-δ mediated transcriptional activity (Figure 1).

PPAR-δ controls transcription both directly and indirectly (1). Direct regulation involves partnering with retinoid X receptor (RXR) and binding to peroxisome proliferator response elements (PPRE) in the enhancers and promoters of its target genes (Figure 1). Furthermore, PPAR-δ mediated transcriptional activation relies on ligand binding and concomitant epigenetic mechanisms that include displacement of co-repressors and recruitment of co-activator associated chromatin-remodeling factors, which orchestrate the framework necessary for transcriptional initiation (18). Over the past decade, PPAR-δ or its direct transcriptional targets have been demonstrated to bear on diverse cellular functions such as stem cell maintenance, cellular differentiation, metabolism and inflammation.

PPAR-δ also regulates a multitude of genes indirectly by affecting the activity of other transcription factors through physical interaction or through signal transduction pathways that impact the function of other transcription factors (Figure 1). For example, PPAR-δ is found to interfere with NFκB pathway (an important pathway in controlling inflammatory gene expression) and attenuate inflammation (19). Moreover, PPAR-δ cooperates with β-catenin (a key transcription factor for cell fate determination) in bone turnover and intestinal tumorigenesis (7, 20).

Gene expression analysis studies in combination with chromatin immunoprecipitation sequencing (ChIP-seq) have identified direct and indirect PPAR-δ regulated genes (21, 22). Well-documented direct targets of PPAR-δ include genes involved in fatty-acid oxidation and lipid metabolism such as Cpt1a, Fabp1 and Pdk4, whereas pro-inflammatory cytokines
like TNF-α and IL-6 are regulated indirectly. Overall, PPAR-δ controls the expression of a large set of genes through different mechanisms that are influenced by the PPAR-δ expression levels, interaction with additional transcription factors as well as the abundance and nature of its ligands. These different levels of control confer versatility to PPAR-δ mediated gene regulation in myriad tissues and cell types during development and disease states such as cancer.

**PPAR-δ in development and cancer**

Several developmental abnormalities have been reported in PPAR-δ-null mice including reduced gestational and postnatal body weight as well as abnormalities in multiple tissues such as adipose tissue, skin, and intestine (23, 24). In adipose tissue, PPAR-δ deficiency leads to a reduction in adipocyte numbers and PPAR-γ expression levels—the PPAR family member that controls adipogenesis (23). While PPAR-δ is not directly implicated in the regulation of adipogenesis, it contributes to the metabolic response of adipose tissue to dietary fatty acids (8, 23). Although PPAR-δ is expendable for homeostatic function in the skin, it plays a critical role in skin repair after injuries that disrupt skin integrity. Also it is understood that agonist-activated PPAR-δ hampers cellular proliferation and induces keratinocyte differentiation (24, 25). Thus, these findings are consistent with the notion that PPAR-δ signaling may possess anti-tumorigenic roles in the skin by preventing the growth and promoting the differentiation of (pre-)malignant cells through antagonizing the expression of proteins known to contribute to keratinocyte hyperproliferation and skin tumorigenesis (24–27). However, these anti-tumorigenic effects of PPAR-δ signaling in the skin may be context specific as it is observed in only some models of skin cancer (28, 29).

In the intestine, PPAR-δ performs critical regulatory functions and modulates intestinal physiology in multiple cell types, yet the underlying mechanisms are poorly understood. For instance, PPAR-δ was identified as a crucial factor in Paneth cell differentiation and thus, implicating it as a significant player in intestinal homeostasis (30). Paneth cells not only possess anti-microbial functions but also constitute a niche component for intestinal stem cells (ISCs) that reside at the bottom of the crypt, a location where PPAR-δ expression is the highest in the intestine (30, 31). By influencing Paneth cell differentiation, PPAR-δ regulates a significant support cell of the ISC, which drives the rapid renewal of the intestinal epithelium. In addition, PPAR-δ contributes to intestinal physiology through the control of lipid absorption, cholesterol trafficking and enteroendocrine cell function in more differentiated or specialized intestinal cell-types (32–34).

Initial reports on the role of PPAR-δ in intestinal tumorigenesis suggested that PPAR-δ is a direct transcriptional target of the Wnt/β-catenin pathway, a pathway that governs intestinal maintenance and tumorigenesis. Adenomatous polyposis coli (APC) orchestrates the destruction of cytoplasmic β-catenin in the absence of an upstream Wnt activation signal to tightly control β-catenin nuclear localization and activity. APC inactivation leads to strong activation of the β-catenin pathway and is the most common initiating oncogenic event of intestinal dysplasia (35). Although early studies demonstrated induction of PPAR-δ in intestinal tumors that were formed upon loss of APC or by chemical mutagenesis, subsequent reports in both rodents and humans failed to establish an unequivocal induction
of PPAR-δ expression or activity in intestinal cancers (36). Several studies have utilized either whole body or intestinal specific genetic ablation of PPAR-δ to delineate the precise function of PPAR-δ in tumor prone APC\textsuperscript{min/+} mice (mice with nonsense mutation in Apc gene that results in a truncated protein) or chemically induced models of intestinal tumorigenesis. While some studies found a pro-tumorigenic role for PPAR-δ, others posited an anti-tumorigenic function. Conflicting results from these loss of function studies have raised important questions regarding the role of PPAR-δ in intestinal tumorigenesis (23, 37–39). In contrast, however, gain of function studies that utilized the PPAR-δ agonist GW501516 more consistently demonstrated that PPAR-δ activation mediates a pro-tumorigenic phenotype in the intestine (40).

These conflicting findings, regarding PPAR-δ necessity in intestinal tumorigenesis, may be due to different genetic strategies used to disrupt PPAR-δ function. Studies that supported an anti-tumorigenic role for PPAR-δ in APC\textsuperscript{min/+} mice utilize germline disruption of PPAR-δ exon 8 (37, 38). Whereas ablation of PPAR-δ by disrupting exon 4 failed to decrease tumor incidence in Apc\textsuperscript{min/+} mice but led to a reduction in size of the largest intestinal adenomas (23). However, deletion of PPAR-δ exon 4 and part of exon 5 significantly diminished tumor numbers in Apc\textsuperscript{min/+} mice, and exon4 deletion reduced dysplastic lesions in Apc\textsuperscript{min/+} mice exposed to chemical injury (39, 41). Some of the discrepancy likely arises from the fact that disruption of exon 8 (the last PPAR-δ exon) may produce a hypomorphic protein, while disruption of exon 4 (an essential portion of the PPAR-δ DNA binding domain) ablates PPAR-δ activity (42). Lastly, it is important to point out that these studies used germline PPAR-δ mutants. More recently, intestine-specific PPAR-δ loss (targeting exon 4) decreased the numbers of dysplastic lesions in response to chemical mutagenesis (42). Another possible confounder in these studies is the use of different genetic backgrounds, which is known to influence tumor susceptibility in Apc\textsuperscript{min/+} mice or to chemical injury (1).

**Dietary regulation of stemness and tumor initiation**

As discussed above, accumulating evidence underscores the importance of PPAR-δ pathway in health and disease. However little is known about how PPAR-δ contributes to the regulation of stemness and tumor initiation in response to diet-induced physiologies. Diet is a modifiable lifestyle factor that has a profound impact on mammalian physiology, health, and disease including cancer. Long-lived mammalian tissue-specific stem cells play a key role in how tissues adapt to diverse diet-induced physiological states. Such stem cells dynamically remodel tissue composition in response to physiological cues by altering the balance between self-renewal and differentiation divisions (43). Factors that increase somatic stem cell self-renewal division rate are implicated to elevate cancer risk (44, 45). This suggests that dietary interventions that boost stem cell self-renewal increase the potential pool of cells that can undergo mutagenesis and give rise to cancer.

Consistent with this notion, we recently demonstrated that a pro-obesity high fat diet (HFD)-activated PPAR-δ program augments the numbers, proliferation and function of ISCs in the mouse intestine, providing a possible explanation to the long-sought link between diet-induced obesity and cancer (7, 46). In addition, intestinal adaptations to a long-term HFD not only enabled ISCs to acquire niche independence (i.e. initiate mini-intestines in culture
without need of their Paneth niche) but also allowed non-stem cell progenitors to obtain stem-cell attributes. These changes effectively augmented the numbers of cells within the intestine that possessed stemness and that could initiate tumors upon loss of the APC tumor suppressor gene (7). Moreover, enforced PPAR-δ activation mimicked many of these effects of a HFD. As mentioned, there are differing opinions on the role of PPAR-δ in intestinal tumor initiation. However, these findings demonstrate that PPAR-δ activation in ISCs and progenitors has pro-tumorigenic effects in the intestine and raises the possibility that PPAR-δ inhibition in the setting of a HFD may dampen tumor initiation, progression, or both.

An important question is whether a HFD has similar stem cell enhancing effects in other tissues. Interestingly, in contrast to the enhanced stemness observed in the intestine, HFD decreases neural progenitor cells proliferation and hippocampal neurogenesis by increasing lipid peroxidation and reducing BDNF levels in hippocampus (47). On the other hand, HFD alters the differentiation potential of bone marrow-derived mesenchymal stem cells (MSCs), subcutaneous adipose-derived stem cells (sqASCs), and infrapatellar fat pad-derived stem cells (IFP). Notably, the fatty acid constituents of the diet in part mediated this effect, implicating a possible role for PPAR-δ signaling (48). Also, the impact of a HFD in hematopoiesis is context dependent. A recent study demonstrated that a maternal HFD compromises the expansion of the fetal HSPC pool and hematopoietic lineage specification. Conversely, adult hematopoiesis is augmented in response to HFD-induced obesity (49, 50). The fact that PPAR-δ-activated fatty acid oxidation drives hematopoietic stem cell self-renewal (51) suggests that HFD-mediated regulation of hematopoiesis may involve PPAR-δ function. Nonetheless, whether a HFD or PPAR-δ is linked to tumor initiation in these tissues warrants further investigation.

CLINICAL-TRANSLATIONAL ADVANCES

Despite the fact that preclinical studies have provided evidence that PPAR-δ agonists possess therapeutic value in the treatment of several metabolic diseases, there are currently no FDA approved agonists for PPAR-δ. (5, 9). This is in contrast to PPAR-α and PPAR-γ, which have FDA approved agonists that are standard of care for metabolic disorders such as hyperlipidemia and diabetes. Although clinical trials revealed that short-term administration of PPAR-δ agonists GW501516 (NCT00841217) (52) and MBX-8025 (NCT00701883) (53) had beneficial effects in patients with metabolic syndrome, preclinical long-term studies in mice indicated that PPAR-δ agonists might have pro-tumorigenic effects, thus dampening enthusiasm for these compounds in human trials.

Several studies have suggested that PPAR-δ expression has prognostic value for cancer patients including those with colorectal cancer (54, 55). However, there are inconsistencies in the reported PPAR-δ expression levels of different human tumors compared to normal tissue as well as how PPAR-δ expression correlates with prognosis. For instance, a study that examined 52 colorectal cancer patients found that PPAR-δ and COX-2 expression in tumors negatively correlates with patient survival (54). However, another study with 141 colorectal cancer patients revealed that higher expression of PPAR-δ in primary colorectal tumors was associated with lower expression of Ki67 (a cellular marker for proliferation), a higher frequency of stage I cases, a lower frequency of later stage cases, and a lower rate of
lymph node metastasis (55). More studies are required to precisely ascertain the molecular mechanisms that PPAR-δ employs during cancer initiation and progression and how this impacts patient prognosis.

PPAR-δ polymorphisms have been associated with physical performance (56), diabetes (57), obesity (58) and cancer (59, 60). A recent study focusing at colorectal cancer patients identified 7 novel variants among 22 inherited or acquired PPARD variants. Interestingly, 4 recurrent variants were detected in or adjacent to exon 4, which encodes an essential portion of the PPAR-δ DNA-binding domain, suggesting that these variants have functional significance (60). Although these variants may have clinical importance, the effect of PPAR-δ polymorphisms on gene expression or function of PPAR-δ is still poorly understood.

Our recent data indicates that HFD-activated PPAR-δ engages a specific β-catenin program that involves expression of genes implicated in intestinal tumorigenesis such as Jag1 and Bmp4 in ISCs and progenitors (7). Future studies need to address whether increased expression of Jag1 or Bmp4 has any prognostic or correlative value in colorectal cancer that arise in obese patients. Furthermore, it will be important to determine the functions of PPAR-δ in the setting of diverse tissues, cell-types, diets, and risk factors that are associated with cancer in humans. The fact that PPAR-δ links dietary regulation of stemness to tumor initiation in the intestine raises the possibility of a new therapeutic approach in the treatment of intestinal cancers in obesity (7) such as exploiting possible PPAR-δ dependencies in tumors that arise in a HFD or obesity. Uncovering the cellular and molecular mechanisms by which PPAR-δ drives its effects may lead to new therapeutic insights, especially in those cancers with high PPAR-δ activity.

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Mechanisms of PPAR-δ mediated gene regulation. Dietary fatty acids, synthetic small molecule agonists (GW501516), intracellular fatty acids and metabolites may activate PPAR-δ pathway. Two major models have been proposed regarding delivery of PPAR-δ ligands. First, fatty acid binding proteins (FABPs) can transport fatty acids to the nucleus. Second, ligands are produced in the nucleus as a result of nuclear lipid metabolism. Ligand binding activates PPAR-δ and leads to regulation of several important biological processes. First, PPAR-δ partners with retinoid X receptor (RXR) and binds to peroxisome proliferator response elements (PPRE) to activate the expression of genes involved in lipid metabolism (1). In addition, PPAR-δ interacts with β-catenin, which is a key transcription factor for cell fate determination and assists β-catenin to induce gene expression in order to modulate stemness in response to dietary cues like fatty acids (2). Lastly, PPAR-δ inhibits inflammatory gene expression by interfering with NFκB pathway (3).