Review

MOLECULAR METABOLISM

Peroxisomes and PPARs: Emerging role as master regulators of cancer metabolism

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ABSTRACT

Cancer is a disease characterized by the acquisition of a multitude of unique traits. It has long been understood that cancer cells divert significantly from normal cell metabolism. The most obvious of metabolic changes is that cancer cells strongly rely on glucose conversion by aerobic glycolysis. In addition, they also regularly develop mechanisms to use lipids and fatty acids for their energy needs. Peroxisomes lie central to these adaptive changes of lipid metabolism.

Peroxisomes are metabolic organelles that take part in over 50 enzymatic reactions crucial for cellular functioning. Thus, they are essential for an effective and comprehensive use of lipids' energy supplied to cells. Cancer cells display a substantial increase in the biogenesis of peroxisomes and an increased expression of proteins necessary for the enzymatic functions provided by peroxisomes. Moreover, the enzymatic conversion of FAs in peroxisomes is a significant source of reactive oxygen and nitrogen species (ROS/RNS) that strongly impact cancer malignancy. Important regulators in peroxisomal FA oxidation and ROS/RNS generation are the transcription factors of the peroxisome proliferator-activated receptor (PPAR) family. This review describes the metabolic changes in tumorigenesis and cancer progression influenced by peroxisomes. We will highlight the ambivalent role that peroxisomes and PPARs play in the different stages of tumor development and summarize our current understanding of how to capitalize on the comprehension of peroxisomal biology for cancer treatment.

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1. INTRODUCTION

Cancer is a disease also characterized by an aberrant cellular metabolism and therefore dissecting the altered metabolic pathways that are causatively linked to the emergence or propagation of tumors remain a major focus of the cancer research during the last 50 years. During the last decade, the advent of novel sensitive methods in determining the altered bioenergetics of the cell coupled with metabolomics, epigenetics and single-cell sequencing provided critical insights into the metabolic reprogramming of cancer cells. Interfering with cancer cell metabolism, in all probability, is not a curative approach, but the particularities of cancer cell metabolism are directly linked to traits like invasiveness, metastasis, and chemoresistance. Consequently, understanding how to block changes in the way cancer cells metabolize and gain energy could be a way to improve response to other therapies and prolong survival. While research on cancer metabolism for decades focused understandably on the changes in glucose metabolism, namely the switch to aerobic glycolysis (Warburg effect) [1,2], cancer cells also differ in how they metabolize lipids and fatty acids (FAs). These changes in FA metabolism are strongly linked to peroxisomes.

Peroxisomes, initially called "microbodies", were first described by J. Rhodin as spherical single membrane entities, measuring approximately 0.1–1.0 μm in diameter [3]. Nobel Laureate Christian de Duve and Pierre Baudhuin deciphered detailed insights into peroxisomal structures and functional properties. This seminal work on microbodies helped to identify numerous microbody-specific enzymes such as urate oxidase, L- and D-amino acid oxidases, and catalase [4]. The term "peroxisome," coined by De Duve [5], was inspired by the catalase activity of these microbodies. Since these pioneering works of the 1960s, our understanding of peroxisome biology in maintaining cellular homeostasis has expanded significantly. These metabolic organelles participate in over 50 enzymatic reactions crucial for cellular functioning [6]. As the name implies, peroxisomes are oxidative organelles. They have essential roles in lipid metabolism, general energy metabolism, and turnover of reactive oxygen species (ROS). The crucial metabolic functions executed by peroxisomes include fatty acid α- and β-oxidation [7,8], biosynthesis of C24-bile acids [9], docosahexaenoic

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acid (DHA) [10,11], ether phospholipids [12] and removal of ROS [13,14]. Consequently, peroxisomes are critical metabolic organelles whose dysfunction can lead to severe metabolic disorders. Defects in genes coding for peroxisomal proteins are associated with their metabolic aberrations [15].

A hallmark of cancer cells is metabolic reprogramming [16]. This is driven by the need to rapidly dividing cancer cells for increased metabolic turnover and is linked to malignant behavior like invasiveness and metastasis. Given the critical role of peroxisomes in cell metabolism, it is not surprising that different types of cancers like colorectal cancer [17], prostate cancer [18,19] as well as breast, ovarian, and bladder cancer [20] are characterized by elevated levels of peroxisomal lipid processing enzymes.

In the last few years, the role of peroxisomes in cancer has attracted more interest. Consequently, in this review, we seek to collectively curate recent scientific developments in understanding peroxisome metabolism and its relevance in cancer. Given their central role in fatty acid metabolism, we will focus not only on the genesis and assembly of peroxisomes but also elucidate on the peroxisome proliferator-activated receptor (PPAR) family PPARs.

2. PEROXISOME BIOGENESIS AND ROLE IN METABOLISM

2.1. Biogenesis of peroxisomes

Peroxisome biogenesis comprises the assembly of a lipid membrane, the import of matrix proteins, and subsequent organelle expansion. Critical for this assembly is a class of several protein families named peroxins (PEXs). PEXs are categorized into three primary groups. The first group, comprising Pex3, Pex16, and Pex19, is crucial for peroxisome membrane assembly. The second group, including PEX2, PEX5, PEX7, PEX10, PEX12, PEX13, and PEX14, facilitates the import of matrix proteins, with PEX5 and PEX7 serving as key transporters. The third group comprises PEX11 isoforms, specifically Pex11α, Pex11β, and Pex11γ, which play complex roles in peroxisome dynamics. Notably, Pex11β has been well-characterized for its involvement in peroxisome elongation and fission, whereas the precise functions of Pex11α and Pex11γ in peroxisome division and proliferation remain less understood [21]. In addition, the peroxins PEX5 act as a transporter, and PEX2, PEX10, and PEX12 form a complex to function as an E3 ubiquitin ligase, thereby assisting the recycling of PEX5 in a ubiquitin modification-dependent process [18]. The peroxisome biogenesis factors PEX3 and PEX16 bind with the endoplasmic reticulum (ER) membrane and post-exit interacts with PEX19, a cycling receptor in the cytosol [22]. PEX19 binds with peroxisomal membrane proteins (PMPs) and docks with PEX3 to add PMPs to the peroxisomal membrane [23]. The proliferation of peroxisomes is mediated by Pex11β, dynamin-like protein 1 (DLP1 aka DNM1L), mitochondrial fission factor (Mff), and mitochondrial fission 1 (Fis1) that are localized to peroxisomes. Docosahexaenoic acid (DHA, C22:6n-3), a poly-unsaturated fatty acid of peroxisomal β-oxidation metabolites, augments hyper-oligomerization of Pex11β thereby forming Pex11β-rich regions in the peroxisome membrane inducing the unidirectional elongation of peroxisomes. Mff and Fis1 localize at the constrictions of the membranes of elongated peroxisomes, where Mff recruits DLP1. This leads to the formation of a complex comprising Pex11β, Mff, and DLP1 that promotes Mff-mediated fission during peroxisomal division along with the involvement of Pex11α and Pex11γ and Fis1 that interacts with DLP1. The energy required to cleave peroxisomal membranes for peroxisomal fission is obtained by the generation of GDP due to hydrolysis of GTP by DLP1 resulting in peroxisomal fission [21,24,25]. The daughter peroxisomes become mature and functional by importing matrix and membrane proteins and may re-enter the membrane expansion component of the cycle (Figure 1).

2.2. Peroxisomal lipid metabolism

Fatty acid oxidation (FAO) is a tightly regulated process that occurs in both peroxisomes and mitochondria; however, the nature and length of fatty acids (FA) processed by these two organelles vary significantly: the oxidation of linear fatty acids with short (<6 carbons) to long (13–21 carbons) chain lengths is carried out by mitochondria [26], while peroxisomes are involved in the oxidation of linear very-long-chain

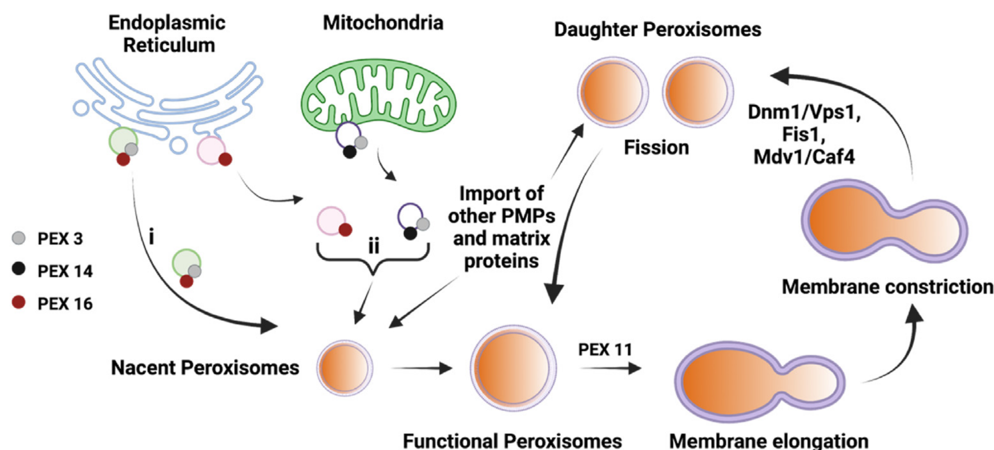

Figure 1: Schematic representation of the peroxisomal biogenesis pathway

ER-mediated *de novo* biogenesis involves formation of peroxisomes from ER-derived vesicles containing both PEX3 and PEX16. It involves fusion of PEX-bound vesicles originating from both the mitochondria (PEX3 and PEX14-bound), and the ER, (PEX16-bound). This is followed by import of peroxisomal membrane protein (PMPs, e.g., PEX19, PEX5, PEX7, PEX1, PEX6). The import of PMP gives rise to functional peroxisomes.

Steps of peroxisome fission: In the elongation/tubulation stage, PEX11 congregate on one end of the peroxisome amongst other PMPs, giving rise to a narrow, tubular structure. During constriction Fis1 recruits Dnm1 to its site of action for the final scission of peroxisomes. Mdv1 and Caf4 are two additional adapter proteins required in yeast. These proteins cluster near PEX11 proteins and forms a “pinch” on the peroxisome. This leads to fission into two asymmetric daughter peroxisomes. The daughter peroxisomes grow in size by importing matrix and membrane proteins and mature into functional peroxisomes which may re-enter the membrane expansion component of the cycle.

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fatty acids (VLCFAs) $\geq$ 22 carbons lengths to generate long-chain acyl-CoA fatty acids and acetyl-CoA. Furthermore, peroxisomes are also essential in the oxidation of branched-chain fatty acids such as pristanic acid and di- or tri-hydroxycholestanoic acids (DHCA/THCA) [26–28]. Evidence supporting the interconnection of peroxisomes and oxidation of VLCFAs came from the observation that the serum levels of VLCFAs and branched-chain fatty acids in patients with peroxisomal disorders were significantly higher [29,30]. In addition, studies with liver tissue subcellular fractionation confirmed that peroxisomes preferentially carried out β-oxidation of VLCFAs [31]. Also, branched-chain fatty acid accumulation in peroxisomal disorder indicated a role of peroxisomes in α-oxidation [32]. In this regard, efficient lipid transport across the peroxisomal membrane remains the most crucial step for any metabolic reaction. Studies have revealed that a particular class of transporters called the peroxisomal ATP-binding cassette (ABC) transporter subfamily D (including members ABCD1, ABCD2, and ABCD3) predominantly mediate the membrane transport process [28]. The mechanism for β-oxidation of FA by peroxisomes involves 2-carbon chain-shortening and formation of a new acyl CoA molecule in four consecutive steps: (1) oxidation; (2) hydration; (3) dehydrogenation; and (4) thiolysis. Some of the critical regulators of these processes have shown implications in cancer. VLCFAs can also serve as ligands for activating nuclear peroxisome proliferator-activated receptor (PPAR) signaling, promoting their own β-oxidation [33]. The main enzymes involved in peroxisomal β-oxidation are acyl-CoA oxidase 1 (ACOX1) and acyl-CoA oxidase 2 (ACOX2), ACOX1 is the primary enzyme responsible for the peroxisomal β-oxidation of VLCFAs and dicarboxylic acids (DCAs). In contrast, ACOX2, also known as branched-chain acyl-CoA oxidase (BCOX), primarily handles the oxidation of CoA esters of pristanic acid and DHCA/THCA). The process involves oxidation of fatty acyl-CoA by ACOX1 and transferring two hydrogens to flavin adenine dinucleotide (FAD), producing $FADH_2$ and enoyl-CoA by ACOX2. Electrons are transferred from $FADH_2$ to O_2, generating H_2O_2 and energy in the form of heat [34]. The hydration of enoyl-CoA forming 3-L-hydroxyacyl-CoA and their subsequent dehydrogenation yielding 3-ketoacyl CoA in an NAD + dependent mechanism, are executed by the multifunctional enzymes named L- and D-bifunctional protein (LBP and DBP), respectively [9,35]. Thiolysis, the final step in peroxisomal fatty acid β-oxidation, is mediated by two chief proteins, 3-ketoacyl-CoA-thiolase 1 (ACAA1; pTH1) and Sterol Carrier Protein X (SCPx; pTH2), leading to the generation of acetyl-CoA and acyl-CoA as end products. Peroxisomes are also involved in the oxidation of some mono- and polyunsaturated FAs [15,36]. This unique function is carried out by auxiliary enzymes such as enoyl-CoA isomerase(s) and 2,4-dienoyl-CoA reductase(s) of the peroxisomes by displacement of the double bond present in mono- and polyunsaturated acyl-CoAs, respectively.

The branched-chain fatty acids have a methyl group at γ-position, which prevents their β-oxidation [26]. The terminal carboxyl group is removed, producing CO_2 by α-oxidation in peroxisomes. β-Oxidation of fatty acids utilizes fatty acids only in the (S) isomeric conformation [37]. However, α-oxidation is a non-stereospecific process, accepting both (R) and (S) fatty acid isomers [38]. Thus, during the β-oxidation of the (R) form of phytanoyl-CoA, α-oxidation comes into play and converts the phytanoyl-CoA (R) form to the (S) form by the action of α-methylacyl-CoA racemase (AMACR) [39]. The end product pristanic acid can undergo peroxisomal β-oxidation. Formyl-CoA, produced in the second step, is further broken down to formate and, eventually, CO_2 (Figure 2) [40]. It is noteworthy that methyl-branched chain fatty acyl-CoA (e.g., pristanoyl-CoA, phytanoyl-CoA) stimulates PPAR-mediated oncogene activation [33].

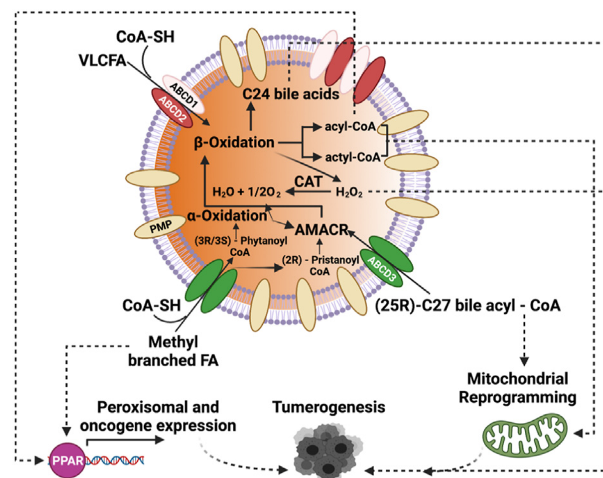

Figure 2: Peroxisomal metabolic modulation drive pro-tumorigenic pathways. Methyl-branched chain fatty acyl-CoA activates peroxisome proliferator activated receptor (PPAR)-mediated oncogene expression. Very-long chain fatty acids (VLCFAs) with CoA-SH enter the β-oxidation pathway generating H_2O_2 as a by-product which may exit the peroxisome and play a role in pro-tumorigenic processes. The end products of VLCFA β-oxidation, acyl-CoA and acetyl-CoA. Acyl-CoA may serve as a PPAR ligand, or be transported to the mitochondria, and potentially contribute to mitochondrial reprogramming. (25R)-C27 bile acids are known to alter mitochondrial function and promote tumorigenesis. (25R)- C27 bile acyl-CoA undergoes β-oxidation to form primary C24 bile acid conjugates, which are pro-tumorigenic at relatively low doses. Note: Dashed lines indicate potential links that may exist between peroxisomal products and pro-tumorigenic progression; Solid lines indicate well-established peroxisomal pathways.

2.3. ROS/RNS metabolism in peroxisomes

It is well understood that a delicate balance in ROS levels is required in healthy cells and microenvironments as higher levels of ROS trigger tumorigenesis by promoting oncogenic mutations and inducing genomic instability. However, after a tumor is established, excessive ROS can prove deleterious for tumor progression [41,42]. Peroxisomes are an essential source of ROS, such as H_2O_2, superoxide ($O\bullet^-$), hydroxyl (•OH), and RNS, including nitric oxide (NO•) radicals. These radicals are produced as by-products during the peroxisomal fatty acid metabolism [6]. H_2O_2 in peroxisomes is produced mainly by the ACOX family of enzymes and other peroxisomal enzymes, such as L-α-hydroxyacid oxidase 1 and 2, and xanthine oxidase (XDH) [43]. The enzymes XDH and the inducible form of nitric oxide synthase (NOS2) are the two sources of superoxide ($O\bullet^-$) and nitric oxide (NO•) radicals in peroxisomes. H_2O_2 and $O\bullet^-$ are produced as by-products of the XDH catalytic cycle [44]. The enzyme NOS2 is a homodimer catalyzing the oxidation of L-arginine, creating NO• and citrulline [45]. Although there is no evidence supporting the existence of enzymes that produce •OH or NO_3^- in peroxisomes, it may be assumed that the peroxisomal H_2O_2 may be responsible for producing •OH through the Fenton reaction. In addition, the presence of enzymatic sources of $O_2\bullet^-$ and NO• generates NO_3^-, a kinetically and thermodynamically favored reaction [46].

A high quantity of ROS/RNS developed in the peroxisomes raises additional concern about how these metabolic specialists counterbalance the ROS leakage or unmanageable ROS-mediated damage to different cellular compartments. The peroxisome is equipped with at least six proteins with antioxidant functions, including superoxide dismutase 1 (SOD1), catalase (CAT), epoxide hydrolase 2 (EPHX2), 'microsomal' glutathione-S-transferase-1 (MGST1), peroxiredoxin-5 (PRDX5), and glutathione-S-transferase kappa 1 (GSTK1) [47].

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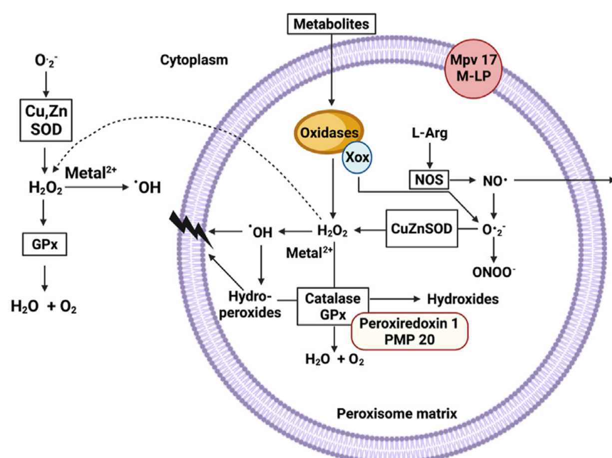

Figure 3: Schematic overview of peroxisomal enzymes involved in ROS production/degradation. Several peroxisomal oxidases (e. g., acyl-CoA oxidase) produce H_2O_2, which is either converted to hydroxyl radicals ($\cdot OH$) or decomposed by catalase and glutathione-peroxidase (GPx). $\cdot OH$ radicals can damage the peroxisomal membrane by lipid peroxidation of unsaturated fatty acids. Hydroperoxides formed as a result are decomposed by catalase and GPx. Peroxisomal oxidases generates superoxide anions ($O_2 \cdot^-$ which are scavenged by manganese superoxide-dismutase (MnSOD) and by copper-zinc superoxide-dismutase (CuZnSOD). The oxidation of L-arginine (l-Arg) to nitric oxide ($NO\cdot$) is catalysed by nitric oxide synthase (NOS). $NO\cdot$ reacts with $O_2 \cdot^-$ radicals to form peroxynitrite ($ONOO^-$). Peroxiredoxin 1 and PMP 20 play role in the degradation of H_2O_2. Correct localization of Mpv17 on peroxisomal membrane is still disputed.

Catalase, the most widely documented peroxisomal enzyme with antioxidant activity, forms a tetramer, accompanied by four heme groups that enable its enzymatic activity [48]. Its primary function is the quenching of peroxisomal H_2O_2 in a catalytic ($2H_2O_2 \rightarrow 2H_2O + O_2$) or peroxidatic ($H_2O_2 + AH_2 \rightarrow A + 2H_2O$) manner [49]. SOD1, a homodimeric enzyme found in the cytosol, the nucleus, and mitochondria, mediates the conversion of $O_2\bullet^-$ to O_2 and H_2O_2 ($2O_2\bullet^- + 2H^+ \rightarrow O_2 + H_2O_2$). It has been reported that this enzyme can be imported into peroxisomes by a complex with 'copper chaperone for SOD1′ via a piggyback mechanism [50]. Glutathione S-transferases (GST) superfamily of enzymes catalyze xenobiotics conjugation and potentially damage oxidative metabolites with glutathione [51]. Studies suggest that GSTK1 and MGST1 might be partially located in peroxisomes, executing xenobiotic detoxification and lipid peroxide products [52,53]. Another enzyme, PRDX5, which relates to the peroxisomal membrane, helps in by thiol-dependent reduction of H_2O_2 to H_2O, alkyl hydroperoxides (ROOH) to their respective alcohols (ROH), and NO_3^- to nitrite (NO_2^-) [54]. EPHX2, a homodimeric enzyme, binds to epoxides converting them to the corresponding dihydrothiols [55]. These enzymes together are also known for ROS elimination action. Apart from these reported enzymes, evidence suggests that peroxisomes also employ low molecular weight, non-enzymatic antioxidant compounds such as glutathione, ascorbic acid, and plasmalogens for combating ROS stress (Figure 3).

3. PEROXISOME METABOLISM IN TUMORIGENESIS AND CANCER PROGRESSION

3.1. Peroxisomal lipid metabolism: PPARs as metabolic master regulators in cancer

Increased rates of FA oxidation are a major contributing factor in the progression of various cancers in organs like the liver, lung, breast [56], and prostate [57]. As discussed previously, many peroxisomal enzymes are involved in regulating FA β-oxidation. Very-long chain polyunsaturated fatty acids (PUFAs) and their derivatives can act as ligands for PPARs, potentially regulating beta-oxidation pathways [58]. PPARs are ligand-activated transcription factors of the nuclear hormone receptor superfamily broadly belonging to three subtypes: PPARα, PPARγ, and PPARβ/δ. It is a well-established fact that the PPAR family members regulate the expression of genes associated with various cellular processes such as adipocyte differentiation, neurological signaling, inflammation, and tumorigenesis [59].

PPAR and peroxisomal activation has been linked to malignancy and poor prognosis in various cancers. Upon ligand activation, PPARs upregulates the expression of peroxisome metabolism genes like ACOX1 [60]. In the context of liver tumors, this leads to increased hepatic FA oxidation [61]. In addition, FA oxidation by ACOX1 also results in H_2O_2 buildup, thereby increasing the oxidative stress as observed in rodents models of liver cancer [61,62]. Overall, it has been shown that enhanced ACOX1 activity in hepatocellular carcinoma (HCC) tissue leads to tumor proliferation and reduces the survival of patients [63]. In this study, increased ACOX1 activity was caused by the downregulation of the lysine deacetylase sirtuin 5 (SIRT5). SIRT5 mediates the desuccinylation of ACOX1 and, thereby, its inhibition.

Gene expression analyses of breast tumors have revealed that relatively increased ACOX1 transcript levels correlate with inferior overall survival for HER2-positive breast cancer patients [64]. Interestingly, regarding breast cancer subtypes, ACOX1 levels were highest in HER2-positive tumors and lowest in triple-negative breast cancer (TNBC).

Peroxisomal activity might also affect response to systemic therapy. Recent studies from biopsy samples of HER2-positive breast cancer patients show methylation of CpG islands in the promoter region of the gene encoding for DBP (HSD17B4) and subsequent downregulation of DBD expression is a predictive marker of response to trastuzumab [65]. In lymphoma models, genetic downregulation of peroxisomal gene expression has shown promising results for therapy-induced apoptosis [66]. Therefore, inhibition of peroxisomal gene expression in multiple cancer types may serve as an 'Achilles' heel' in therapy-induced cell death.

Branched-chain FA is catabolized by α-oxidation before entering the β-oxidation pathway. As FAs in the (S) isomer conformation can only be processed via β-oxidation, the enzyme AMACR, which mediates the (R) to (S) conversion, plays an integral part in the processing of branched-chain FAs. AMACR is reported to be overexpressed in many types of cancers [67—69] including colon [70,71], gastric [72], breast [73], renal, and hepatocellular carcinoma [74]. It is a biomarker in prostate cancer diagnosis [75]. Immunostaining studies with normal prostate gland tissue surrounding cancer foci showing higher AMACR levels have been reported in several studies with prostate cancer patients. Elevated levels of AMACR expression in the tumor microenvironment may indicate the onset or progression of prostate cancer [20]. Studies with genetic silencing or chemical inhibition of AMACR in over-expressing prostate cancer line (LAPC-4) reduced cell proliferation by arresting cells in the G2-M cell cycle phase. Significant reduction in tumor burden of xenograft tumors models of myxofibrosarcoma (soft tissue sarcoma) cells (NMFH-2) was observed upon AMACR genetic knockdown [76]. Together, these studies emphasize the importance of AMACR as a drug target, and efforts are being made to design novel inhibitors of this enzyme.

In a tumor cell, PPARα and PPARγ exhibit controversial roles [77]. PPARγ enables cancer-associated fibroblasts and adipocytes to become donors of substrate for tumor growth by their metabolic reprogramming. Angiopoietin-like 4 (ANGPTL4), a secretory protein

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encoded by a target gene of PPARs, is known to trigger oncogenic processes like inflammatory signaling, extracellular matrix rearrangement, anoikis resistance, and metastasis, making it a potential and attractive drug target for cancer treatment [77].

4. PPARS AND MALIGNANCY

4.1. PPAR α

The few studies on the role of PPARα indicate a pro-carcinogenic, pro-proliferative effect. In breast cancer stem cells, GW6471 (a PPARα antagonist) is anti-proliferative and pro-apoptotic. At the same time, Wy14643 (a PPARα agonist) induces the clonal expansion of breast cancer mammospheres *via* nuclear receptor-$\kappa\beta$ (NF- $\kappa\beta$)/interleukin-6 (IL-6) axis, SLUG, Notch3, and Jagged 1 [78,79]. The high lipid turnover rate and energy demand required to maintain cancer stemness and self-renewal in pancreatic and colorectal cancer stem cells are ensured by PPARα signaling.

4.2. Anti-tumorigenic activity of PPARγ

PPARγ is a regulator of cell differentiation. Consequently, PPARγ agonists like thiazolidinedones (TZDs) promote differentiation of cancer stem cells by restraining yes-associated protein 1 (YAP) transcriptional activity and highlight a novel connection between PPARγ agonist in inducing adipogenesis, thereby mimicking the tumor-suppressive hippo pathway in osteosarcoma [80]. Gene expression analysis revealed that the molecular mechanism of action was by the induction of lipid metabolism pathways by TZDs while suppressing targets of the Hippo-YAP pathway, Wnt signaling, and cancer-related proliferation pathways. A significant finding that TZD action was restricted to the high Sox2 expressing cancer stem cell population and is dependent on PPARγ expression has been reported; whilst affecting tumor cell growth and cell fate by cytoplasmic sequestration of the transcription factors SOX2 and YAP required for tumorigenicity [80]. Similarly, activation of PPARγ by troglitazone, another TZD, caused a reversal of gene expression associated with colon cancer and inhibited tumor growth, malignancy, and de-differentiation of colon cancer cells [81]. Ligand activation of the PPARγ transcriptional pathway is also involved in the terminal differentiation of malignant breast epithelial cells, evidenced by extensive lipid accumulation, and changes in breast epithelial gene expression resulting in reduced growth and malignancy [82]. PPARγ agonists exert anti-inflammatory and pro-apoptotic activity by triggering NFκB trans-repression, and modulation of BCL-2 class proteins via PI3K/Akt pathway [83]; ciglitazone and 15-deoxy-D12,14-prostaglandin J2 (15d-PGJ2), (both PPARγ agonists) exhibited anti-proliferative activity in brain tumor stem cells *via* the inhibition of Sox2 while enhancing Nanog expression [84]. Even though the mechanism of action of PPARγ agonists in regulating differentiation and self-renewal remains unclear, PPARγ is known to attenuate extracellular matrix (ECM) remodeling and epithelial—mesenchymal transition (EMT) by the suppression of matrix metalloproteinases and antagonizing Smad3-dependent transcriptional activity, leading to reduced tumor invasion and metastasis in lung cancer [77,85,86] (Figure 4 (a)).

4.3. Pro-tumorigenic activity of PPARγ

PPARγ is generally overexpressed in liposarcoma, colon, breast, and prostate carcinomas [87,88]. PPARγ agonists have exhibited pro-tumorigenic activity in colorectal cancer [89,90], renal and bladder cancers [91,92]. In prostate cancer, PPARγ overexpression activates Akt3, inhibiting nuclear export protein CRM1 and leading to the retention of PPARγ co-activator 1α (PGC1α). PGC1α again elevates the mitochondrial ATP output in cancer cells to facilitate the extensive energy requirement for EMT and metastasis of tumors [93]. In the genetic breast cancer model, MMTV-PyV co-transgenic expression of a constitutively active PPARγ in the mammary gland accelerated tumor development significantly [94]. In thyroid cancer, PPARγ protein expression is said to be linked with the aggressiveness of thyroid cancer cells, wherein depletion of PPARγ in anaplastic thyroid cancer cells demonstrated decreased growth and invasion *in vitro*, as opposed to its aggressive growth and invasion in PPARγ overexpressed thyroid cancer cells [95]. Studies with a liver-specific Pten knockout mouse model revealed that pro-tumorigenic signaling of PPARγ was mediated by Akt2 and by repression hepatocyte nuclear factor 1α (HNF1α) [77,96,97] (Figure 4B).

Thus, the evidence for the broad role of PPARγ remains inconclusive. A possible interpretation of the published data so far could be that PPARγ blocks the acquisition of stem cell-like characteristics during transformation, thereby inhibiting certain traits connected to malignancy (invasiveness, metastasis, chemoresistance), but on the other hand, PPARγ is required to match the high metabolic needs of cancer cells. The increased metabolic capacity of elevated PPARγ might be needed for cancer cells to act on their metastatic, proliferative, and invasive potential. However, as comprehensive experimental data is missing, this interpretation remains speculative. Further research could focus on the balance of this dual aspect of PPARγ and might also shed light on a stage-specific requirement for certain levels of PPARγ expression during tumorigenesis and manifestation.

4.4. PPARβ/δ

Another member of the nuclear receptor factor peroxisome proliferator-activated receptor family, PPARβ/δ, regulates its target gene expression either by transcriptional activation or repression through ligand-dependent and independent mechanisms and through interaction with other transcription factors. Apart from its significant function in intermediary metabolism, it has been shown to play a role in inflammation, differentiation, apoptosis, and processes involved in tumorigenesis. Clinically, the expression of PPARβ/δ and its target genes is correlated with poor outcomes in cancers. However, the mechanism of action and its role in cancer cell proliferation remains controversial [98].

It has been proposed that PPARβ/δ can be targeted for the prevention and/or treatment of diseases, including diabetes, dyslipidemias, metabolic syndrome, and cancer, due to its role in physiological functions ranging from enhancing FA catabolism, improving insulin sensitivity, inhibiting inflammation and increasing oxidative myofibers. It is also known to interact directly with the p65 subunit of NFκB, leading to inhibition of NFκB-dependent signaling, or direct interaction with ERK5 or STAT3 accounting for its anti-inflammatory activities [99]. A significant finding was reported wherein PPARβ/δ which is highly expressed in endothelial cells, upon pharmacological activation with PPARβ/δ agonists, has shown to increase endothelial cell proliferation *in vitro* and to intensify tumor angiogenesis *in vivo*, enhancing tumor progression and metastases, suggestive of its role in the regulation of the angiogenic switch in tumor progression. The molecular mechanism of action in the promotion of tumor-angiogenesis is mediated via activation of the PDGF/PDGFR pathway, c-Kit, and probably the VEGF/VEGFR pathway [100].

4.5. PPARs mediated metabolic-immune regulation in cancer

Recent studies emphasized the adaptive metabolic strategies implemented by immune cells: the competition with cancer cells in the tumor microenvironment for nutrition and survival renders their

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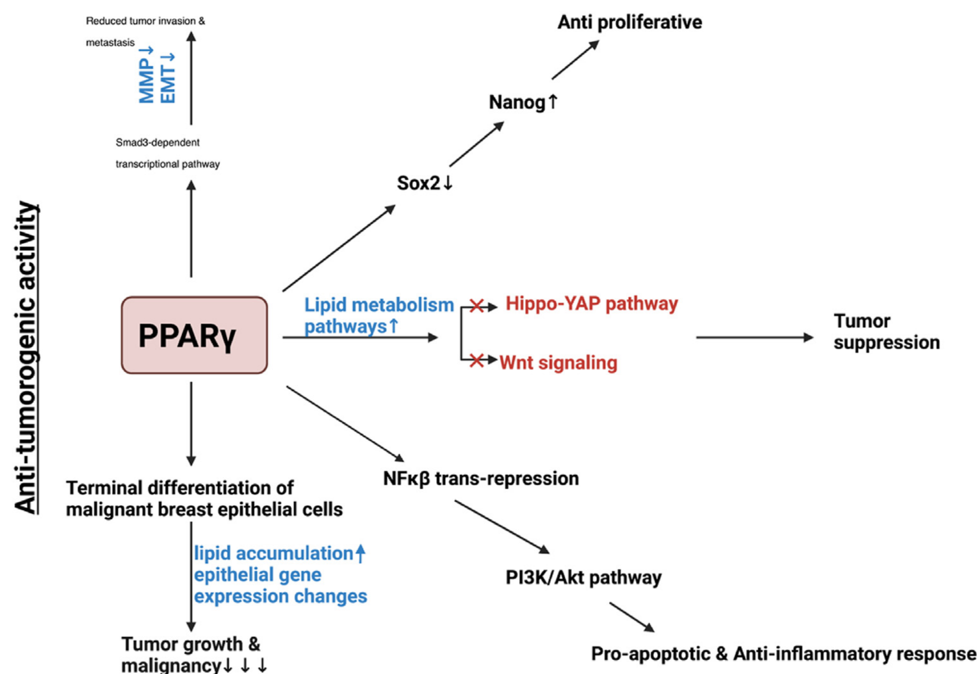
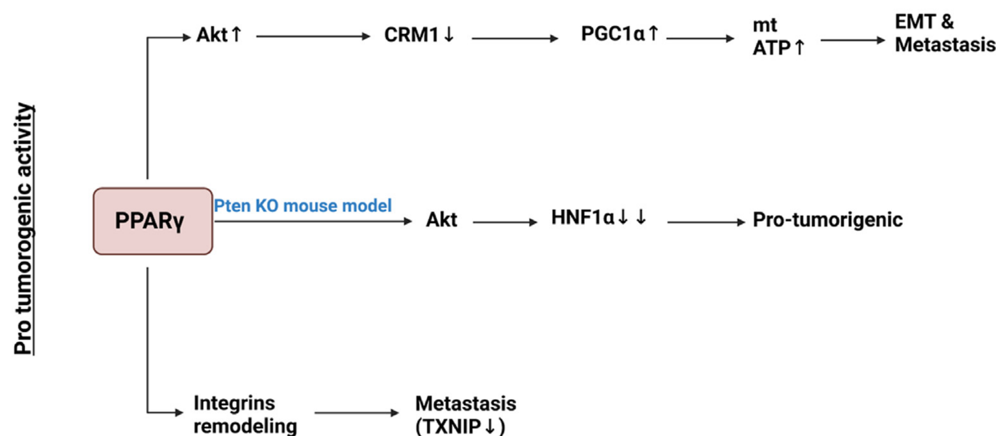


(a) Anti-tumorigenic roles of PPARγ.



(b) Pro-tumorigenic activity of PPARγ.

Figure 4: (a) **Anti-tumorigenic roles of PPARγ.**
Activation of PPARγ by troglitazone or TZDs induces lipid metabolism pathways and suppresses targets of the Hippo-YAP pathway, Wnt signaling and cancer-related proliferation pathways in osteosarcoma [80]. PPARγ agonists exert anti-inflammatory and pro-apoptotic activity by triggering NF-κβ trans-repression and modulation of BCL-2 class of proteins via PI3K/Akt pathway [83]. Ciglitazone and 15d-PGJ2, both PPARγ agonists, exert anti-proliferative activity in brain tumor stem cells via the inhibition of Sox2 while enhancing Nanog expression [84]. PPARγ via suppression of matrix metalloproteinases and antagonizing Smad3-dependent transcriptional activity attenuates extracellular matrix (ECM) remodeling, epithelial—mesenchymal transition (EMT) mediated tumor invasion and metastasis in lung cancer [77,85,86]. Ligand activation of PPARγ transcriptional pathway mitigates terminal differentiation of malignant breast epithelial cells by extensive lipid accumulation, epithelial gene expression changes inhibiting tumor growth and malignancy in breast cancer [82].
(b) **Pro-tumorigenic activity of PPARγ.**
Pro-tumorigenic signaling of PPARγ mediated by Akt2 via repression of hepatocyte nuclear factor 1α (HNF1α) [77,96,97]. In prostate cancer, the EMT mediated prostate cancer metastasis is facilitated by PPARγ overexpression mediated activation of Akt3 pathway inhibiting nuclear export protein, CRM1 leading to the retention of PPARγ co-activator 1α (PGC1α) resulting in elevated mitochondrial ATP output facilitating metastasis [93]. In melanoma, activation of PPARγ results in remodeling of expression and localization of integrins promoting distal metastases with reduced expression of thioredoxin-interacting protein (TXNIP) [120].

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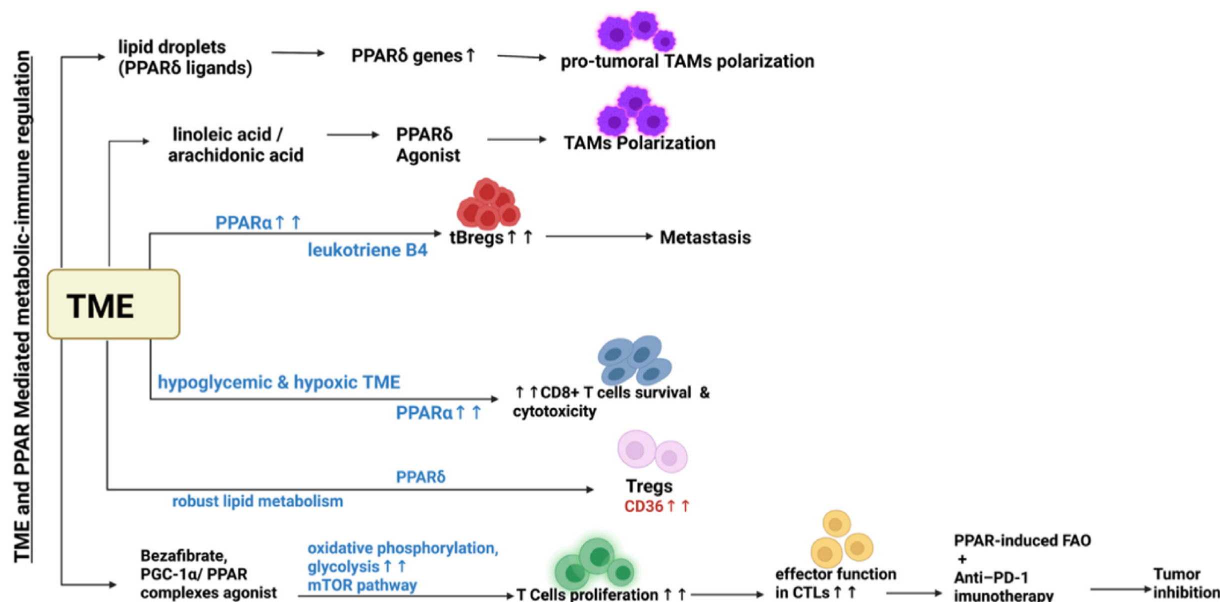

Figure 5: Metabolic-immune regulation in cancer mediated by PPARs. In breast cancer, PPARγ cleavage at Asp64 leads to lipid droplet formation in tumor associated macrophages (TAMs). High concentrations of linoleic acid and arachidonic acid can act as agonists of PPARδ causing active polarization of TAMs in the TME [111,112] Lipid droplets serve as source of PPARδ ligands in ovarian cancer-causing TAM polarization. In the TME, PPARδ regulates survival benefits for intra-tumoral T_{regs} with higher CD36 expression and more robust lipid metabolism by modulating mitochondrial fitness by lactate utilization. In colon cancer, Bezafibrate, an agonist of PGC-1α/PPAR complexes, increased proliferation of naïve T cells via mitochondrial activation and upregulation of the mTOR pathway and is a potential candidate for combinatorial therapy with anti—PD-1 immunotherapy [117]. PPARα activation and catabolism of fatty acids in tumor infiltrating $CD8^{+}$ T cells can enhance their survival and retain cytotoxicity in hypoglycemic and hypoxic TME [118]. PPARα activation by metabolites of the 5-lipoxygenase pathway such as leukotriene B4 produced by tumor cells orchestrates breast cancer metastasis and tumor evasion by the induction of immunosuppressive regulatory B cells, designated tB_{regs}, making it an attractive pharmacological target [119].

immune functions compromised. The immunosuppressive phenotype of tumor infiltrating immune cells, including macrophages, dendritic cells, T lymphocytes, and others, is due to their survival strategies adopted by lipid metabolism reprogramming toward FA oxidation [101].

During tumor progression, lipid accumulation has been reported in tumor infiltrating immune cells, including dendritic cells (DCs) [102,103], macrophages [104,105], T_{reg} cells [106] and effector T cells [107,108], indicating the role of the tumor microenvironment (TME) in reprogramming the lipid metabolism of immune cells, impacting host immune surveillance and anti-tumor immunity [109,110].

PPARs are implicated in this lipid accumulation and in the more general mediation of metabolic-immune regulation in cancer. Caspase 1-mediated reduction of medium-chain acyl-CoA dehydrogenase through cleaving PPARγ at Asp64 leads to increased lipid droplet formation in tumor associated macrophages (TAMs) in a late-stage murine breast tumor model. Also, active polarization of TAMs is facilitated by high concentrations of linoleic acid and arachidonic acid that can act as agonists of PPARδ [111,112]. In ovarian cancer, lipid droplet serves as a source of PPARδ ligands leading to the upregulation of PPARδ target genes and pro-tumoral TAMs M2-polarization [113]. Finally, the immunosuppressive cytokine IL-10 is a downstream effector of PPARδ activation [114].

During tumor progression, gastric cancer cells with RHOA Y42 mutation produced high FA levels that provided a sufficient metabolic advantage to T_{regs} as they exhibit selective dependency on FA oxidation compared to other subsets of T-cells [115,116].

Even though programmed cell death-1 (PD-1) blockade cancer immunotherapy has been successful, its efficacy is challenged due to the loss of functional effector T-cell number *via* terminal differentiation—induced apoptosis. In a murine colon cancer model, Bezafibrate, an agonist of PGC-1α/PPAR complexes, upregulated oxidative phosphorylation as well as glycolysis, increased proliferation of naïve T cells via mitochondrial activation and upregulation of the mTOR pathway and improved effector function in CTLs; inhibited apoptosis as evidenced by upregulation of anti-apoptotic BCL-2 proteins, increased fatty acid oxidation (FAO) and mitochondrial respiratory capacity, supporting the energy demands of cells [117]. This opens the possibility of using PPAR-induced FAO in T cells as a combinatorial approach to improve response to anti—PD-1 therapy.

Studies on PPARα signaling have revealed that its activation and catabolism of fatty acids in tumor infiltrating CD8+ T cells can enhance their survival in hypoglycemic and hypoxic TME and retain the cytotoxic activity of these cells [118]. An exciting study reports that distal breast cancer metastasis is facilitated by the induction of immunosuppressive regulatory B cells, designated tB_{regs}, orchestrated by the activation of PPARα by metabolites of the 5-lipoxygenase pathway such as leukotriene B4 produced by tumor cells. Thus, apart from FA oxidation and metabolic signal transduction, PPARα is involved with the programming and differentiation of tB_{regs}, making it a novel target for pharmacological control of tB_{reg} mediated tumor evasion [119] (Figure 5).

5. CONCLUSION

Changes in cell metabolism are a hallmark of cancer. Cancer cells, with their increased proliferation and protein synthesis, demand an increased energy turnover. As peroxisomes are a critical player in supplying energy from the oxidation of certain FAs, especially VLCFAs

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and BCFAs, it is not surprising to find the misregulation of peroxisome biogenesis in many cancers. Furthermore, the high peroxisomal activity contributes to the high levels of reactive oxygen species (ROS) in tumors. Although ROS as cell toxic entities is detrimental to cancer cell survival, they also drive a more malignant phenotype by increasing mutation rate and promoting upregulation of pathways steering invasiveness. Controlling peroxisome biogenesis and activity especially targeting PPARs in the TME, holds great promise and unexplored potential. Moreover, their function as receptors makes them assessable targets for small molecule inhibitors and activators. Various drugs targeting PPARs are already available, at least for pre-clinical studies, although clinical applications in all likeliness would necessitate novel, more specific drugs. Another caveat is that despite the potential impact of PPARs on the cross-talk between tumor stroma and epithelium, or tumor microenvironment, it is difficult to attribute a pro- or anti-tumorigenic role for different PPAR isotypes as they seem to be influenced by many factors such as cancer and its sub-types, tumor-stage, and stromal cell types. More research is required, especially directed at deciphering the balance between the pro- and anti-tumorigenic activity of PPARS.

PPARs are also mediators of macrophage polarization and determine T-cell activation and differentiation, implicating their activation as a strategy for altering immune cell functions leading to better therapeutic interventions in cancer. Post-translational studies on the regulation of PPARs, will help develop novel synthetic compounds for targeted and cell-specific therapy. Considering the ambiguity of PPARs as pro- or anti-tumorigenic regulators with tumor specific responses, diverse molecular approaches, gene transfection studies for overexpression or silencing of genes, pharmacological induction of PPARs, along with genetic knockdown animal models for PPARs, studies on microRNAs supported with genomics, transcriptomics, proteomics and metabolomics guided approaches could in totality assist in arriving at meaningful conclusions for PPAR targeted anti-cancer therapy. However, the effect of the genetic predisposition for polymorphisms and mutations in PPARs cannot be ruled out, that in turn, influences the administration of PPAR agonists as a preventive measure for cancer. Nanoparticles as targeted release systems for TME-responsive drugs and delivery of PPAR ligands; immunotherapy, the use of naturally occurring exosomes with reduced immunogenicity, increased bioavailability, and biocompatibility as drug carriers are some of the recent advancements to target PPARs in TME for precision oncology.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Anggi Muhtar Pratama: Writing — original draft, Visualization, Investigation, Formal analysis, Data curation. **Mansi Sharma:** Writing — review & editing, Methodology, Formal analysis. **Srivatsava Naidu:** Writing — review & editing, Supervision, Formal analysis. **Heike Bömmel:** Formal analysis, Data curation. **Samudyata C. Prabhuswamimath:** Formal analysis, Data curation. **Thati Madhusudhan:** Formal analysis, Data curation. **Hevi Wihadmadyatami:** Writing — review & editing. **Akash Bachhuka:** Writing — review & editing, Supervision, Conceptualization. **Srikanth Karnati:** Writing — review & editing, Project administration, Formal analysis, Conceptualization.

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DECLARATION OF COMPETING INTEREST

We declare: **There are no conflicts of interests, for the** article titled "Peroxisomes and PPARs: Emerging Roles as Master Regulators of Cancer Metabolism and Immunity".

DATA AVAILABILITY

No data was used for the research described in the article.

REFERENCES

[1] DeBerardinis RJ, Lum JJ, Hatzivassiliou G, Thompson CB. The biology of cancer: metabolic reprogramming fuels cell growth and proliferation. Cell Metabol 2008;7(1):11—20.

[2] Bayley JP, Devilee P. The Warburg effect in 2012. Curr Opin Oncol 2012;24(1):62—7.

[3] Rhodin J. Correlation of ultrastructural organization and function in normal and experimentally changed proximal convoluted tubule cells in the mouse kidney. *Ph.D. thesis*. Stockholm: Karolinska Institute; 1954. Aktiebolaget Godvil.

[4] De Duve C, Baudhuin P. Peroxisomes (microbodies and related particles). Physiol Rev 1966;46:323—57. https://doi.org/10.1152/physrev.1966.46.2.323.

[5] de Duve D. The peroxisome: a new cytoplasmic organelle. Proc R Soc Lond B Biol Sci 1969;173:71—83.

[6] Wanders RJ, Waterham HR. Biochemistry of mammalian peroxisomes revisited. Annu Rev Biochem 2006;75:295—332. https://doi.org/10.1146/annurev.biochem.74.082803.133329.

[7] Lazarow PB, De Duve C. A fatty acyl-CoA oxidizing system in rat liver peroxisomes; enhancement by clofibrate, a hypolipidemic drug. Proc Natl Acad Sci U S A 1976;73:2043—6. https://doi.org/10.1073/pnas.73.6.2043.

[8] Mihalik SJ, Rainville AM, Watkins PA. Phytanic acid alpha-oxidation in rat liver peroxisomes. Production of alpha-hydroxyphytanoyl-CoA and formate is enhanced by dioxygenase cofactors. Eur J Biochem 1995;232:545—51. https://doi.org/10.1111/j.1432-1033.1995.545zz.x.

[9] Ferdinandusse S, Denis S, Faust PL, Wanders RJ. Bile acids: the role of peroxisomes. J Lipid Res 2009;50:2139—47. https://doi.org/10.1194/jlr.R900009-JLR200.

[10] Moore SA, Hurt E, Yoder E, Sprecher H, Spector AA. Docosahexaenoic acid synthesis in human skin fibroblasts involves peroxisomal retroconversion of tetracosahexaenoic acid. J Lipid Res 1995;36:2433—43.

[11] Su HM, Moser AB, Moser HW, Watkins PA. Peroxisomal straight-chain Acyl-CoA oxidase and D-bifunctional protein are essential for the retroconversion step in docosahexaenoic acid synthesis. J Biol Chem 2001;276:38115—20. https://doi.org/10.1074/jbc.M106326200.

[12] Braverman NE, Moser AB. Functions of plasmalogen lipids in health and disease. Biochim Biophys Acta 2012;1822:1442—52. https://doi.org/10.1016/j.bbadis.2012.05.008.

[13] Smith JJ, Aitchison JD. Peroxisomes take shape. Nat Rev Mol Cell Biol 2013;14:803—17. https://doi.org/10.1038/nrm3700.

[14] Jain IH, Calvo SE, Markhard AL, Skinner OS, To TL, Ast T, et al. Genetic screen for cell fitness in high or low oxygen highlights mitochondrial and lipid metabolism. Cell 2020;181:716—727.e711. https://doi.org/10.1016/j.cell.2020.03.029.

[15] Waterham HR, Ferdinandusse S, Wanders RJ. Human disorders of peroxisome metabolism and biogenesis. Biochim Biophys Acta 2016;1863:922—33. https://doi.org/10.1016/j.bbamcr.2015.11.015.

[16] DeBerardinis RJ, Chandel NS. Fundamentals of cancer metabolism. Sci Adv 2016;2:e1600200. https://doi.org/10.1126/sciadv.1600200.

 © 2024 Published by Elsevier GmbH. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

[17] Shukla N, Adhya AK, Rath J. Expression of alpha - methylacyl - coenzyme A racemase (AMACR) in colorectal neoplasia. J Clin Diagn Res 2017;11:Ec35–8. https://doi.org/10.7860/jcdr/2017/25303.9727.

[18] Cai M, Sun X, Wang W, Lian Z, Wu P, Han S, et al. Disruption of peroxisome function leads to metabolic stress, mTOR inhibition, and lethality in liver cancer cells. Cancer Lett 2018;421:82–93. https://doi.org/10.1016/j.canlet.2018.02.021.

[19] Benjamin DI, Cozzo A, Ji X, Roberts LS, Louie SM, Mulvihill MM, et al. Ether lipid generating enzyme AGPS alters the balance of structural and signaling lipids to fuel cancer pathogenicity. Proc Natl Acad Sci U S A 2013;110:14912–7. https://doi.org/10.1073/pnas.1310894110.

[20] Zhou M, Chinnaiyan AM, Kleer CG, Lucas PC, Rubin MA. Alpha-Methylacyl-CoA racemase: a novel tumor marker over-expressed in several human cancers and their precursor lesions. Am J Surg Pathol 2002;26:926–31. https://doi.org/10.1097/00000478-200207000-00012.

[21] Fujiki Y, Abe Y, Imoto Y, Tanaka AJ, Okumoto K, Honsho M, et al. Recent insights into peroxisome biogenesis and associated diseases. J Cell Sci 2020;133. https://doi.org/10.1242/jcs.236943.

[22] Aranovich A, Hua R, Rutenberg AD, Kim PK. PEX16 contributes to peroxisome maintenance by constantly trafficking PEX3 via the ER. J Cell Sci 2014;127:3675–86. https://doi.org/10.1242/jcs.146282.

[23] Fang Y, Morrell JC, Jones JM, Gould SJ. PEX3 functions as a PEX19 docking factor in the import of class I peroxisomal membrane proteins. J Cell Biol 2004;164:863–75. https://doi.org/10.1083/jcb.200311131.

[24] Itoyama A, Honsho M, Abe Y, Moser A, Yoshida Y, Fujiki Y. Docosahexaenoic acid mediates peroxisomal elongation, a prerequisite for peroxisome division. J Cell Sci 2012;125:589–602. https://doi.org/10.1242/jcs.087452.

[25] Itoyama A, Michiyuki S, Honsho M, Yamamoto T, Moser A, Yoshida Y, et al. Mff functions with Pex11pβ and DLP1 in peroxisomal fission. Biol Open 2013;2:998–1006. https://doi.org/10.1242/bio.20135298.

[26] Lodhi IJ, Semenkovich CF. Peroxisomes: a nexus for lipid metabolism and cellular signaling. Cell Metabol 2014;19:380–92. https://doi.org/10.1016/j.cmet.2014.01.002.

[27] Islinger M, Voelkl A, Fahimi HD, Schrader M. The peroxisome: an update on mysteries 2.0. Histochem Cell Biol 2018;150:443–71. https://doi.org/10.1007/s00418-018-1722-5.

[28] Morita M, Imanaka T. Peroxisomal ABC transporters: structure, function and role in disease. Biochim Biophys Acta 2012;1822:1387–96. https://doi.org/10.1016/j.bbadis.2012.02.009.

[29] Brown 3rd FR, McAdams AJ, Cummins JW, Konkol R, Singh I, Moser AB, et al. Cerebro-hepato-renal (Zellweger) syndrome and neonatal adrenoleukodystrophy: similarities in phenotype and accumulation of very long chain fatty acids. Johns Hopkins Med J 1982;151:344–51.

[30] Poulos A, van Crugten C, Sharp P, Carey WF, Robertson E, Becroft DM, et al. Prenatal diagnosis of Zellweger syndrome and related disorders: impaired degradation of phytanic acid. Eur J Pediatr 1986;145:507–10. https://doi.org/10.1007/bf02429053.

[31] Singh I, Moser AE, Goldfischer S, Moser HW. Lignoceric acid is oxidized in the peroxisome: implications for the Zellweger cerebro-hepato-renal syndrome and adrenoleukodystrophy. Proc Natl Acad Sci U S A 1984;81:4203–7. https://doi.org/10.1073/pnas.81.13.4203.

[32] Wanders RJ, Vreken P, Ferdinandusse S, Jansen GA, Waterham HR, van Roermund CW, et al. Peroxisomal fatty acid alpha- and beta-oxidation in humans: enzymology, peroxisomal metabolite transporters and peroxisomal diseases. Biochem Soc Trans 2001;29:250–67. https://doi.org/10.1042/0300-5127:0290250.

[33] Dahabieh MS, Di Pietro E, Jangal M, Goncalves C, Witcher M, Braverman NE, et al. Peroxisomes and cancer: the role of a metabolic specialist in a disease of aberrant metabolism. Biochim Biophys Acta Rev Cancer 2018;1870:103–21. https://doi.org/10.1016/j.bbcan.2018.07.004.

[34] Chu S, Huang Q, Alvares K, Yeldandi AV, Rao MS, Reddy JK. Transformation of mammalian cells by overexpressing H2O2-generating peroxisomal fatty acyl-CoA oxidase. Proc Natl Acad Sci U S A 1995;92:7080–4. https://doi.org/10.1073/pnas.92.15.7080.

[35] Houten SM, Denis S, Argmann CA, Jia Y, Ferdinandusse S, Reddy JK, et al. Peroxisomal L-bifunctional enzyme (Ehhadh) is essential for the production of medium-chain dicarboxylic acids. J Lipid Res 2012;53:1296–303. https://doi.org/10.1194/jlr.M024463.

[36] Van Veldhoven PP. Biochemistry and genetics of inherited disorders of peroxisomal fatty acid metabolism. J Lipid Res 2010;51:2863–95. https://doi.org/10.1194/jlr.R005959.

[37] Singh H, Brogan M, Johnson D, Poulos A. Peroxisomal beta-oxidation of branched chain fatty acids in human skin fibroblasts. J Lipid Res 1992;33:1597–605.

[38] Jansen GA, Wanders RJ. Alpha-oxidation. Biochim Biophys Acta 2006;1763:1403–12. https://doi.org/10.1016/j.bbamcr.2006.07.012.

[39] Schmitz W, Fingerhut R, Conzelmann E. Purification and properties of an alpha-methylacyl-CoA racemase from rat liver. Eur J Biochem 1994;222:313–23. https://doi.org/10.1111/j.1432-1033.1994.tb18870.x.

[40] Westin MAK, Hunt MC, Alexson SEH. Peroxisomes contain a specific phytanoyl-CoA/pristanoyl-CoA thioesterase acting as a novel auxiliary enzyme in alpha- and beta-oxidation of methyl-branched fatty acids in mouse. J Biol Chem 2007;282:26707–16. https://doi.org/10.1074/jbc.M703718200.

[41] Michiels C, Tellier C, Feron O. Cycling hypoxia: a key feature of the tumor microenvironment. Biochim Biophys Acta 2016;1866:76–86. https://doi.org/10.1016/j.bbcan.2016.06.004.

[42] Tubbs A, Nussenzweig A. Endogenous DNA damage as a source of genomic instability in cancer. Cell 2017;168:644–56. https://doi.org/10.1016/j.cell.2017.01.002.

[43] Antonenkov VD, Grunau S, Ohlmeier S, Hiltunen JK. Peroxisomes are oxidative organelles. Antioxidants Redox Signal 2010;13:525–37. https://doi.org/10.1089/ars.2009.2996.

[44] Angermüller S, Bruder G, Völkl A, Wesch H, Fahimi HD. Localization of xanthine oxidase in crystalline cores of peroxisomes. A cytochemical and biochemical study. Eur J Cell Biol 1987;45:137–44.

[45] Del Río LA. Peroxisomes as a cellular source of reactive nitrogen species signal molecules. Arch Biochem Biophys 2011;506:1–11. https://doi.org/10.1016/j.abb.2010.10.022.

[46] Pacher P, Beckman JS, Liaudet L. Nitric oxide and peroxynitrite in health and disease. Physiol Rev 2007;87:315–424. https://doi.org/10.1152/physrev.00029.2006.

[47] Fransen M, Nordgren M, Wang B, Apanasets O. Role of peroxisomes in ROS/RNS-metabolism: implications for human disease. Biochim Biophys Acta 2012;1822:1363–73. https://doi.org/10.1016/j.bbadis.2011.12.001.

[48] Kirkman HN, Gaetani GF. Catalase: a tetrameric enzyme with four tightly bound molecules of NADPH. Proc Natl Acad Sci U S A 1984;81:4343–7. https://doi.org/10.1073/pnas.81.14.4343.

[49] Vetrano AM, Heck DE, Mariano TM, Mishin V, Laskin DL, Laskin JD. Characterization of the oxidase activity in mammalian catalase. J Biol Chem 2005;280:35372–81. https://doi.org/10.1074/jbc.M503991200.

[50] Islinger M, Li KW, Seitz J, Völkl A, Lüers GH. Hitchhiking of Cu/Zn superoxide dismutase to peroxisomes–evidence for a natural piggyback import mechanism in mammals. Traffic 2009;10:1711–21. https://doi.org/10.1111/j.1600-0854.2009.00966.x.

[51] Sala A, Lanciotti M, Valsecchi MG, di Michele P, Dufour C, Haupt R, et al. Genotypes of the glutathione S-transferase superfamily do not correlate with outcome of childhood acute lymphoblastic leukemia. Leukemia 2003;17:981–3. https://doi.org/10.1038/sj.leu.2402888.

[52] Islinger M, Lüers GH, Zischka H, Ueffing M, Völkl A. Insights into the membrane proteome of rat liver peroxisomes: microsomal glutathione-S-

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transferase is shared by both subcellular compartments. Proteomics 2006;6: 804—16. https://doi.org/10.1002/pmic.200401347.
[53] Morel F, Rauch C, Petit E, Piton A, Theret N, Coles B, et al. Gene and protein characterization of the human glutathione S-transferase kappa and evidence for a peroxisomal localization. J Biol Chem 2004;279:16246—53. https://doi.org/10.1074/jbc.M313357200.
[54] Knoops B, Goemaere J, Van der Eecken V, Declercq JP. Peroxiredoxin 5: structure, mechanism, and function of the mammalian atypical 2-Cys peroxiredoxin. Antioxidants Redox Signal 2011;15:817—29. https://doi.org/10.1089/ars.2010.3584.
[55] Decker M, Arand M, Cronin A. Mammalian epoxide hydrolases in xenobiotic metabolism and signalling. Arch Toxicol 2009;83:297—318. https://doi.org/10.1007/s00204-009-0416-0.
[56] Ma Y, Temkin SM, Hawkridge AM, Guo C, Wang W, Wang XY, et al. Fatty acid oxidation: an emerging facet of metabolic transformation in cancer. Cancer Lett 2018;435:92—100. https://doi.org/10.1016/j.canlet.2018.08.006.
[57] Balaban S, Nassar ZD, Zhang AY, Hosseini-Beheshti E, Centenera MM, Schreuder M, et al. Extracellular fatty acids are the major contributor to lipid synthesis in prostate cancer. Mol Cancer Res 2019;17:949—62. https://doi.org/10.1158/1541-7786.Mcr-18-0347.
[58] Hostetler HA, Kier AB, Schroeder F. Very-long-chain and branched-chain fatty acyl-CoAs are high affinity ligands for the peroxisome proliferator-activated receptor alpha (PPARalpha). Biochemistry 2006;45:7669—81. https://doi.org/10.1021/bi060198l.
[59] Tyagi S, Gupta P, Saini AS, Kaushal C, Sharma S. The peroxisome proliferator-activated receptor: a family of nuclear receptors role in various diseases. J Adv Pharm Technol Res 2011;2:236—40. https://doi.org/10.4103/2231-4040.90879.
[60] Rakhshandehroo M, Knoch B, Müller M, Kersten S. Peroxisome proliferator-activated receptor alpha target genes. PPAR Res 2010;2010. https://doi.org/10.1155/2010/612089.
[61] Misra P, Reddy JK. Peroxisome proliferator-activated receptor-α activation and excess energy burning in hepatocarcinogenesis. Biochimie 2014;98:63—74. https://doi.org/10.1016/j.biochi.2013.11.011.
[62] Yeldandi AV, Rao MS, Reddy JK. Hydrogen peroxide generation in peroxisome proliferator-induced oncogenesis. Mutat Res 2000;448:159—77. https://doi.org/10.1016/s0027-5107(99)00234-1.
[63] Chen XF, Tian MX, Sun RQ, Zhang ML, Zhou LS, Jin L, et al. SIRT5 inhibits peroxisomal ACOX1 to prevent oxidative damage and is downregulated in liver cancer. EMBO Rep 2018;19. https://doi.org/10.15252/embr.201745124.
[64] Kim S, Lee Y, Koo JS. Differential expression of lipid metabolism-related proteins in different breast cancer subtypes. PLoS One 2015;10:e0119473. https://doi.org/10.1371/journal.pone.0119473.
[65] Fujii S, Yamashita S, Yamaguchi T, Takahashi M, Hozumi Y, Ushijima T, et al. Pathological complete response of HER2-positive breast cancer to trastuzumab and chemotherapy can be predicted by HSD17B4 methylation. Oncotarget 2017;8:19039—48. https://doi.org/10.18632/oncotarget.15118.
[66] Dahabieh MS, Ha Z, Di Pietro E, Nichol JN, Bolt AM, Goncalves C, et al. Peroxisomes protect lymphoma cells from HDAC inhibitor-mediated apoptosis. Cell Death Differ 2017;24:1912—24. https://doi.org/10.1038/cdd.2017.115.
[67] Ananthanarayanan V, Deaton RJ, Yang XJ, Pins MR, Gann PH. Alpha-methylacyl-CoA racemase (AMACR) expression in normal prostatic glands and high-grade prostatic intraepithelial neoplasia (HGPIN): association with diagnosis of prostate cancer. Prostate 2005;63:341—6. https://doi.org/10.1002/pros.20196.
[68] Box A, Alshalalfa M, Hegazy SA, Donnelly B, Bismar TA. High alpha-methylacyl-CoA racemase (AMACR) is associated with ERG expression and with adverse clinical outcome in patients with localized prostate cancer. Tumour Biol 2016;37:12287—99. https://doi.org/10.1007/s13277-016-5075-1.
[69] Lotan TL, Gupta NS, Wang W, Toubaji A, Haffner MC, Chaux A, et al. ERG gene rearrangements are common in prostatic small cell carcinomas. Mod Pathol 2011;24:820—8. https://doi.org/10.1038/modpathol.2011.7.
[70] Chen ZM, Ritter JH, Wang HL. Differential expression of alpha-methylacyl coenzyme A racemase in adenocarcinomas of the small and large intestines. Am J Surg Pathol 2005;29:890—6. https://doi.org/10.1097/01.pas.0000167364.90899.59.
[71] Jiang Z, Fanger GR, Banner BF, Woda BA, Algate P, Dresser K, et al. A dietary enzyme: alpha-methylacyl-CoA racemase/P504S is overexpressed in colon carcinoma. Cancer Detect Prev 2003;27:422—6. https://doi.org/10.1016/j.cdp.2003.07.003.
[72] Jindal Y, Singh A, Kumar R, Varma K, Misra V, Misra SP, et al. Expression of alpha methylacyl CoA racemase (AMACR) in gastric adenocarcinoma and its correlation with Helicobacter pylori infection. J Clin Diagn Res 2016;10: Ec10—2. https://doi.org/10.7860/jcdr/2016/19539.8721.
[73] Witkiewicz AK, Varambally S, Shen R, Mehra R, Sabel MS, Ghosh D, et al. Alpha-methylacyl-CoA racemase protein expression is associated with the degree of differentiation in breast cancer using quantitative image analysis. Cancer Epidemiol Biomarkers Prev 2005;14:1418—23. https://doi.org/10.1158/1055-9965.Epi-04-0607.
[74] Went PT, Sauter G, Oberholzer M, Bubendorf L. Abundant expression of AMACR in many distinct tumour types. Pathology 2006;38:426—32. https://doi.org/10.1080/00313020600922470.
[75] Lin PY, Cheng KL, McGuffin-Cawley JD, Shieu FS, Samia AC, Gupta S, et al. Detection of alpha-methylacyl-CoA racemase (AMACR), a biomarker of prostate cancer, in patient blood samples using a nanoparticle electrochemical biosensor. Biosensors 2012;2:377—87. https://doi.org/10.3390/bios2040377.
[76] Li CF, Fang FM, Lan J, Wang JW, Kung HJ, Chen LT, et al. AMACR amplification in myxofibrosarcomas: a mechanism of overexpression that promotes cell proliferation with therapeutic relevance. Clin Cancer Res 2014;20:6141—52. https://doi.org/10.1158/1078-0432.Ccr-14-1182.
[77] Cheng HS, Yip YS, Lim EKY, Wahli W, Tan NS. PPARs and tumor microenvironment: the emerging roles of the metabolic master regulators in tumor stromal-epithelial crosstalk and carcinogenesis. Cancers (Basel) 2021;13. https://doi.org/10.3390/cancers13092153.
[78] Castelli V, Catanesi M, Alfonsetti M, Laezza C, Lombardi F, Cinque B, et al. Pparα-selective antagonist GW6471 inhibits cell growth in breast cancer stem cells inducing energy imbalance and metabolic stress. Biomedicines 2021;9. https://doi.org/10.3390/biomedicines9020127.
[79] Papi A, Guarnieri T, Storci G, Santini D, Ceccarelli C, Taffurelli M, et al. Nuclear receptors agonists exert opposing effects on the inflammation dependent survival of breast cancer stem cells. Cell Death Differ 2012;19: 1208—19. https://doi.org/10.1038/cdd.2011.207.
[80] Basu-Roy U, Han E, Rattanakorn K, Gadi A, Verma N, Maurizi G, et al. PPARγ agonists promote differentiation of cancer stem cells by restraining YAP transcriptional activity. Oncotarget 2016;7:60954—70. https://doi.org/10.18632/oncotarget.11273.
[81] Sarraf P, Mueller E, Jones D, King FJ, DeAngelo DJ, Partridge JB, et al. Differentiation and reversal of malignant changes in colon cancer through PPARgamma. Nat Med 1998;4:1046—52. https://doi.org/10.1038/2030.
[82] Mueller E, Sarraf P, Tontonoz P, Evans RM, Martin KJ, Zhang M, et al. Terminal differentiation of human breast cancer through PPAR gamma. Mol Cell 1998;1:465—70. https://doi.org/10.1016/s1097-2765(00)80047-7.
[83] Peters JM, Shah YM, Gonzalez FJ. The role of peroxisome proliferator-activated receptors in carcinogenesis and chemoprevention. Nat Rev Cancer 2012;12:181—95. https://doi.org/10.1038/nrc3214.
[84] Pestereva E, Kanakasabai S, Bright JJ. PPARγ agonists regulate the expression of stemness and differentiation genes in brain tumour stem cells. Br J Cancer 2012;106:1702—12. https://doi.org/10.1038/bjc.2012.161.

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[85] Reka AK, Kurapati H, Narala VR, Bommer G, Chen J, Standiford TJ, et al. Peroxisome proliferator-activated receptor-gamma activation inhibits tumor metastasis by antagonizing Smad3-mediated epithelial-mesenchymal transition. Mol Cancer Therapeut 2010;9:3221–32. https://doi.org/10.1158/1535-7163.Mct-10-0570.

[86] Shen B, Chu ES, Zhao G, Man K, Wu CW, Cheng JT, et al. PPARgamma inhibits hepatocellular carcinoma metastases in vitro and in mice. Br J Cancer 2012;106:1486–94. https://doi.org/10.1038/bjc.2012.130.

[87] DuBois RN, Gupta R, Brockman J, Reddy BS, Krakow SL, Lazar MA. The nuclear eicosanoid receptor, PPARgamma, is aberrantly expressed in colonic cancers. Carcinogenesis 1998;19:49–53. https://doi.org/10.1093/carcin/19.1.49.

[88] Tontonoz P, Singer S, Forman BM, Sarraf P, Fletcher JA, Fletcher CD, et al. Terminal differentiation of human liposarcoma cells induced by ligands for peroxisome proliferator-activated receptor gamma and the retinoid X receptor. Proc Natl Acad Sci U S A 1997;94:237–41. https://doi.org/10.1073/pnas.94.1.237.

[89] Pino MV, Kelley MF, Jayyosi Z. Promotion of colon tumors in C57BL/6J-APC(min)/+ mice by thiazolidinedione PPARgamma agonists and a structurally unrelated PPARgamma agonist. Toxicol Pathol 2004;32:58–63. https://doi.org/10.1080/01926230490261320.

[90] Yang K, Fan KH, Lamprecht SA, Edelmann W, Kopelovich L, Kucherlapati R, et al. Peroxisome proliferator-activated receptor gamma agonist troglitazone induces colon tumors in normal C57BL/6J mice and enhances colonic carcinogenesis in Apc1638 N/+ Mlh1+/- double mutant mice. Int J Cancer 2005;116:495–9. https://doi.org/10.1002/ijc.21018.

[91] Han E, Jang SY, Kim G, Lee YH, Choe EY, Nam CM, et al. Rosiglitazone use and the risk of bladder cancer in patients with type 2 diabetes. Medicine (Baltim) 2016;95:e2786. https://doi.org/10.1097/md.0000000000002786.

[92] Taub M. Cancer drug troglitazone stimulates the growth and response of renal cells to hypoxia inducible factors. Biochem Biophys Res Commun 2016;471:342–7. https://doi.org/10.1016/j.bbrc.2016.02.018.

[93] Galbraith LCA, Mui E, Nixon C, Hedley A, Strachan D, MacKay G, et al. PPAR-gamma induced AKT3 expression increases levels of mitochondrial biogenesis driving prostate cancer. Oncogene 2021;40:2355–66. https://doi.org/10.1038/s41388-021-01707-7.

[94] Saez E, Rosenfeld J, Livolsi A, Olson P, Lombardo E, Nelson M, et al. PPAR gamma signaling exacerbates mammary gland tumor development. Genes Dev 2004;18:528–40. https://doi.org/10.1101/gad.1167804.

[95] Wood WM, Sharma V, Bauerle KT, Pike LA, Zhou Q, Fretwell DL, et al. PPARγ promotes growth and invasion of thyroid cancer cells. PPAR Res 2011;2011:171765. https://doi.org/10.1155/2011/171765.

[96] Panasyuk G, Espeillac C, Chauvin C, Pradelli LA, Horie Y, Suzuki A, et al. PPARγ contributes to PKM2 and HK2 expression in fatty liver. Nat Commun 2012;3:672. https://doi.org/10.1038/ncomms1667.

[97] Patitucci C, Couchy G, Bagattin A, Cañeque T, de Reyniès A, Scoazec JY, et al. Hepatocyte nuclear factor 1α suppresses steatosis-associated liver cancer by inhibiting PPARγ transcription. J Clin Invest 2017;127:1873–88. https://doi.org/10.1172/jci90327.

[98] Müller R. PPARβ/δ in human cancer. Biochimie 2017;136:90–9. https://doi.org/10.1016/j.biochi.2016.10.019.

[99] Peters JM, Gonzalez FJ. Sorting out the functional role(s) of peroxisome proliferator-activated receptor-beta/delta (PPARbeta/delta) in cell proliferation and cancer. Biochim Biophys Acta 2009;1796:230–41. https://doi.org/10.1016/j.bbcan.2009.06.002.

[100] Wagner KD, Du S, Martin L, Leccia N, Michiels JF, Wagner N. Vascular PPARβ/δ promotes tumor angiogenesis and progression. Cells 2019;8. https://doi.org/10.3390/cells8121623.

[101] Zhang M, Wei T, Zhang X, Guo D. Targeting lipid metabolism reprogramming of immunocytes in response to the tumor microenvironment stressor: a potential approach for tumor therapy. Front Immunol 2022;13:937406. https://doi.org/10.3389/fimmu.2022.937406.

[102] Herber DL, Cao W, Nefedova Y, Novitskiy SV, Nagaraj S, Tyurin VA, et al. Lipid accumulation and dendritic cell dysfunction in cancer. Nat Med 2010;16:880–6. https://doi.org/10.1038/nm.2172.

[103] Yin X, Zeng W, Wu B, Wang L, Wang Z, Tian H, et al. PPARα inhibition overcomes tumor-derived exosomal lipid-induced dendritic cell dysfunction. Cell Rep 2020;33:108278. https://doi.org/10.1016/j.celrep.2020.108278.

[104] Luo Q, Zheng N, Jiang L, Wang T, Zhang P, Liu Y, et al. Lipid accumulation in macrophages confers protumorigenic polarization and immunity in gastric cancer. Cancer Sci 2020;111:4000–11. https://doi.org/10.1111/cas.14616.

[105] Su P, Wang Q, Bi E, Ma X, Liu L, Yang M, et al. Enhanced lipid accumulation and metabolism are required for the differentiation and activation of tumor-associated macrophages. Cancer Res 2020;80:1438–50. https://doi.org/10.1158/0008-5472.Can-19-2994.

[106] Pacella I, Procaccini C, Focaccetti C, Miacci S, Timperi E, Faicchia D, et al. Fatty acid metabolism complements glycolysis in the selective regulatory T cell expansion during tumor growth. Proc Natl Acad Sci U S A 2018;115:E6546–55. https://doi.org/10.1073/pnas.1720113115.

[107] Ma X, Bi E, Lu Y, Su P, Huang C, Liu L, et al. Cholesterol induces CD8(+) T cell exhaustion in the tumor microenvironment. Cell Metabol 2019;30:143–156.e145. https://doi.org/10.1016/j.cmet.2019.04.002.

[108] Ma X, Xiao L, Liu L, Ye L, Su P, Bi E, et al. CD36-mediated ferroptosis dampens intratumoral CD8(+) T cell effector function and impairs their antitumor ability. Cell Metabol 2021;33:1001–1012.e1005. https://doi.org/10.1016/j.cmet.2021.02.015.

[109] Li Y, Wan YY, Zhu B. Immune cell metabolism in tumor microenvironment. Adv Exp Med Biol 2017;1011:163–96. https://doi.org/10.1007/978-94-024-1170-6_5.

[110] Zeng W, Yin X, Jiang Y, Jin L, Liang W. PPARα at the crossroad of metabolic-immune regulation in cancer. FEBS J 2021. https://doi.org/10.1111/febs.16181. 10.1111/febs.16181.

[111] Niu Z, Shi Q, Zhang W, Shu Y, Yang N, Chen B, et al. Caspase-1 cleaves PPARγ for potentiating the pro-tumor action of TAMs. Nat Commun 2017;8:766. https://doi.org/10.1038/s41467-017-00523-6.

[112] Odegaard JI, Ricardo-Gonzalez RR, Red Eagle A, Vats D, Morel CR, Goforth MH, et al. Alternative M2 activation of Kupffer cells by PPARdelta ameliorates obesity-induced insulin resistance. Cell Metabol 2008;7:496–507. https://doi.org/10.1016/j.cmet.2008.04.003.

[113] Schumann T, Adhikary T, Wortmann A, Finkernagel F, Lieber S, Schnitzer E, et al. Deregulation of PPARβ/δ target genes in tumor-associated macrophages by fatty acid ligands in the ovarian cancer microenvironment. Oncotarget 2015;6:13416–33. https://doi.org/10.18632/oncotarget.3826.

[114] Park J, Lee SE, Hur J, Hong EB, Choi JI, Yang JM, et al. M-CSF from cancer cells induces fatty acid synthase and PPARβ/δ activation in tumor myeloid cells, leading to tumor progression. Cell Rep 2015;10:1614–25. https://doi.org/10.1016/j.celrep.2015.02.024.

[115] Kempkes RWM, Joosten I, Koenen H, He X. Metabolic pathways involved in regulatory T cell functionality. Front Immunol 2019;10:2839. https://doi.org/10.3389/fimmu.2019.02839.

[116] Kumagai S, Togashi Y, Sakai C, Kawazoe A, Kawazu M, Ueno T, et al. An oncogenic alteration creates a microenvironment that promotes tumor progression by conferring a metabolic advantage to regulatory T cells. Immunity 2020;53:187–203.e188. https://doi.org/10.1016/j.immuni.2020.06.016.

[117] Chowdhury PS, Chamoto K, Kumar A, Honjo T. PPAR-induced fatty acid oxidation in T cells increases the number of tumor-reactive CD8(+) T cells and facilitates anti-PD-1 therapy. Cancer Immunol Res 2018;6:1375–87. https://doi.org/10.1158/2326-6066.Cir-18-0095.

[118] Zhang Y, Kurupati R, Liu L, Zhou XY, Zhang G, Hudaihed A, et al. Enhancing CD8(+) T cell fatty acid catabolism within a metabolically challenging tumor microenvironment increases the efficacy of melanoma immunotherapy. Cancer Cell 2017;32:377–391.e379. https://doi.org/10.1016/j.ccell.2017.08.004.

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[119] Wejksza K, Lee-Chang C, Bodogai M, Bonzo J, Gonzalez FJ, Lehrmann E, et al. Cancer-produced metabolites of 5-lipoxygenase induce tumor-evoked regulatory B cells via peroxisome proliferator-activated receptor α. J Immunol 2013;190:2575—84. https://doi.org/10.4049/jimmunol.1201920.

[120] Meylan P, Pich C, Winkler C, Ginster S, Mury L, Sgandurra M, et al. Low expression of the PPARγ-regulated gene thioredoxin-interacting protein accompanies human melanoma progression and promotes experimental lung metastases. Sci Rep 2021;11:7847. https://doi.org/10.1038/s41598-021-86329-5.

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