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Targeting PPAR ligands as possible approaches for metabolic reprogramming of T cells in cancer immunotherapy

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ABSTRACT

Despite the prominent progress in understanding cancer immunosurveillance mechanisms, there are some types of problems which have been identified to hinder effective and successful immunotherapy of cancers. Such problems have been ascribed to the tumor abilities in the creation of a tolerant milieu that can impair immune responses against cancer cells. In the present study, we represent possible approaches for metabolic reprogramming of T cells in cancer immunotherapy to overcome tumor metabolic impositions on immune responses against cancer cells. Metabolic suppression of effector immune cells in tumor milieu is one of the important strategies recruited by tumor cells to escape from immunogenic cell death. We have investigated the metabolic reprogramming of T cells as a method and a possible new target for cancer immunotherapy. Synergic effects of PPAR ligands in immunotherapy of cancers on the metabolic reprogramming of T cells have been noticed by several studies as a new target of cancer immunotherapy. The current wealth of data like this promises a future scenario which the consideration of metabolic restriction in the tumor microenvironment and administration of therapeutic agents such as PPAR ligands to overcome metabolic restrictions on T cells (refreshing their functionality) may be effective and enhance the accountability and efficacy of cancer immunotherapy.

1. Introduction

Cancer prevalence is increasing such that the number of newly diagnosed cases in 2018 has amounted to 18.1 million. Although the main causes of cancers have been attributed to genetic disorders and DNA mutation, other factors such as inflammation and infectious diseases, diet, lack of exercise, tobacco, alcohol, and industrial exposures are considered as remarkable related risk factors for the development of cancers [1,2].

Paul Ehrlich for the first time used the term cancer immunosurveillance. After Paul Ehrlich's theory, several experimental evidence have confirmed that host defense against tumors depends on immune responses [3,4]. Obviously, the host immune system can detect many cancer antigens and arrange an immune response against them. Nonetheless, tumor expansion indicates that the cancer cells must have escaped from the immune system. Surprisingly, despite the existence of several immunogenic antigens in many cancers, in most cases, the tumor immunogenic cell death may be unachievable [5].

In the recent decade, the cancer treatment era has been revolutionized by immunotherapy through immune response modulation against tumor cells and solving the shortcomings of highly morbid and insufficient therapeutic approaches such as radiotherapy and chemotherapy [6].

In recent years, new studies have been conducted in understanding the signaling pathways regulating immune responses against tumor cells and the potentiality of immunotherapy in cancer treatment. However, there are many obstacles hindering successful immunotherapy such as the influences of negative regulatory pathways, secretion of inhibitory factors, generation of the tolerant microenvironment by tumors, and antigen switching potentiality by the outgrowth of escaped mutants [7].

Although new therapies have brought a significant cure rate into cancer treatment, in most cases, complete destruction of tumors has not been executable. Among all parameters and factors hindering immunological responses against cancer cells, tumor microenvironment impositions on effector immune cells have been the subject of intense

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research. One of the important immunosuppressive effects of the tumor microenvironment has been attributed to immune cells metabolic regulation by the tumor microenvironment.

Along with the stimulation of T lymphocytes to gain effector phenotype, several other metabolic alterations occur as well which affects the functionality of T cells. In addition, cancer cells produce and release various metabolites in tumor milieu which can suppress the activity of T cells [8,9]. The production of ATP in tumor cells depends on glucose conversion to lactate via aerobic glycolysis rather than oxidative phosphorylation in mitochondria [10]. Hence, in comparison with normal cells, cancer cells consume higher amounts of glucose to meet their metabolic requirements. Furthermore, tumor cells produce higher amounts of end-products of metabolic pathways such as lactic acid and carbonic acid compared to normal cells due to higher metabolic rates [11].

Cytotoxic T lymphocytes are central players in controlling infectious diseases and cancer. Tumor-infiltrated $CD8^+$ T lymphocytes undergo metabolic exhaustion in the tumor microenvironment. Hence, the metabolic reprogramming of tumor-specific T cells may provide an important therapeutic approach for cancer treatment [12].

In the previous studies, the mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) have been considered as the main intracellular energy sensors that control and regulate metabolic reprogramming in immune cells. Recently, it has been reported that the activation of PPARs as mitochondrial biogenesis key regulators can lead to metabolic reprogramming of T cells and increase antitumor immunity [13–15].

Under the scope of this review, we investigate the chance of treatment with PPAR agonists for the metabolic reprogramming of active T cells and enhancing their antitumor activity in the tumor microenvironment. It can be expected that immunotherapy procedures such as programmed cell death protein 1 (PD-1) blockade may have better efficacy in combination with therapies regulating T cell metabolism in the tumor microenvironment. It is believed that persistent PD-1 ligation can enforce T cell exhaustion, a T lymphocyte dysfunction state that arises during cancer and chronic infections [16–18].

2. Metabolic regulation of immune cells by tumor microenvironment

To gain effector function in T cells stimulation process, several alterations occur in metabolic pathways as well, which affects the T cells functionality. In addition, cancer cells produce and release various types of metabolites in tumor milieu which may suppress the activity of effector T cells [8].

In 1920, Warburg reported glycolysis as the major source of energy production in cancer cells even under normal oxygen concentrations. As a result, ATP production in cancer cells depends on aerobic glycolysis and conversion of glucose to lactate [10]. Production of ATP via glycolysis is inefficient due to the decreased rate of ATP production per glucose unit. Therefore, cancer cells consume higher amounts of glucose compared to normal cells to meet their metabolic needs [19]. In addition, due to the higher metabolic rates in tumor cells, they produce a higher number of protons (H^+) in comparison to normal cells [11].

On the other side, the metabolic profile of T lymphocytes is determined based on their differentiation state. Resting naïve T cells metabolic needs mainly depend on mitochondrial oxidation of fatty acids or pyruvate. After encounter with antigen and stimulation of T cells, metabolic and signaling pathways within T lymphocytes shift toward functionality and proliferation. These alterations mainly include metabolic changes focused on the production of biosynthetic intermediates such as nucleic acids, proteins, and components of the membrane, which are necessary for proliferation and cell growth [20]. The acquisition of effector function has specific metabolic and biosynthetic needs and T cells increase glycolysis and glucose uptake upon activation. Moreover, effector T lymphocytes have higher rates of glycolysis, fatty acid synthesis, and amino acid metabolism similar to most cancerous cells. Memory T cells stay in the blood circulation after terminating the immunogenic responses by the rapid responses to the same antigen. It has been shown that memory cells metabolism mainly depends on mitochondrial oxidative phosphorylation as well as naïve T cells. Regulatory T cells are not usually affected by tumor microenvironment metabolites and they have the same metabolic profile as exist in naïve cells, however, Th17 and Th1 cells depend mainly on glycolysis, indicating that Treg cells preserve their function in tumor microenvironment [21]. Transcription factor FOXP3 in Treg cells can suppress Myc and glycolysis through metabolic reprogramming which can subsequently increase oxidative phosphorylation. These adaptations lead to survival of Treg cells in lactate-rich and low glucose environments such as tumor milieu. This explains how Treg cells can remain functional in tumor microenvironment and suppress effector T lymphocytes [22].

Metabolic fate within T cells can be determined by various signaling pathways. One of the members of the phosphatidylinositol 3-kinase (PI3K) pathway, namely the mammalian target of rapamycin (mTOR), regulates different processes and pathways inside the cells [23]. mTORC1 activation by PI3K determines the type of T cell subsets. Aside from PI3K, other mechanisms including the essential nutrients availability can activate mTORC1. Effector T cells generation requires mTORC1 activation, which up-regulates the pentose phosphate pathway and glycolysis. Moreover, the lack of mTORC1 mostly results in Treg cell generation [24,25]. On the contrary, AMPK can negatively regulate mTORC1 and inhibit the glycolysis pathway, although it enhances the production of ATP by mitochondrial oxidative phosphorylation [26].

The similarity of metabolic pathways among cancer cells and activated T lymphocytes in tumor microenvironment makes a competitive situation for amino acids, glucose, and other nutrients uptake (Fig. 1). Around most solid tumors, the higher nutrients uptake and glycolysis rate as well as poor vascularization can impair the activity of effector T lymphocytes. It has been demonstrated that a high rate of glycolysis by tumor cells can lead to glucose depletion in tumor milieu, making T cells exhausted with low cytokine production and anti-cancer ability [27]. Nutrient deprivation and high metabolic needs of activated T lymphocytes in tumor milieu can lead to regulatory T cells survival as they are able to produce energy from sources other than glucose. As a result, the restriction of tumor-specific effector T cells may be further boosted in the tumor microenvironment.

Aside from deprivation of key nutrients in tumor milieu, tumor-produced end-products that are toxic for T cells can suppress their activity and functions. Lactate is one of the most important waste products that accumulate in the tumor microenvironment, due to the high rate of glycolysis by tumor cells. Accumulation of lactate has been indicated to reduce 95 % of cytotoxic T cells cytokine production and proliferation and 50 % of T cells cytotoxic activity. In addition, glycolytic metabolism in the active T cells can produce and secrete lactate. Intracellular lactate accumulation is harmful to effector T lymphocytes and their metabolic status relies upon the secretion of lactate. Increased extracellular concentration of lactate due to cancer cell metabolism blocks the secretion of lactate by T cells [28]. Furthermore, lactate has been demonstrated to impair $CD8^+$ T and $CD4^+$cells motility through interference with chemokine ligands [29].

Another waste product that can be produced and secreted by cancer cells is adenosine, which has immunomodulatory impacts. Extracellular ATP hydrolysis results in adenosine. production and adenosine receptor (A2R) has immunosuppressive effects [30]. In addition, Treg cells can express CD39, leading to extracellular ATP hydrolysis [31].

Overall, comprehending the metabolic differences and similarities between different types of T lymphocytes and tumor cells is important to improve the efficacy of anti-cancer immune responses.

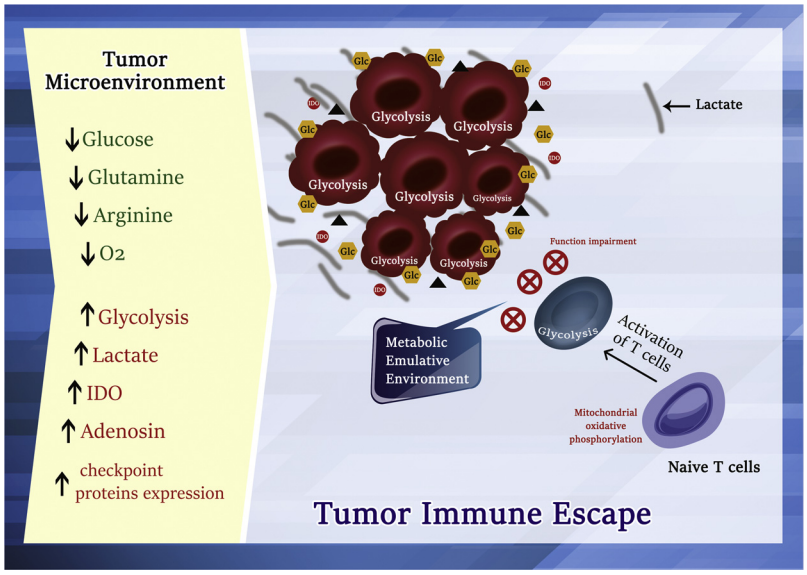

Fig. 1. Metabolic competition between effector T cells (using glycolysis pathway after activation) and tumor cells in tumor milieu due to similarity of metabolic pathways (aerobic glycolysis) along with deprivation of glucose and other nutrients can result in tumor-specific cytotoxic T cells function impairment. Increased amounts of lactate, adenosine, Indoleamine 2,3-dioxygenase (IDO), end checkpoint protein expression can intensify inhibitory effects of tumor microenvironment on effector T cells exacerbating their impaired function.

3. Peroxisome proliferator-activated receptors (PPARs)

PPARs, known as members of the nuclear receptor family, are ligand-activated transcription factors with different isotypes including PPARα, PPARβ/δ, and PPARγ [32–34]. It is believed that PPARs are at the lipid metabolism and inflammation crossroad regulating both processes. Activity and expression levels of PPARs can be affected by diet, nutrient, and metabolic status. In general, and aside from their overlapping functions, the three PPARs are free fatty acid sensors that can control several metabolic programs which are necessary for energy homeostasis [35]. PPARα can be expressed in several metabolically active tissues, particularly liver, and upregulates many genes involved in fatty acid utilization including the genes for fatty acid uptake, activation of fatty acids and their transport process into mitochondria, mitochondrial and peroxisomal β-oxidation of fatty acids, some enzymes in mitochondrial respiration, and hepatic clearance of very-low-density lipoproteins [36–38]. Fibrate drugs are PPARα agonists that activate lipid catabolism and lower plasma triglycerides [37,38]. Interestingly, PPARα can be upregulated by fasting and is required during the ketogenesis for ketone bodies production by the liver, which provide a large energy source for other tissues [39]. PPARγ is known as one of the important regulators of adipocyte differentiation. This regulator has an axial role in lipid metabolism by promoting free fatty acid uptake and accumulation of triacylglycerol in the liver and adipose tissue [40]. In addition to well-known effects of PPARγ on metabolic systems, there are several pieces of evidence suggesting that PPARγ also has important regulatory effects on the immune system particularly T cells [41]. Thiazolidinedione drugs are known as PPARγ agonists that can alter the transcription levels of different genes involved in glucose and lipid metabolism, as well as the modification of energy requirements by PPARγ ligation. Some candidate genes that can be categorized as the targets of PPARγ agonists are glucokinase, lipoprotein lipase, GLUT4 glucose transporter, fatty acyl-CoA synthase, fatty acid-binding protein, and fatty acid transporter protein [42]. PPARβ/δ may have a central role in the ability of cells to thrive in harsh conditions. PPARβ/δ can be activated by high concentrations of free fatty acids and is ubiquitously expressed in many tissues [43]. Following PPARβ/δ activation, it can mediate the transcription of genes such as antioxidant genes (catalases) [44]. PPARβ/δ prevents hematopoietic stem cell exhaustion and enhances the endurance capacity of muscle cells by lowering oxidative stress [45]. Using PPARβ/δ agonists in vitro up-regulates the expression of genes involved in fatty acid catabolism and promotes fatty acid oxidation in skeletal muscles [46,47]. Notably, PPARs can be regulated by co-activators such as PPAR gamma coactivator 1α (PGC1α) belonging to the PGC-1 family of transcription co-activators controlling the metabolic status [48].

4. PPAR ligands and metabolic reprogramming of effector T cells

It has been demonstrated that T cells in the tumor microenvironment may undergo several inhibitory mechanisms leading to T cell dysfunction. Most recently, tumor-specific T cell reinvigoration has been noticed as a new therapeutic method in cancer immunotherapy [49]. After T cells priming and gaining effector phenotype, several alterations in metabolic pathways can happen within T cells which affect the functionality of T cells. Moreover, tumor cells can produce and secrete various types of metabolites in tumor milieu which suppress T cells activity [8]. Similar metabolism of activated T cells and cancer cells (aerobic glycolysis) may result in a competition between these cells for glucose uptake. Interestingly, a higher rate of glycolysis can restrict the functions of effector T cells. It seems that an increased rate of glycolysis in the tumor microenvironment by tumor cells can deplete glucose leading to impairment of the anti-tumor ability of T cells [27]. Using molecules and drugs targeting metabolic pathways within T cells can result in stable and durable anti-tumor responses. In another word, manipulation of T cells metabolism can be considered as a target to improve T cells response against tumor cells [50]. Previous studies have indicated that reducing tumor metabolic burden on T cells can contribute to create a condition supporting the effectiveness and survival of T cells in the tumor microenvironment. Examples of these contributions are as follows: 1) GLUT1 inhibition can potentially ameliorate anti-tumor T cell responses [51]; 2) Metformin can inhibit acetyl-CoA carboxylase through activation of AMPK and promoting fatty acid oxidation [52]; and 3) In the presence of hexokinase inhibitor 2-deoxyglucose (2-DG), which may suppress glycolysis, in-vitro primed T cells can show enhanced anti-tumor activity [51]. In the past decade, especially in recent years, PPAR-γ agonists have received much attention because of having synergic effects with anti-cancer therapies via mitochondrial activation in effector T cells [53]. These medications, which have the ability to activate PPAR-γ, alter the transcription of different genes involved in glucose and lipid metabolism, as well as the modification of energy requirements (Fig. 2) [54]. Treatment with PPARs increases the expression of fatty acid transporter and also they can affect lipid and glucose metabolism [55]. In an interesting study, Scharping and colleagues have reported that a progressive loss of PPAR-gamma coactivator 1 α (PGC1α), which programs mitochondrial

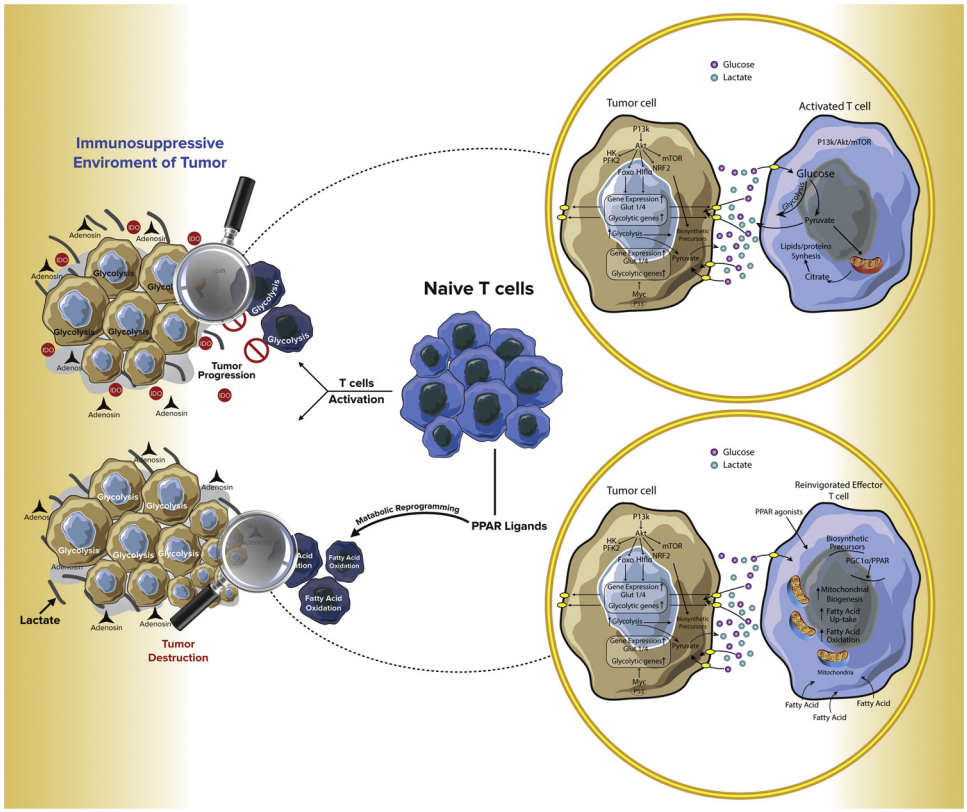

Fig. 2. Switching from naïve to effector or cytotoxic phenotype of CD8+ T cells can change the metabolic pathways toward aerobic glycolysis. Glycolysis metabolic pathway of effector T cells can interfere with the same metabolism of tumor cells (glycolysis) in tumor microenvironment leading to exacerbation of effector T cells disability along with other immunosuppressive factors. The similarity of metabolic pathways in tumor cells and cytotoxic T cells, deprivation of glucose and other essential nutrients along with the existence of lactate (as one of the waste products) can induce an emulative environment between effector immune cells and tumor cells which affect the functionality of T cells. Metabolically-altered tumor-specific effector T cells using PPAR ligands through activation of fatty acid oxidation pathways may help T lymphocytes to overcome exhausted phenotype as well as other metabolic restrictions in tumor milieu and reinvigorate activated T lymphocytes leading to tumor immunogenic cell death.

biogenesis, exists in tumor-specific T lymphocytes. They suggested that the metabolic reprogramming of T cells through the enforced expression of PGC1α in the tumor microenvironment may represent a potential strategy for dysfunctional T cell reinvigoration in cancer immunotherapy [15]. Our very recent study showed that activation of AMPK by metformin can subsequently activate PGC1α/PPAR which may have positive effects on metabolic reprogramming of tumor-infiltrated T cells leading to enhancement of oxidative phosphorylation and fatty acid oxidation in effector T cells helping them to survive energy and nutrient deprivation in tumor milieu [56]. Increasing fatty acid catabolism within $CD8^+$ tumor-infiltrating T cells can improve their ability to slow tumor progression. Promoting T cell fatty acid catabolism via PPAR-α ligands can increase the efficacy of melanoma immunotherapy. It has been indicated that using fenofibrate as an PPAR-α agonist has synergic effects with PD-1 blockers in immunotherapy of cancers through metabolic reprogramming of effector T cells [57]. Bezafibrate as a PGC-1α/ PPAR complex agonist has been shown to increase fatty acid oxidation and mitochondrial respiratory capacity which can increase mitochondrial oxidative phosphorylation and glycolysis in $CD8^+$ T lymphocytes at the same time leading to enhanced anti-tumor immunity during PD-1 blockade [53]. In this study, bezafibrate did not show any large effect on cancer cells as the used dosage was less than 1/10 the dose that can show cytotoxicity toward cancer cells [58]. Impaired glycolysis pathways within T cells in the tumor microenvironment can be an amplifier for PD-1 inhibitory effects on effector immune cells in the tumor milieu. Concerning this, Patsoukis and co-workers have reported that up-regulation of fatty acid oxidation can increase the longevity of T cells in cancers and chronic infections, and may result in T cells reinvigoration in the tumor microenvironment. These researchers have also noted that exhausted T cell reinvigoration somehow depends on the reserve of lipids, which probably are the only energy generation source by fatty acid oxidation in T lymphocytes receiving PD-1 signals [59]. Memory T cells necessarily need catabolic metabolism of fatty acid oxidation to sustain their survival and bioenergetics and metabolic properties of PD-1 stimulated T lymphocytes to display a surprising similarity to those memory cells [60]. Another study has also reported that mitochondrial activation agents such as PPAR-γ can have synergic effects with PD-1 blockade therapy and increase T cell dependent anti-tumor responses [61]. Studies have demonstrated that upon monotherapy with PD-1 blockade, dysfunctional effector T cells can regain their functionality, but they will die due to terminal differentiation and energy restriction in tumor microenvironment. Thus, scientists have suggested metabolic modulation of T cells in addition to anti-PD-1 immunotherapy of cancer [62–64]. Mulki and colleagues have shown that mTORC1-PPARγ pathway is required for proliferation and full activation of $CD4^+$ T cells. They noted that PPARγ can directly express genes associated with fatty acid uptake in T helper ($CD4^+$) cells (in both human and mice), resulting in acquisition of an activated phenotype for $CD4^+$ T cells [65]. In a review article, Lichtor and colleagues have concluded that thiazolidinediones as PPAR-γ agonists can have synergic benefits in immunotherapy of brain tumors via up-regulation of lipid metabolism [66]. Another study has shown that regulation of fatty acid oxidation by PPAR ligands can control asymmetric division and exhaustion of hematopoietic stem cells [67]. Interestingly, it has also been reported that PPAR-γ agonists may have positive transcriptional regulatory effects on development of human dendritic cells (DCs) through controlling lipid metabolism [68].

While some studies have reported the benefits of PPAR-γ agonists on T cells metabolic reprogramming leading to the function preservation of effector T cells in the inhibitory milieu of the tumor microenvironment, there are also studies indicating that PPAR-γ agonists may cause cell growth arrest and apoptosis in immune cells and tumor cells. Due to the metabolic reprogramming within cells following treatment with PPAR-γ agonists, it is believed that they may result in cell growth arrest and cell death in a broad spectrum of cells particularly tumor cells [69–71]. It has been demonstrated that activation of PPAR-γ pathway in T cells may induce apoptosis/cell death and act as a potent anti-inflammatory signal [72]. It has also been reported that PPAR-γ can mediate the inhibition of T helper cells [73,74]. Clark et al. reported

that murine T helper cells can be affected by PPARγ leading to inhibition of IL-2 secretion, while, IL-2-induced proliferation won't be affected [75]. In another study Klotz and colleagues showed that administration of PPARγ in autoimmune encephalomyelitis can ameliorate histopathological signs and clinical course of the disease via NFκB DNA-binding activity and prevention of inflammation only in absence of acute relapse phase [76]. The immunoregulatory effects of PPARγ have also been reported in a study by Hontecillas and coworkers. They reported that deletion of macrophage-specific PPARγ may exacerbate the clinical and pathological symptoms of inflammatory bowel disease [77]. Elsewhere, it was reported that PPAR-γ ligand activation can lead to apoptosis and cell death in transformed, but not normal T lymphocytes [78].

Aside from these types of reports, at first, it can be stated that PPAR-γ agonists generally have positive effects on tumor destruction. Several studies have demonstrated that PPAR ligands like thiazolidinedione compounds can be effective in the prevention of cancers and also can be used as adjuvant therapy in cancer treatment [79–83]. Secondly, as we discussed above, recent studies have a tendency toward exploring the benefits and positive effects of PPARs in the immunotherapy of cancer.

5. Conclusion

Although it is undeniable that immunotherapy has improved the treatment of cancers, *in vivo* studies and clinical trials have shown that in some cases successful immunotherapy and tumor destruction by the immune system may be unachievable due to multiple immunosuppressive parameters affecting the appropriate immune responses against tumor cells. Metabolic impositions of tumor microenvironment on tumor-specific effector T cells have amounted as one of the axial obstacles which can impair the functionality of T cells in the tumor milieu. We targeted PPAR agonists as a therapeutic agent causing T cells metabolic reprogramming. These agonists may help to reverse the exhausted phenotype of T cells in tumor microenvironment helping other immunotherapy methods like PD-1 monoclonal antibodies in cancer treatment. The obtained data and the co-administration of PPAR agonists with immunotherapeutic agents may provide new horizons for increasing the accountability and efficacy of cancer treatment. Regarding the novelty of PPAR ligands effects on T cell metabolic reprogramming in the tumor microenvironment and their synergic effects with cancer immunotherapy, as well as the presence of a limited number of studies, it is recommended conducting complementary studies in this field.

Declaration of Competing Interest

The authors have no conflicts of interest regarding this research or its funding.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://www.doi.org/10.1016/j.imlet.2020.01.006.

References

[1] P. Kanavos, The rising burden of cancer in the developing world, Ann. Oncol. 17 (suppl_8) (2006) viii15–viii23.
[2] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (6) (2018) 394–424.
[3] G.P. Dunn, A.T. Bruce, H. Ikeda, L.J. Old, R.D. Schreiber, Cancer immunoediting: from immunosurveillance to tumor escape, Nat. Immunol. 3 (11) (2002) 991.
[4] G.P. Dunn, L.J. Old, R.D. Schreiber, The immunobiology of cancer immunosurveillance and immunoediting, Immunity 21 (2) (2004) 137–148.
[5] S.-R. Woo, L. Corrales, T.F. Gajewski, Innate immune recognition of cancer, Annu. Rev. Immunol. 33 (2015) 445–474.
[6] S.L. Topalian, C.G. Drake, D.M. Pardoll, Immune checkpoint blockade: a common denominator approach to cancer therapy, Cancer Cell 27 (4) (2015) 450–461.
[7] G.A. Rabinovich, D. Gabrilovich, E.M. Sotomayor, Immunosuppressive strategies that are mediated by tumor cells, Annu. Rev. Immunol. 25 (2007) 267–296.
[8] V.A. Gerriets, R.J. Kishton, A.G. Nichols, A.N. Macintyre, M. Inoue, O. Ilkayeva, P.S. Winter, X. Liu, B. Priyadharshini, M.E. Slawinska, Metabolic programming and PDHK1 control CD4+ T cell subsets and inflammation, J. Clin. Invest. 125 (1) (2015) 194–207.
[9] S. Bahrambeigi, D. Sanajou, V. Shafiei-Irannejad, Major fundamental factors hindering immune system in defense against tumor cells; the link between insufficiency of innate immune responses, metabolism, and neurotransmitters with effector immune cells disability, Immunol. Lett. (2019).
[10] O. Warburg, On the origin of cancer cells, Science 123 (3191) (1956) 309–314.
[11] A. Schulze, A.L. Harris, How cancer metabolism is tuned for proliferation and vulnerable to disruption, Nature 491 (7424) (2012) 364.
[12] L. Zhang, P. Romero, Metabolic control of CD8+ t cell fate decisions and antitumor immunity, Trends Mol. Med. 24 (1) (2018) 30–48.
[13] D. Finlay, D.A. Cantrell, Metabolism, migration and memory in cytotoxic T cells, Nat. Rev. Immunol. 11 (2) (2011) 109.
[14] J. Blagih, F. Coulombe, E.E. Vincent, F. Dupuy, G. Galicia-Vázquez, E. Yurchenko, T.C. Raissi, G.J. van der Windt, B. Viollet, E.L. Pearce, The energy sensor AMPK regulates T cell metabolic adaptation and effector responses in vivo, Immunity 42 (1) (2015) 41–54.
[15] N.E. Scharping, A.V. Menk, R.S. Moreci, R.D. Whetstone, R.E. Dadey, S.C. Watkins, R.L. Ferris, G.M. Delgoffe, The tumor microenvironment represses T cell mitochondrial biogenesis to drive intratumoral T cell metabolic insufficiency and dysfunction, Immunity 45 (2) (2016) 374–388.
[16] A. Crawford, J.M. Angelosanto, C. Kao, T.A. Doering, P.M. Odorizzi, B.E. Barnett, E.J. Wherry, Molecular and transcriptional basis of CD4+ T cell dysfunction during chronic infection, Immunity 40 (2) (2014) 289–302.
[17] E.J. Wherry, S.-J. Ha, S.M. Kaech, W.N. Haining, S. Sarkar, V. Kalia, S. Subramaniam, J.N. Blattman, D.L. Barber, R. Ahmed, Molecular signature of CD8+ T cell exhaustion during chronic viral infection, Immunity 27 (4) (2007) 670–684.
[18] E.J. Wherry, T cell exhaustion, Nat. Immunol. 12 (6) (2011) 492.
[19] G.L. Semenza, D. Artemov, A. Bedi, Z. Bhujwalla, K. Chiles, D. Feldser, E. Laughner, R. Ravi, J. Simons, P. Taghavi, "The Metabolism of Tumours": 70 Years Later, the Tumour Microenvironment: Causes and Consequences of Hypoxia and Acidity: Novartis Foundation Symposium 240, Wiley Online Library, 2001, pp. 251–264.
[20] R.J. Kishton, M. Sukumar, N.P. Restifo, Metabolic regulation of T cell longevity and function in tumor immunotherapy, Cell Metab. 26 (1) (2017) 94–109.
[21] K.E. Beckermann, S.O. Dudzinski, J.C. Rathmell, Dysfunctional T cell metabolism in the tumor microenvironment, Cytokine Growth Factor Rev. 35 (2017) 7–14.
[22] A. Angelin, L. Gil-de-Gómez, S. Dahiya, J. Jiao, L. Guo, M.H. Levine, Z. Wang, W.J. Quinn III, P.K. Kopinski, L. Wang, Foxp3 reprograms t cell metabolism to function in low-glucose, high-lactate environments, Cell Metab. 25 (6) (2017) 1282–1293 e7.
[23] J.O. Lipton, M. Sahin, The neurology of mTOR, Neuron 84 (2) (2014) 275–291.
[24] M. Laplante, D.M. Sabatini, mTOR signaling at a glance, J. Cell. Sci. 122 (20) (2009) 3589–3594.
[25] G.M. Delgoffe, K.N. Pollizzi, A.T. Waickman, E. Heikamp, D.J. Meyers, M.R. Horton, B. Xiao, P.F. Worley, J.D. Powell, The kinase mTOR regulates the differentiation of helper T cells through the selective activation of signaling by mTORC1 and mTORC2, Nat. Immunol. 12 (4) (2011) 295.
[26] R.D. Michalek, V.A. Gerriets, S.R. Jacobs, A.N. Macintyre, N.J. MacIver, E.F. Mason, S.A. Sullivan, A.G. Nichols, J.C. Rathmell, Cutting edge: distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4+ T cell subsets, J. Immunol. (2011) 1003613.
[27] C.-H. Chang, J. Qiu, D. O'Sullivan, M.D. Buck, T. Noguchi, J.D. Curtis, Q. Chen, M. Gindin, M.M. Gubin, G.J. van der Windt, Metabolic competition in the tumor microenvironment is a driver of cancer progression, Cell 162 (6) (2015) 1229–1241.
[28] K. Fischer, P. Hoffmann, S. Voelkl, N. Meidenbauer, J. Ammer, M. Edinger, E. Gottfried, S. Schwarz, G. Rothe, S. Hoves, Inhibitory effect of tumor cell–derived lactic acid on human T cells, Blood 109 (9) (2007) 3812–3819.
[29] R. Haas, J. Smith, V. Rocher-Ros, S. Nadkarni, T. Montero-Melendez, F. D'Acquisto, E.J. Bland, M. Bombardieri, C. Pitzalis, M. Perretti, Lactate regulates metabolic and pro-inflammatory circuits in control of T cell migration and effector functions, PLoS Biol. 13 (7) (2015) e1002202.
[30] X.R. Wu, X.S. He, Y.F. Chen, R.X. Yuan, Y. Zeng, L. Lian, Y.F. Zou, N. Lan, X.J. Wu, P. Lan, High expression of CD73 as a poor prognostic biomarker in human colorectal cancer, J. Surg. Oncol. 106 (2) (2012) 130–137.
[31] G. Borsellino, M. Kleinewietfeld, D. Di Mitri, A. Sternjak, A. Diamantini, R. Giometto, S. Höpner, D. Centonze, G. Bernardi, M.L. Dell'Acqua, Expression of ectonucleotidase CD39 by Foxp3+ Treg cells: hydrolysis of extracellular ATP and immune suppression, Blood 110 (4) (2007) 1225–1232.
[32] T. Sher, H.F. Yi, O.W. McBride, F.J. Gonzalez, cDNA cloning, chromosomal mapping, and functional characterization of the human peroxisome proliferator

activated receptor, Biochemistry 32 (21) (1993) 5598–5604.
[33] I. Issemann, S. Green, Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators, Nature 347 (6294) (1990) 645.
[34] S. Yasmin, V. Jayaprakash, Thiazolidinediones and PPAR orchestra as antidiabetic agents: from past to present, Eur. J. Med. Chem. 126 (2017) 879–893.
[35] S.J. Bensinger, P. Tontonoz, Integration of metabolism and inflammation by lipid-activated nuclear receptors, Nature 454 (7203) (2008) 470.
[36] P. Lefebvre, G. Chinetti, J.-C. Fruchart, B. Staels, Sorting out the roles of PPARα in energy metabolism and vascular homeostasis, J. Clin. Invest. 116 (3) (2006) 571–580.
[37] C. Duval, M. Müller, S. Kersten, PPARα and dyslipidemia, Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids 1771 (8) (2007) 961–971.
[38] M. Rakhshandehroo, G. Hooiveld, M. Müller, S. Kersten, Comparative analysis of gene regulation by the transcription factor PPARα between mouse and human, PLoS One 4 (8) (2009) e6796.
[39] S. Kersten, J. Seydoux, J.M. Peters, F.J. Gonzalez, B. Desvergne, W. Wahli, Peroxisome proliferator–activated receptor α mediates the adaptive response to fasting, J. Clin. Invest. 103 (11) (1999) 1489–1498.
[40] M. Ahmadian, J.M. Suh, N. Hah, C. Liddle, A.R. Atkins, M. Downes, R.M. Evans, PPARγ signaling and metabolism: the good, the bad and the future, Nat. Med. 19 (5) (2013) 557.
[41] R.A. Daynes, D.C. Jones, Emerging roles of PPARs in inflammation and immunity, Nat. Rev. Immunol. 2 (10) (2002) 748.
[42] Y.-X. Wang, PPARs: diverse regulators in energy metabolism and metabolic diseases, Cell Res. 20 (2) (2010) 124.
[43] G.S. Harmon, M.T. Lam, C.K. Glass, PPARs and lipid ligands in inflammation and metabolism, Chem. Rev. 111 (10) (2011) 6321–6340.
[44] V.A. Narkar, M. Downes, T.Y. Ruth, E. Embler, Y.-X. Wang, E. Banayo, M.M. Mihaylova, M.C. Nelson, Y. Zou, H. Juguilon, AMPK and PPARδ agonists are exercise mimetics, Cell 134 (3) (2008) 405–415.
[45] K. Ito, A. Carracedo, D. Weiss, F. Arai, U. Ala, D.E. Avigan, Z.T. Schafer, R.M. Evans, T. Suda, C.-H. Lee, A PML–PPAR-δ pathway for fatty acid oxidation regulates hematopoietic stem cell maintenance, Nat. Med. 18 (9) (2012) 1350.
[46] Y.-X. Wang, C.-H. Lee, S. Tiep, T.Y. Ruth, J. Ham, H. Kang, R.M. Evans, Peroxisome-proliferator-activated receptor δ activates fat metabolism to prevent obesity, Cell 113 (2) (2003) 159–170.
[47] D. Holst, S. Luquet, V. Nogueira, K. Kristiansen, X. Leverve, P.A. Grimaldi, Nutritional regulation and role of peroxisome proliferator-activated receptor δ in fatty acid catabolism in skeletal muscle, Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids 1633 (1) (2003) 43–50.
[48] J. Lin, C. Handschin, B.M. Spiegelman, Metabolic control through the PGC-1 family of transcription coactivators, Cell Metab. 1 (6) (2005) 361–370.
[49] D.S. Thommen, T.N. Schumacher, T Cell Dysfunction in Cancer, Cancer Cell 33 (4) (2018) 547–562.
[50] E. Dugnani, V. Pasquale, C. Bordignon, A. Canu, L. Piemonti, P. Monti, Integrating T cell metabolism in cancer immunotherapy, Cancer Lett. 411 (2017) 12–18.
[51] M. Sukumar, J. Liu, Y. Ji, M. Subramanian, J.G. Crompton, Z. Yu, R. Roychoudhuri, D.C. Palmer, P. Muranski, E.D. Karoly, Inhibiting glycolytic metabolism enhances CD8+ T cell memory and antitumor function, J. Clin. Invest. 123 (10) (2013) 4479–4488.
[52] E.L. Pearce, M.C. Walsh, P.J. Cejas, G.M. Harms, H. Shen, L.-S. Wang, R.G. Jones, Y. Choi, Enhancing CD8 T-cell memory by modulating fatty acid metabolism, Nature 460 (7251) (2009) 103.
[53] P.S. Chowdhury, K. Chamoto, A. Kumar, T. Honjo, 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. 6 (11) (2018) 1375–1387.
[54] H. Hauner, The mode of action of thiazolidinediones, Diabetes Metab. Res. Rev. 18 (S2) (2002) S10–S15.
[55] B. Cha, T. Ciaraldi, L. Carter, S. Nikoulina, S. Mudaliar, R. Mukherjee, J. Paterniti Jr., R. Henry, Peroxisome proliferator-activated receptor (PPAR) γ and retinoid X receptor (RXR) agonists have complementary effects on glucose and lipid metabolism in human skeletal muscle, Diabetologia 44 (4) (2001) 444–452.
[56] S. Bahrambeigi, V. Shafiei-Irannejad, Immune-mediated anti-tumor effects of metformin; targeting metabolic reprogramming of T cells as a new possible mechanism for anti-cancer effects of metformin, Biochem. Pharmacol. (2019) 113787.
[57] Y. Zhang, R. Kurupati, L. Liu, X.Y. Zhou, G. Zhang, A. Hudaihed, F. Filisio, W. Giles-Davis, X. Xu, G.C. Karakousis, Enhancing CD8+ T cell fatty acid catabolism within a metabolically challenging tumor microenvironment increases the efficacy of melanoma immunotherapy, Cancer Cell 32 (3) (2017) 377–391 e9.
[58] D. Panigrahy, A. Kaipainen, S. Huang, C.E. Butterfield, C.M. Barnés, M. Fannon, A.M. Laforme, D.M. Chaponis, J. Folkman, M.W. Kieran, PPARα agonist fenofibrate suppresses tumor growth through direct and indirect angiogenesis inhibition, Proc. Natl. Acad. Sci. 105 (3) (2008) 985–990.
[59] N. Patsoukis, K. Bardhan, P. Chatterjee, D. Sari, B. Liu, L.N. Bell, E.D. Karoly, G.J. Freeman, V. Petkova, P. Seth, PD-1 alters T-cell metabolic reprogramming by inhibiting glycolysis and promoting lipolysis and fatty acid oxidation, Nat. Commun. 6 (2015) 6692.
[60] G.J. van der Windt, B. Everts, C.-H. Chang, J.D. Curtis, T.C. Freitas, E. Amiel, E.J. Pearce, E.L. Pearce, Mitochondrial respiratory capacity is a critical regulator of CD8+ T cell memory development, Immunity 36 (1) (2012) 68–78.
[61] K. Chamoto, P.S. Chowdhury, A. Kumar, K. Sonomura, F. Matsuda, S. Fagarasan, T. Honjo, Mitochondrial activation chemicals synergize with surface receptor PD-1 blockade for T cell-dependent antitumor activity, Proc. Natl. Acad. Sci. 114 (5) (2017) E761–E770.
[62] P.M. Odorizzi, K.E. Pauken, M.A. Paley, A. Sharpe, E.J. Wherry, Genetic absence of PD-1 promotes accumulation of terminally differentiated exhausted CD8+ T cells, J. Exp. Med. 212 (7) (2015) 1125–1137.
[63] P.C. Tumeh, C.L. Harview, J.H. Yearley, I.P. Shintaku, E.J. Taylor, L. Robert, B. Chmielowski, M. Spasic, G. Henry, V. Ciobanu, PD-1 blockade induces responses by inhibiting adaptive immune resistance, Nature 515 (7528) (2014) 568.
[64] P. Chowdhury, K. Chamoto, T. Honjo, Combination therapy strategies for improving PD-1 blockade efficacy: a new era in cancer immunotherapy, J. Intern. Med. 283 (2) (2018) 110–120.
[65] M. Angela, Y. Endo, H.K. Asou, T. Yamamoto, D.J. Tumes, H. Tokuyama, K. Yokote, T. Nakayama, Fatty acid metabolic reprogramming via mTOR-mediated inductions of PPARγ directs early activation of T cells, Nat. Commun. 7 (2016) 13683.
[66] T. Lichtor, A. Spagnolo, R.P. Glick, D.L. Feinstein, PPAR-, PPAR Research 2008, (2008).
[67] V. Lallemand-Breitenbach, H. de Thé, Hematopoietic stem cells burn fat to prevent exhaustion, Cell Stem Cell 11 (4) (2012) 447–449.
[68] I. Szatmari, D. Töröcsik, M. Agostini, T. Nagy, M. Gurnell, E. Barta, K. Chatterjee, L. Nagy, PPARγ regulates the function of human dendritic cells primarily by altering lipid metabolism, Blood 110 (9) (2007) 3271–3280.
[69] C. Grommes, G.E. Landreth, M.T. Heneka, Antineoplastic effects of peroxisome proliferatoractivated receptor γ agonists, Lancet Oncol. 5 (7) (2004) 419–429.
[70] J.-A. Kim, K.-S. Park, H.-I. Kim, S.-Y. Oh, Y. Ahn, J.-W. Oh, K.-Y. Choi, Troglitazone activates p21Cip/WAF1 through the ERK pathway in HCT15 human colorectal cancer cells, Cancer Lett. 179 (2) (2002) 185–195.
[71] M.G. Posch, C. Zang, W. Mueller, U. Lass, A. von Deimling, E. Elstner, Somatic mutations in peroxisome proliferator-activated receptor-γ are rare events in human cancer cells, Med. Sci. Monit. 10 (8) (2004) BR250–BR254.
[72] S.G. Harris, R.P. Phipps, The nuclear receptor PPAR gamma is expressed by mouse T lymphocytes and PPAR gamma agonists induce apoptosis, Eur. J. Immunol. 31 (4) (2001) 1098–1105.
[73] X.Y. Yang, L.H. Wang, T. Chen, D.R. Hodge, J.H. Resau, L. DaSilva, W.L. Farrar, Activation of human T lymphocytes is inhibited by peroxisome proliferator-activated receptor γ (PPARγ) agonists PPARγ co-association with transcription factor NFAT, J. Biol. Chem. 275 (7) (2000) 4541–4544.
[74] A.C. Li, C.K. Glass, PPAR-and LXR-dependent pathways controlling lipid metabolism and the development of atherosclerosis, J. Lipid Res. 45 (12) (2004) 2161–2173.
[75] R.B. Clark, D. Bishop-Bailey, T. Estrada-Hernandez, T. Hla, L. Puddington, S.J. Padula, The nuclear receptor PPARγ and immunoregulation: PPARγ mediates inhibition of helper T cell responses, J. Immunol. 164 (3) (2000) 1364–1371.
[76] L. Klotz, M. Schmidt, T. Giese, M. Sastre, P. Knolle, T. Klockgether, M.T. Heneka, Proinflammatory stimulation and pioglitazone treatment regulate peroxisome proliferator-activated receptor γ levels in peripheral blood mononuclear cells from healthy controls and multiple sclerosis patients, J. Immunol. 175 (8) (2005) 4948–4955.
[77] R. Hontecillas, W.T. Horne, M. Climent, A.J. Guri, C. Evans, Y. Zhang, B.W. Sobral, J. Bassaganya-Riera, Immunoregulatory mechanisms of macrophage PPAR-γ in mice with experimental inflammatory bowel disease, Mucosal Immunol. 4 (3) (2011) 304.
[78] S.G. Harris, R.P. Phipps, Prostaglandin D2, its metabolite 15-d-PGJ2, and peroxisome proliferator activated receptor-γ agonists induce apoptosis in transformed, but not normal, human T lineage cells, Immunology 105 (1) (2002) 23–34.
[79] D. Panigrahy, L.Q. Shen, M.W. Kieran, A. Kaipainen, Therapeutic potential of thiazolidinediones as anticancer agents, Expert Opin. Investig. Drugs 12 (12) (2003) 1925–1937.
[80] J.A. Brockman, R.A. Gupta, R.N. DuBois, Activation of PPARγ leads to inhibition of anchorage-independent growth of human colorectal cancer cells, Gastroenterology 115 (5) (1998) 1049–1055.
[81] P. Sarraf, E. Mueller, D. Jones, F.J. King, D.J. DeAngelo, J.B. Partridge, S.A. Holden, L.B. Chen, S. Singer, C. Fletcher, Differentiation and reversal of malignant changes in colon cancer through PPARγ, Nat. Med. 4 (9) (1998) 1046.
[82] J.M. Seargent, E.A. Yates, J.H. Gill, GW9662, a potent antagonist of PPARγ, inhibits growth of breast tumour cells and promotes the anticancer effects of the PPARγ agonist rosiglitazone, independently of PPARγ activation, Br. J. Pharmacol. 143 (8) (2004) 933–937.
[83] B. Yousefi, A. Azimi, M. Majidinia, V. Shafiei-Irannejad, R. Badalzadeh, B. Baradaran, N. Zarghami, N. Samadi, Balaglitazone reverses P-glycoprotein-mediated multidrug resistance via upregulation of PTEN in a PPARγ-dependent manner in leukemia cells, Tumor Biol. 39 (10) (2017) 1010428317716501.