

Lipid_Metabolic_Features_of_T

Lipid Metabolic Features of T cells in the Tumor Microenvironment

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Running title: Lipid metabolism of T cells in TME

Abstract

The tumor microenvironment (TME) is characterized by discrete changes in metabolic features of cancer and immune cells, with various implications. Cancer cells take up most of the available glucose to support their growth, thereby leaving immune cells with insufficient nutrients to expand. In the relative absence of glucose, T cells switch the metabolic program to lipid-based sources, which is pivotal to T-cell differentiation and activation in nutrient-stressed TME. Although consumption of lipids should provide an alternative energy source to starving T cells, a literature survey has revealed that it may not necessarily lead to antitumor responses. Different subtypes of T cells behave differently in various lipid overload states, which widely depends upon the kind of free fatty acids (FFA) engulfed. Key lipid metabolic genes provide cytotoxic T cells with necessary nutrients for proliferation in the absence of glucose, thereby favoring antitumor immunity, but the same genes cause immune evasion in T_{mem} and T_{reg}. This review aims to detail the complexity of differential lipid metabolism in distinct subtypes of T cells that drive the antitumor or pro-tumor immunity in specific TME states. We have identified key drug targets related to lipid metabolic rewiring in TME.

Keywords: Lipid; T-cells; tumor microenvironment (TME); PD-L1/2; CD36

Introduction

Our bodies utilize lipids for various fundamental processes, ranging from the major energy source to the synthesis of vital macromolecules such as cholesterol, membrane phospholipids, and hormones. Like most cells, T cells are heavily dependent on lipid consumption for energy needs, but their naiveté, activation, and effector functions are influenced by the subtype and quantity of lipid intake [1]. A number

7
27 of surface and intracellular proteins, such as differentiation 36 (CD36), fatty acid-binding protein (FABP),
28 fatty acid transporter protein (FATP), and sterol regulatory-element binding proteins (SREBPs), are
29 responsible for processing lipids in T cells. Under normal circumstances, quiescent T cells process lipids
30 into more energy-efficient oxidative phosphorylation (OXPHOS), which is replaced by aerobic glycolysis
31 once T cells are activated. A complex cascade of co-stimulatory triggers channel T cells into T-regulatory
32 cells (T_{regs}) and helper T cells (Th cells), each with differential metabolic shifts. As the immune response
33 approaches an end, activated T cells undergo apoptosis or are converted to nondividing T memory cells
34 that revert to OXPHOS [2, 3].

35 The tumor microenvironment (TME) is a complex space characterized by multiple cell types and
36 their interwoven interactions, predominantly favoring cancerous growth. The interdependence of nutrients,
37 vasculature, and metabolic demands actively shapes the cellular fate in TME. The specialized metabolic
38 switches, nutrient preferences, cellular growth demands, and secretion of various intrinsic and extrinsic
39 factors prime the particular kind of cell in TME to behave in a specific manner [4, 5]. For example,
40 growth signals and upregulation of metabolic features in tumor cells make them more suitable for
41 proliferation, while immune cells undergo tumor evasion after metabolic switch at the same time [6, 7].
42 As proliferating cells, in contrast to normal cells, require macromolecule biosynthesis and redox
43 homeostasis in addition to their normal energy needs [8-10], rapidly growing cancerous cells overtake
44 metabolic control in TME, resulting in compromised nutrients supply to immune system cells [11]. In fact,
45 the effector functions of innate and adaptive cells are partially controlled by their ability to consume
46 glucose, which is mediated by glucose transporter-1 (GLUT1) receptors [12]. A glycolytic challenge
47 within TME curbs the effector function of immune cells on one side while enabling tumor cells with
48 additional glucose to thrive on the other. Beyond the evident impact of glucose metabolism on immune
49 cell reprogramming in TME, the role of lipid metabolism remains relatively poorly studied despite its
50 conceivable implications.

51 Cancer typically withstands nutrient deprivation by interacting with nearby stromal cells. Cancer
52 cells activate neighboring adipocytes to provide a sustained supply of lipids for tumor survival and

53 proliferation [13, 14]. Another important source of lipids in TME are cancer-associated fibroblasts [15,
54 16]. Moreover, cancer cells reprogramming to initiate de novo lipid synthesis, upregulation of fatty acid
55 binding, and uptake of proteins ensures the surplus energy source in TME. Preferential accumulation of
56 lipids in TME, greater availability of fatty acids to cancer cells, and subsequent immune evasion are the
57 hallmarks of the lipid metabolism features in TME. Although the metabolic narrative of cancer is
58 increasingly accepted, scattered data remain a challenge. This review aims to identify and highlight the
59 lipid metabolic features of T cells in TME.

60

61 Genes involved in fatty acid-driven differentiation of T cells in TME

62 Activated T cells have greater metabolic demands to assist their proliferation, which requires
63 higher de novo fatty acid synthesis (FAS), manifested by the conversion of glucose to fatty acids [17].
64 Previous studies have revealed that sterol-responsive element-binding proteins (SREBPs) induce FAS in
65 activated T cells via mTORC1 [18-20], while naïve T cells and memory T cells (T_{mem}) maintain fatty acid
66 oxidation (FAO) as the default metabolic program. FAS has to go through various steps mediated by key
67 enzymes before lipid synthesis can occur. Some of these enzymes affect the rewiring of T cells. For
68 instance, it has been found that $CD8^+$ T cells cannot expand without SREBP signaling during viral
69 infection; however, it was expendable for homeostatic growth. SREBPs in T_{effs} induce the expression of
70 enzymes fatty acid synthetase (FASN), acetyl-CoA carboxylase (ACC) and hydroxy-methyl-glutaryl-CoA
71 reductase (HMGCR) [17]. Seon Ah Lim et al. have reinforced these observations in a mouse model of
72 TME, showing that inhibition of SREBP-dependent lipid synthesis and metabolic reprogramming in T_{regs}
73 initiates a robust antitumor response without causing autoimmune disorders. It has been further proven
74 that depletion of an obligatory SREBP factor SCAP curtails tumor growth and upgrades anti-PD-1
75 immunotherapy [21]. Similarly, Yang-An Wen et al. confirmed the tumor growth suppression after the
76 knockdown of either SREBP1 or SREBP2 target genes required for lipid biosynthesis [22]. At least
77 theoretically, depletion of SREBPs in cancer cells and T_{regs} yields anticancer benefits; however, deletion
78 of SREBPs in T_{effs} can affect their blast, which may lead to immune evasion. These SREBPs might be

context-dependent drug targets. Further research is required to ascertain them in all subsets of T cells and cancer cells in complex TME.

In addition to SREBPs, ACC is another widely studied lipogenic gene in this direction, which has led to similar results. For instance, Luciana Berod and colleagues found that TH17 cells, but not T_{regs} , rely on the *de novo* lipid synthesis mediated by ACC1. T_{regs} do not follow this scheme as they tend to utilize exogenous FFAs. T cell-specific deletion of ACC1 in mice is able to ameliorate autoimmune disease through anti-inflammatory actions [23]. Similarly, CD8+ T-cell expansion and proliferation are severely curtailed in the absence of ACC1 and subsequently restored by exogenous fatty acid supply [24]. Inhibition and activation of ACC1 favor peripheral T_{regs} and Th17 cell differentiation, respectively, under TME [25].

FAS required for proliferation is heavily based on acetyl-CoA produced from glycolysis. Inhibition of FAS-related enzymes such as SREBPs, ACC1, or downstream targets leads to defective effector T-cell responses [26]. Although modulation of SREBPs or downstream pathways is rarely attempted in cancer, they may be good therapeutic targets for the future.

FAO, a key bioenergetic pathway [27], displays a critical role in the development of tolerogenic dendritic cells (DCs) [28]. Interestingly, DCs of cancerous origin tend to accumulate oxidized lipids, thereby suppressing T-cell effector functions, which indirectly favors tumor progression [29]. It is speculated that accumulated fatty acids support FAO and therefore promote tolerogenicity in the cancer setting [30]. Furthermore, a carnitine palmitoyltransferase-1A (CPT1A) inhibitor, etomoxir, has immunomodulatory actions on CD8⁺ T_{mem} cell differentiation [31]. However, Brenda Raud et al. have pointed out the flexible metabolic fuel choices of T_{mem} and found that CPT1A-mediated long chain fatty acid oxidation (LC-FAO) is expendable for the expansion of CD8⁺ T cell memory [32].

PD-L1/2 in T-cell metabolism in TME

³ Programmed death ligand-1/2 (PD-L1/2) belongs to CD28 family, and is predominantly expressed on tumors and tumor-infiltrating myeloid cells [33, 34]. PD-L1/2 has been suspected to play a

105 negative role in TME by suppressing antitumor immunity by regulating inhibitory cascade on effector T
106 cells [35, 36]. For example, a recent report has suggested that PD-1 participates in the metabolic
107 reprogramming of activated T cells [37] by reducing Akt (protein kinase B) activation and subsequently
108 inhibiting mammalian target rapamycin (mTOR) activity [37-39]. Indeed, reduced activation of mTOR in
109 PD-1⁺ CD8⁺ T cells activates transcription factor forkhead box O1 (FoxO1), allowing the survival of
110 exhausted CD8 T cells [39]. As glycolysis is necessary for T cells to obtain the required amount of energy
111 for proliferation, the diversion from glycolysis to FAO likely sabotages antitumor immunity in TME. The
112 preferential diversion from glycolysis to FAO leads to the longevity of T_{mem} cells, which possess
113 substantial mitochondrial spare respiratory capacity (SRC) [40]. Consistently, inhibition of the PD-1
114 pathway in the early phases of a viral infection leads to raised mTOR signaling in virus-specific CD8⁺ T
115 cells, resulting in quicker infection clearance [41]. Certainly, mTOR and Akt are key lipid regulators
116 within the cell [42]. Similarly, inhibition of PD-1/PD-L1 leads to extensive cytotoxic T-cell infiltration
117 into TME as reported in ex vivo, in vitro, and in vivo experimental models [43]. Blocking PD-1 in cancer
118 patients leads to decreased tumor progression and improved survival [44, 45].

119 PD-1 has also been reported in T-cell exhaustion, which is counterproductive to immunity [46].
120 Exhaustion of PD-1-associated CD8⁺ T-cell existed in chronic viral infections in mice [47] and in
121 clinical studies [48-50]. It is not surprising that, in 2014, FDA approved the first blocking antibody
122 targeting PD-1 to treat metastatic melanoma, and up to August 2017, many drugs against the PD-1
123 pathway had been applied in various cancers [46]. However, a recent study has contradicted the holistic
124 benefits of PD-1 blockade in TME as distinct responsiveness of T-cell subpopulations to PD-1 blockade
125 was observed. The study observed that effector and central memory phenotypes were among the most
126 affected T-cell subpopulations after PD-1 blockade but had different gene expression profiles with PD-L1
127 in comparison to PD-L2 [51].

128

129 **T cells in TME of obese states**

130 Although it is well established that obesity and lipid overload states are obvious causes of cancer
131 and its progression [52-55], it has rarely been investigated how these conditions rewire the T-cell
132 differentiation and metabolic switch in TME. Alison E Ringel et al. have recently addressed this important
133 question and demonstrated how obesity shifts the metabolic program of TME to inhibit T-cell function
134 and promote tumor growth. Researchers have systematically shown in a murine model that a high-fat diet
135 (HFD) is differentially taken up by tumor cells in TME as compared to CD8⁺ T cells, which leads to
136 modified fatty acid partitioning, diminished CD8⁺ T-cell infiltration, and promotion of tumorigenesis [56].
137 Of course, preferential fat consumption by tumor cells makes localized T cells less efficient as fat is
138 required to raise the number and plasticity of T cells in TME.

139 There are several other genes and enzymes with limited evidence but with potential to be good
140 drug targets. The consumption of fat is not only restricted to activate the T cells, but it is also evident that
141 under normal circumstances ⁸ de novo cardiolipin synthesis keeps the function of CD8⁺ T cells intact.
142 Mauro Corrado and colleagues demonstrated poor T-cell antigenic responses in T cells deficient in the ⁸
143 cardiolipin-synthesizing enzyme—protein tyrosine phosphatase, mitochondrial-1 (PTPMT1). PTPMT1-
144 dependent cardiolipin synthesis is also important for mitochondrial fitness, especially during T_{mem} cell
145 differentiation or nutrition scarcity [57]. Monoacylglycerol lipase (MGL) hydrolyzes monoglycerides into
146 glycerol and fatty acids. It is abundantly present in tumor cells, and MGL knockout (KO) mice exhibit a
147 reduced tumor size compared with control mice. Interestingly, the reduction in tumor progression is
148 associated with a parallel ²² upregulation in the number of CD8⁺ T cells. Furthermore, naïve CD8⁺ T cells
149 exhibit enhanced tumoricidal activity in MGL KO mice [58]. P4HA2 is a metabolism-related gene that is
150 upregulated in cervical cancer tissues, and negatively correlates with CD8⁺ T cells. Knockdown of
151 P4HA2 suppresses lipid droplet storage in cancer cells [59]. Teresa Manzo and colleagues demonstrated a
152 progressive ⁵ accumulation of long-chain fatty acids (LCFAs), which, instead of providing an energy
153 source, hamper the mitochondrial function and rewire the lipid metabolism pathways. In addition,
154 intrapancreatic CD8⁺ T cells ⁵ inhibit the very long-chain acyl-CoA dehydrogenase (VLCAD) enzyme,
155 which worsens the accumulation of LCFAs and very-long-chain fatty acids (VLCFA), subsequently

156 inducing lipotoxicity. In fact, recently obesity has also been described as a booster of antitumor
157 pharmacotherapy in some cancers [60], but the mechanism remains unknown.

158

159 MDSCs in T-cell lipid (de)regulation

160 Myeloid-derived suppressive cells (MDSCs) manifest negative regulatory activity by promoting
161 immunosuppression in immune-related diseases [61, 62]. In tumors, MDSCs accelerate tumor
162 proliferation, tumor expansion, and immune escape, thereby further exacerbating the TME [63, 64].
163 MDSCs reshape TME by inhibiting T cells and natural killer (NKT) cells while inducing regulatory T
164 cells (T_{regs}) and regulatory B cells (B_{regs}) [65, 66]. From recent studies, it is evident that lipid metabolism
165 in tumor-infiltrating MDSCs (T-MDSCs) is rewired for raised fatty acid uptake, FAO upgrade, oxygen
166 consumption rate (OCR), mitochondrial mass, and expression of core FAO enzymes [67]. It is interesting
167 to note that only T-MDSCs, but not splenic MDSCs, raise lipid uptake [68], which implies that only
168 infiltrating MDSCs undergo lipid metabolic reprogramming. This differential scheme of pro-tumor
169 metabolic features sheds light on the complexity of TME.

170 In mammals, Liver X receptors (LXRs) are involved in lipid homeostasis. Previous studies have
171 revealed that administration of LXR agonists initiates MDSC apoptosis and reduces tumor volume [69,
172 70]. In addition, lectin-type oxidized LDL receptor 1 (LOX-1) is present in PMN-MDSCs of cancer
173 patients but is absent in healthy individuals [71]. Similarly, Caijun Wu et al. noticed the enhanced
174 immunosuppressive role of monocytic MDSCs after administration of a multidose clinical regimen of
175 gemcitabine (GEM). These authors have implicated that the deregulation of lipid metabolism in residual
176 tumor cells is partially responsible for promoting immunosuppression [72]. It is plausible to conclude that
177 tumor-derived MDSCs are forced to rewire lipid metabolism primarily because of robust lipid storage and
178 related signaling activation.

179

180 CD36 and T-cell regulation in TME

181 CD36 is a scavenger receptor of oxidized lipids, and is expressed in multiple cell types, including
182 T cells [73, 74]. Previous studies have highlighted that tumor-associated immune cells undergo CD36-
183 oriented lipid metabolic reprogramming, which leads to immune evasion and cancer progression [75].
184 Shihao Xu and coworkers have reported that CD8⁺ tumor-infiltrating lymphocytes (TILs) are responsive
185 to lipids in the TME, mediated by CD36, which is associated with progressive T-cell dysfunction. It has
186 been explained that T-cell dysfunction occurs in a CD36-dependent manner, which leads to a raise in
187 oxidized low-density lipoproteins (OxLDL) in T cells, promotion of lipid peroxidation downstream, and
188 occurrence of ferroptosis. Interestingly, overexpression of glutathione peroxidase 4 reverses lipid
189 peroxidation to improve the effector capacity of T cells [76]. Similar evidence has been provided by other
190 research groups, associating overexpression of CD36 with shorter survival of melanoma patients with
191 tumor-infiltrating CD8⁺ T cells, while CD36-depleted CD8⁺ T cells showed greater antitumor potential
192 and survival compared with wild-type CD8⁺ T cells [77-80].

193 Importantly, there are very few identified metabolic drug targets that work in the same direction in both
194 T_{regs} and T_{effs}. As presented above, metabolic drug targets are often context- and T-cell subtype-
195 dependent, in which T_{regs} and T_{effs} promote or inhibit tumor, respectively. However, CD36 offers a rare
196 opportunity because its deletion on both T_{regs} and T_{effs} results in enhanced antitumor activities [81]. For
197 instance, Wang et al. stated that genetic knockdown of CD36 in T_{reg} cells reduced tumor growth and
198 intratumoral T_{reg} cells, promoting the antitumor function of tumor-infiltrating lymphocytes [82]. Although
199 only few studies have been reported in this direction, CD36 presents a viable common drug target that
200 requires future research.

201

202 **Effects of lipid metabolism on T_{regs}**

203 The relative ratio of cytotoxic T cells and T_{regs} in TME plays a pivotal role in tumor progression
204 and immune evasion [83]. T_{regs} contribute to immune evasion in TME [84-86]. Systematic ablation of
205 T_{regs} in several cancer types has resulted in tumor suppression and cellular alterations within the TME [87,
206 88]. It is suspected that cytotoxic T_{effs} and T_{regs} follow different activation and proliferation pathways as

207 T_{regs} are abundant even in the unfavorable metabolic states in TME [89]. Indeed, Weinberg et al. have
208 stressed the necessity of mitochondrial metabolism in T_{regs} to maintain their immunosuppressive function
209 [90]. A recent study has shown raised production of FFAs by RHOA Y42-mutated gastric cancer,
210 modulated via the PI3K pathway, which favors the accumulation of T_{regs} in a low-glucose TME. Similarly,
211 the expression levels of FAS, CPT-1, PPAR α , and PPAR γ were also higher in gastric cancer with RHOA
212 Y42 mutation [91]. It remains unknown what metabolic switch enables T_{regs} to expand and proliferate
213 differently from T_{effs} in the same TME. However, one study confirmed that intratumoral T_{regs} indirectly
214 promote M2-like TAMs by boosting SREBP1-dependent lipid metabolism and then limiting the CD8⁺ T-
215 produced interferon-gamma (IFN γ), thereby leading to tumor progression and orchestrating tumor-
216 associated immunosuppression [92]. In addition, inhibition of FABP5 on T_{regs} causes mitochondrial
217 alterations characterized by impaired lipid metabolism, reduced OXPHOS, and loss of cristae structure.
218 The authors concluded that FABP5 is a gatekeeper of mitochondrial integrity, which is necessary for
219 normal functioning of T_{regs} [93]. An interesting observation regarding the complicity of T_{regs} and tumor
220 cells to suppress the T-cell functioning has recently been highlighted. Xia Liu et al. pointed out that
221 senescent T cells presented unbalanced lipid metabolism, while tumor cells and T_{reg} cells have driven
222 increased expression of IVA phospholipase A₂, which is responsible for modified lipid metabolism and
223 senescence observed in T cells. The inhibition of group IVA phospholipase A₂ initiated reprogramming in
224 effector T-cell lipid metabolism, thereby stopping T-cell senescence in cancer models in vivo and in vitro
225 [94].

226

227 Unconventional T cells in TME

228 $\gamma\delta$ T cells are capable of differentiating into various subtypes of immune cells depending on the
229 TME conditions [95]. Although the scientific knowledge on $\gamma\delta$ T cells is underdeveloped and their
230 proclivity as pro-tumorigenic or anticancer immune cells is still unclear [96-98], $\gamma\delta$ T cells are potential
231 agents against cancer cells [99]. Various studies have reported the chameleon-like nature of $\gamma\delta$ T cells,
232 pointing at the flexibility they exhibit in TME [100-102]. The phenomenon has been successfully

233 explained in squamous cell carcinoma [103] and colorectal cancer [104], where it has been suggested that
234 TME conditions can affect the proliferation and functional nature of $\gamma\delta$ T-cells. For example, a recent
235 study has highlighted two distinct subtypes of $\gamma\delta$ T cells, namely, antitumoral IFN- γ -producing $\gamma\delta$ T cells
236 ($\gamma\delta$ IFN cells) and IL17-producing $\gamma\delta$ T cells ($\gamma\delta$ 17 cells) [105]. Interestingly, it has been shown that V δ 2
237 cells are activated, independent of MHC, by small lipid molecules, phosphoantigens (pAgs), which are
238 derived from the mevalonate pathway [106-108]. Furthermore, Emmanuel Scotet et al. identified two
239 different lipid-related ligands of V γ 9V δ 2 TCR in tumor cells, namely apolipoprotein A1 (Apo-A1) and
240 ATP synthase/F1-ATPase (high-affinity apo A-I receptor). These authors revealed that Apo-A1, which is
241 abundant in high-density lipoproteins (HDL), is needed for the activation of V γ 9V δ 2 T cells by tumors
242 expressing F1-ATPase [109]. Similarly, a related study by Rodrigues et al. showed that V δ 2 T cells
243 express low-density lipoprotein (LDL) receptors when they are activated and their functions can be
244 modified once LDL attaches to their activated receptors. It has also been demonstrated that expression
245 levels of IFN, NKG2D, and DNAM-1 are downregulated when V γ 9V δ 2 T cells are treated with LDL-
246 cholesterol [110]. Furthermore, host-derived lipids from lung-infiltrating CD1d+B-1a cells are able to
247 induce $\gamma\delta$ T cells for the induction of IL-17A [111].

248 As a specialized type of T lymphocytes, Natural killer T cells (NKT cells) recognize lipid
249 antigens presented through CD1d [112, 113]. NKT cells are divided into two distinct types, including I
250 and II NKT cells, which regulate the immune response in the development and progression of tumor
251 [114-116]. Both type I and type II NKT cells show intermodulation, but type I NKT cells are known to
252 increase antitumor responses, while type II NKT cells are inclined towards pro-cancer activities [117],
253 with some contextual exceptions where type I can also suppress tumor immunity [115, 118, 119].
254 However, tumor growth in TME is bound to consume more lipids to support its rapid proliferation and
255 meet excessive energy needs. De novo lipid synthesis, greater and preferential fatty acid uptake from
256 surrounding tissues in TME, and altered equilibrium of polyunsaturated fatty acids (PUFAs) and saturated
257 fatty acids (SFAs) change the lipid repertoire of tumor cells, which can affect membrane fluidity, cell-cell
258 interaction, and membrane protein landscape, subsequently affecting the downstream signaling cascade

259 [120, 121] in cancers [122, 123]. The changes in lipid repertoire are also linked to the altered structure of
260 bio-in cancer cells [124]. In this context, HFD rich in SFA can negatively affect the capability of DCs to
261 activate naïve T cells [125], which is critical for antitumor responses. The availability of lipids is
262 necessary for the NKT cells development [126] as mice deficient in lysosomal lipid transfer enzyme
263 Niemann Pick C (NPC) 2 have a decreased number of type I NKT cells [127]. There is no doubt that
264 excess lipid states lead to the activation of type I NKT cells, which generates a proinflammatory
265 environment in obese patients [128], while CD1d^{-/-} mice show reduced inflammation under similar
266 conditions [129]. Furthermore, the antitumor potential of NKT cells in obesity is reduced and does not
267 inhibit tumor growth [130]. However, human studies were unable to show any changes in the number of
268 NKT cells in a hepatocellular carcinoma (HCC) model [131]. It is interesting to note that higher lipids
269 increase the NKT cell proliferation, leading to proinflammatory responses, but an obese state reduces
270 NKT cells, causing hindrance in tumor immunity. Further research in this direction is vital and has the
271 potential to unveil anticancer drug targets.

272

273 Conclusion

274 Lipid metabolic features differ in their ability to initiate antitumor or pro-tumor responses in
275 glucose-diminished TME infiltrated by cytotoxic T cells, T_{regs}, T_{mem}, and NKT cells (Figure 1). It may be
276 oversimplified to argue that lipids proliferate T_{effs} and regress T_{regs}/T_{mem} in complicated TMEs where
277 diversified forms of lipids exist. The predisposition of TME to attract and utilize excessive lipids leaves
278 little energy for T_{effs} to expand. In a complex TME, the identification of lipid-based T-cell drug targets is
279 context-dependent as the same genes or enzymes responsible for attracting lipids to T cells preferentially
280 contribute to cancer cell fat intake. The type of lipid intake peculiarly affects different subsets of T cells.
281 Formulation of a definitive hypothesis in this regard is too early. It is necessary to explore the expression
282 difference of the same gene in different subtypes of T cells under TME to mark it as a drug target.
283 Although CD36, SREBPs, PD-L1/2, FABP5, CPT-1, ACC1, GLUT1, and FAS has shown promising
284 prospects to be potential metabolic drug targets of cancer, their context-dependence and varied

285 implications in T-cell subtypes urge for more research. Identifying the differential expression of lipid-
286 related genes, gatekeepers, and enzymes on T-cell subsets and cancer cells that can be manipulated to
287 draw clinical gains presents an opportunity for future research.

288

289

290

291 **Figure legends**

292 **Figure 1. Differential T-cell responses after metabolic rewiring in response to lipids within TME.**

293 Raised expression of CD36 leads to T-cell dysregulation and immune evasion in TME. Excess lipids
294 generate differential responses in T-MDSCs and S-MDSCs, leading to the activation of T_{regs} and causing
295 T-cell dysregulation. Similarly, PD-1/PD-L1 complex converts glycolysis to FAO, thereby affecting T-
296 cell exhaustion and playing a role in tumor progression. Under the state of metabolic competition within
297 TME, T cells may opt to consume more lipids to compensate for depleted glucose and in-process lead to
298 T cells activation.

299 **TME:** Tumor microenvironment; **FAO:** Fatty acid oxidation; **T-MDSCs:** Tumor MDSCs; **S-MDSCs:**
300 Splenic MDSCs; **oxLDL:** Oxidized low-density lipoproteins; **T_{regs}:** T regulatory cells; **SREBPs:** Sterol-
301 responsive element-binding proteins

302 **Raised OxLDL intake:** Raised intake of oxidized low-density lipoproteins (OxLDL) increases lipid
303 peroxidation downstream and causes ferroptosis in T cells, leading to suppression of antitumor immunity.

304 **Lipids induce metabolic reprogramming:** Myeloid-derived suppressive cells (MDSCs) rewiring lipid
305 metabolism have a direct role in remodeling TME by repressing T cells as well as natural killer (NK) cells
306 and generating regulatory T cells (T_{regs}) and regulatory B cells (B_{regs}), supporting immune escape.

307 **Metabolic reprogramming:** As glycolysis is necessary for T cells to obtain the required amount of
308 energy for proliferation, PD-1/PD-L1 – involved metabolic reprogramming from glycolysis to fatty acid
309 oxidation (FAO) causes T-cell exhaustion, which is likely to sabotage antitumor immunity in TME.

310 **Antitumor metabolic reprogramming:** Sterol-responsive element-binding proteins (SREBPs) increase
311 activated T cells with greater metabolic demands by enhancing fatty acid synthesis (FAS), therefore
312 driving the antitumor immunity.

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