The function of T cells is critically dependent on their ability to generate metabolic building blocks to fulfil energy demands for proliferation and consecutive differentiation into various T helper (Th) cells. Th cells then have to adapt their metabolism to specific microenvironments within different organs during physiological and pathological immune responses. In this context, Th2 cells mediate immunity to parasites and are involved in the pathogenesis of allergic diseases including asthma, while CD8+ T cells and Th1 cells mediate immunity to viruses and tumors. Importantly, recent studies have investigated the metabolism of Th2 cells in more detail, while others have studied the influence of Th2 cell-mediated type 2 immunity on the tumor microenvironment (TME) and on tumor progression. We here review recent findings on the metabolism of Th2 cells and discuss how Th2 cells contribute to antitumor immunity. Combining the evidence from both types of studies, we provide here for the first time a perspective on how the energy metabolism of Th2 cells and the TME interact. Finally, we elaborate how a more detailed understanding of the unique metabolic interdependency between Th2 cells and the TME could reveal novel avenues for the development of immunotherapies in treating cancer.

**Keywords:** Th2 cells, tumor microenvironment, metabolism, tissue adaption, immune surveillance, immunometabolism

**INTRODUCTION**

Immune cells including T cells are capable of mounting immune responses against tumors. The ability of the immune system to detect and eliminate neoplastic cells is known as tumor immune surveillance (1, 2). Tumor immune surveillance is to a significant part mediated by CD8+ cytotoxic T lymphocytes (CTLs). During antitumor immune responses, CTLs recognize tumor peptides presented by major histocompatibility complexes (MHC) I through their T cell receptor (TCR). Consecutively, CTLs are capable to kill tumor cells by the release of perforins and granzyme B or by a mechanism that involves Fas ligand (FasL, CD95L)-mediated apoptosis of target cells (1, 2).
It is of note that also various CD4+ T cell populations have been detected in tumors, although their role within the tumor microenvironment (TME) is less well understood compared to CD8+ CTLs. For instance, CD4+ regulatory T cells (Tregs) are known to inhibit CTL function in tumors, while T helper (Th)1 cells participate in antitumor immunity by releasing IFN-γ and TNF (3–5). However, the role of Th2 cells and type 2 immunity during antitumor immune responses is less well understood. Th2 cells are best known to provide immunity against parasites and their pathogenic role in allergic diseases is well established and has been recently reviewed (6–8), while the regulation and function of Th2 cells in the TME is largely neglected and more controversial (9). Yet, therapeutically effective CD4+ CAR T cells have been shown to express a Th1 and, importantly, also a Th2 gene signature and to secrete both Th1 and Th2 cytokines (5, 10).

The TME is a unique metabolic niche, which differs between various tumor types and affected organs (11, 12). Importantly, many recently reviewed studies have shown that the TME and its metabolite composition directly affects the energy metabolism, gene expression and effector function of CTLs, Tregs and Th1 cells (11, 13, 14). How Th2 cells adapt to the TME and how tumors, vice versa, affect Th2 cell function is less established. In this review, we thus highlight studies investigating the metabolism of Th2 cells and summarize the role of Th2 cells in the TME. We then combine the evidence from both types of studies to discuss interactions of the TME and Th2 cell metabolism and function with a perspective and outline for future studies. At the end, we provide an outlook how a better understanding of this unique interdependency could help to establish new therapeutic strategies for cancer treatment.

The Energy Metabolism of Th2 Cells

The type of energy metabolism that is used by T cells depends on their activation level, their differentiation phenotype and the specific environment they operate in (15–18). While naïve T cells primarily use oxidative lipid metabolism, their activation requires the supply with sufficient building blocks to guarantee proliferation. T cells fulfill these energy demands by metabolic reprogramming, which involves the upregulation of glycolysis and lipid metabolism (19, 20). High glycolysis rates require the activation of mammalian Target of Rapamycin (mTOR)-1 and 2, Myc, Hypoxia-inducible factor 1α (HIF-1α) and increased expression of the glucose transporter (GLUT)1 (21–23). Lipid synthesis is promoted by the transcription factors mTORC1 and sterol regulatory element-binding protein (SREBP), which regulate critical enzymes involved in lipid metabolism such as the Acetyl-CoA carboxylase (ACI) (24). Strikingly, pharmacological and genetic deletion of ACC1 completely prevents the generation of almost all effector Th cell lineages (25, 26).

Following activation in secondary lymphatic organs, T cells migrate to their target organs. The specific metabolic environment in these organs also affects the energy metabolism and effector function of different T cell populations, such as shown for instance in the melanoma TME, in which low glucose levels inhibit aerobic glycolysis and the tumoricidal function of CD4+ and CD8+ T cells (27, 28). In this context, lung Th2 cells are mainly characterized by an upregulation of genes related to lipid oxidation and synthesis (29–31). Table 1 summarizes studies investigating the Th2 cell metabolism in more detail (Table 1). Th2 cells in the lung were shown to upregulate the expression of the peroxisome proliferator-activated receptor-γ (PPAR-γ) (31, 43), a nuclear receptor that is induced by IL-4 receptor (IL-4R) ligation and signal transducer and activator of transcription (STAT6) activation (34, 44, 45). In lung Th2 cells, the transcription factor PPAR-γ regulates the expression of different genes that are critical for Th2 cell differentiation and effector function. Among them were the genes Gata3, Stat5, Il5 and Il13 (30, 39). In line with that observation, deletion of PPAR-γ in CD4+ T cells improved asthmatic airway inflammation and, on the flipside, reduced Th2-mediated immunity to Heligmosomoides (H.) polygyrus infection. In these studies, Th2 cells showed reduced IL-5 and IL-13 production in the absence of PPAR-γ (31, 43).

Importantly, in Th2 cells PPAR-γ also controls genes involved in fatty acid uptake and lipolysis (e.g. Ldlr, Scrb2, Vdr, Plin2, and Fabp5). In addition, also pharmacological inhibition of glycolysis by 2-DG reduced Th2 cytokine production during asthmatic airway inflammation in vivo (30). A more detailed review of these mechanisms and the metabolic requirements of Th2 cells was recently published by Coquet and colleagues (29).

Taken together, early T cells undergo metabolic reprogramming and upregulate glycolysis to generate building blocks for proliferation. Following differentiation into the Th2 lineage, signals from inflamed tissues such as the lung during allergic asthma or parasite infection activate genes related to fatty acid uptake and lipid oxidation in Th2 cells.

Th2 Cell-Mediated Immunity to Tumors

Compared to studies on CTLs, evidence for the function of Th2 cells in the TME is relatively sparse. However, studies have shown that Th2 cells and type 2 immunity indeed take part in tumor immune surveillance by e.g. reducing the size of even established tumors (9, 48, 49; Table 2).

A major difference between recognition of tumor cells by CD4+ T cells and CD8+ CTLs cells is that the latter detect antigens presented by MHC I complexes. However, tumors have the ability to develop mechanisms to evade recognition by CTLs (85–87). These mechanisms include the downregulation of MHC I molecules and/or losing the immunogenic target antigen CTLs are directed against (88). On the other side, tumor antigens can also be presented by bystander antigen presenting cells (APCs) via MHC II complexes to CD4+ T cells in tumors.

Through the MHC II complex pathway, Th2 cells can initiate antitumor responses. The involvement of type 2 immunity in antitumor immune responses is reflected by studies showing that IFN-γ-deficient and, importantly, also mice deficient for the Th2 cytokines IL-4 and IL-5 show reduced tumor clearance (51). Furthermore, injection of IL-4 enhanced tumor clearance and correlated with increased infiltration of eosinophils, macrophages, neutrophils and in part lymphocytes. In addition, neutralizing IL-5 by monoclonal antibodies restored tumor growth (50, 57, 58, 62, 65). The latter studies demonstrated that Th2 cytokines are important in anti-tumor
immunity, although they do not provide direct evidence for an involvement of Th2 cells. With regard to this, it needs to be emphasized that Th2 cytokine production and type 2 immunity is not only mediated by Th2 cells but also to a significant part by type 2 innate lymphoid cells (ILC2s). ILC2s also secrete Th2 cytokines, depend on the Th2 transcription factor GATA3 but lack TCR expression (89–91). Currently, there is strong evidence that ILC2s contribute to anti-tumor immunity towards different types of tumors (92–94). However, ILC2s were also reported to be capable of exerting pro-tumor functions, revealing a more ambiguous role in immune responses against tumors than initially expected. The role of ILC2 in anti-tumor immunity was reviewed in-depth recently (95).

While the studies mentioned above report an involvement of type 2 immunity in anti-tumor immune responses, there are also further studies existing that show a direct influence of Th2 cells on tumor growth and progression: With regard to this, A20-Ovalbumin (OVA) expressing B cell lymphomas were cleared by the injection of either OVA-specific Th1 or, importantly, Th2 CD4+ T cells into tumor bearing host mice (61). Of note, another studied found that adoptively transferred OVA-specific CD4+ Th2 cells, but not Th1 cells, inhibit the growth of lung metastases produced by an OVA-transfected B16 melanoma (B16-OVA) (49). Importantly, the Th2-mediated antitumor response in the latter study was mediated through eosinophils and the expression of the eosinophil chemokine eotaxin. Confirmingly, eradication of tumors by adoptive transfer of tumor-specific Th2 cells was observed by another study (56). In addition, in a very recent study, Ming and colleagues showed that the transforming growth factor-β receptor 2 in CD4+ (but strikingly not CD8+) T cells is important in providing a host-directed protective Th2 response dependent on the Th2 cytokine IL-4 against tumors (96). The latter study provides strong and recent evidence that type 2 immunity mediates anti-tumor effects through tissue defense mechanisms.

Immunity to tumors by Th2 cells is to a significant part mediated by Th2 cytokines and through secondary recruitment of tumoricidal myeloid cells such as eosinophils, which often act in concert with macrophages (49, 67). Indeed, depletion of granulocytes completely abolished anti-tumor immunity (48, 62). Furthermore, IL-5-deficient mice showed impaired numbers of eosinophils in the tumor and a consequent loss of anti-tumor immunity (51). Conversely, IL-5 overexpressing mice develop fewer tumors and, if so, had high eosinophil numbers within the TME (66). In line with this observation, others reported an association of increased eosinophil numbers and an overall prolonged survival (52–54, 59, 60). Besides eosinophils and alternative activated M2 macrophages, also mast cells, B cells and type 2 CD8+ T cells contribute to Th2-mediated anti-tumor immunity, which was, however, reviewed elsewhere (48). In this
TABLE 2 | Studies on the role of Th2 cells on tumors.

Evidence of Th2 cell antitumor activity

| Study Type | Description |
|------------|-------------|
| 50 (Study) | Perilymphatic injection of IL-4 into CE-2 and TS/A tumors inhibits tumor growth and induces immune memory |
| 48 (Review) | Th2 cells can inhibit but also facilitate tumor growth, progression and metastasis |
| 51 (Study) | Th1 and Th2 cells are, unlike CD8+ T cells, independent of MHC I expression in tumor cells and play a significant role in initiating antitumor responses; Th2 cells exert antitumor effects via the recruitment of eosinophils |
| 52, 53 (Study) | Eosinophil infiltration in oesophageal squamous cell carcinoma is a predictor of a favourable clinical outcome in humans |
| 54 (Study) | Eosinophil infiltration predicts survival in patients with gastric cancer |
| 55 (Study) | Depletion of TGF-β receptor 2 disinhibits type 2 immunity to cancer in a breast cancer model by inducing tumor hypoxia and cell death through vasculature remodeling |
| 56 (Study) | Transfer of Th2 cells eradicates subcutaneous myeloma and B cell lymphoma and is dependent on arginase produced by M2 macrophages |
| 49 (Study) | Transfer of OVA-specific Th2 (but not Th1 cells) into tumor bearing mice cleared lung and visceral melanoma metastases via the recruitment of M2 macrophages |
| 57 (Study) | Injection of IL-4 into mice prohibited TS/A tumor growth via the recruitment of eosinophils, neutrophils and macrophages into the TME |
| 58 (Study) | TS/A tumors engineered to express IL-4 in mice were rejected via induction of necrotic areas by eosinophils and neutrophils |
| 59, 60 (Study) | Eosinophilic infiltration predicts a favourable prognosis in patients with colorectal cancer |
| 61 (Study) | Transfer of OVA-specific Th1 and Th2 cells in OVA expressing lymphomas is able to clear the tumors |
| 62 (Study) | TS/A in mice engineered to express IL-4 were rejected in an eosinophil and CD8+ dependent way |
| 63 (Review) | Eosinophils are important in regulating immune responses in the TME and can exert anti-tumor effects in colorectal cancer |
| 64 (Study) | Th2 cells can exert antitumor effects by recruiting eosinophils |
| 65 (Study) | IL-4 exerts anti-tumor effects via the recruitment of eosinophils |
| 66 (Study) | Enhanced IL-5 expression in mice protected from MCA-induced fibrosarcoma via the recruitment of eosinophils |
| 67 (Study) | A type 2 immune microenvironment induced by a biologic urinary bladder matrix scaffold inhibits melanoma tumor function |

Evidence of Th2 cell pro tumor activity

| Study Type | Description |
|------------|-------------|
| 68 (Study) | Breast cancer cells indirectly stimulate their own growth by instructing CD4+ T cells to secrete the Th2 cytokine IL-13 |
| 69 (Study) | IL-4 induces EMT in colon cancer cells via STAT6 dependent transcription of EMT promoting proteins |
| 70 (Study) | IL-4 promotes the expression of antiapoptotic genes in various human cancers in vitro |
| 71, 72 (Study) | Successful therapy of lung tumors and melanoma in mice was associated with a shift towards a Th1-Response |
| 73 (Study) | Survival of patients with pancreatic cancer is negatively associated with Th2 cell infiltration |
| 74 (Study) | IL-4 expressing CD4+ T cells enhance metastasis by instructing macrophages to activate epidermal growth factor signalling in breast cancer cells |
| 75 (Study) | IL-5 in the tumor intestinal fluid is associated with a poor prognosis |
| 76 (Study) | High risk HPV infections cause a type 2 inflammation and create an immunosuppressive environment |
| 77 (Study) | IL-13 deficient mice showed a slower progression of prostate cancer |
| 78 (Study) | IL-4 stimulates proliferation in human pancreatic cancer cells via MAPK, Akt-1, STAT3 and insulin receptor phosphorylation |
| 79 (Review) | IL-4 and IL-13 receptors are possible targets for cancer therapy |
| 80 (Review) | IL-13 negatively regulates antitumor immune surveillance |
| 81 (Study) | Expression of the IL-4 receptor subunit α enhances malignancy of human pancreatic cancers in vitro and in vivo |
| 82 (Study) | Th2 cell infiltration in human breast cancer is associated with unfavourable genetic properties of the tumour |
| 83 (Study) | IL-5 facilitates lung metastasis from melanoma, lung and colon cancers via recruitment of eosinophils to the lung |
| 84 (Study) | CCL5 recruits Th2 cells and mediates metastasis in breast cancer |

context, it needs to be emphasized that especially mast cells are also strong producers of Th2 cytokines and can exert pro- and anti-tumor effects (97). So far, however, strongest evidence comes from studies demonstrating anti-tumor activity of eosinophils (63, 64).

Of note, there is also evidence suggesting that Th2 immunity promotes cancer genesis, progression and metastasis. One study for instance found that remission of transplanted lung tumors into mice was accompanied by a shift from Th2 towards Th1 cells. In this study, the authors found that a predominant Th2 response in the TME is associated with an unfavorable outcome (71). One report showed a Th1 skewing to be associated with successful immune modulatory therapy of cancer (72). Others demonstrated an association of Th2 cells in the TME with the progression of breast cancer and cervical neoplasia (75, 76, 82). In addition, in breast cancer, colorectal cancer and lung cancer, type 2 immunity has been shown to enhance metastasis (69, 74, 83, 84). As possible mechanisms for the above listed observations, direct effects of IL-4 on cancer cells, an increase in tumor-associated macrophages and IL-5-dependent eosinophil recruitment at the site of metastasis were discussed. In general, many studies suggest a direct effect of Th2 cytokines on cancer cells and tumor progression, while others lack mechanistic explanations. Of note, direct evidence for pro-tumor effects of Th2 cells, particularly, does not exist (68, 70, 77, 78, 80, 81).

Taken together, Th2 cells were shown to mediate pro- and anti-tumor effects. While, traditionally, type 2 immunity was implicated in an inhibition of anti-tumor responses, a number of studies provide convincing evidence demonstrating that Th2 cells indeed mediate anti-tumor immunity. Of note, these studies do not only provide correlativo analyses, but apply adoptive Th2 cell transfer experiments (49, 56, 61) or perform pharmacological administration of Th2 cytokines to tumor.
The Tumor Microenvironment (TME)

Tumor cells are recognized and eliminated by innate and adaptive immune cells. Thus, the immune system in principle has an impressive ability to keep neoplastic cells in check before tumor cells enter uncontrolled expansion (1, 2). The fact that the immune system can attack tumors is the basis for antitumor immunotherapy such as immune checkpoint blockade or adoptive cell transfer of engineered T cells (100, 101). However, tumors possess several mechanisms to evade tumor immune surveillance (102), which is why some patients do not respond to immunotherapy. To a significant part, these evasion mechanisms involve the metabolic modulation of the TME (11, 103, 104). The metabolic TME is mainly characterized by a high cancer cell metabolism and a consecutive starvation of immune cells including effector T cells.

Tumors enable their rapid growth rate through glycolysis, which generates metabolic intermediates for the synthesis of amino acids, nucleotides, and fatty acids (105). Through glycolysis, tumor cells consume high levels of glucose from their surrounding environment and produce high amounts of lactate (106, 107). Both, reduced glucose and high lactate concentrations within the TME, results in immnosuppression (108, 109). Differentiation of naïve T cells into effector T cells crucially depends on metabolic reprogramming, which is facilitated by glucose uptake through GLUT1 and aerobic glycolysis (19, 21–23). Glucose deprivation in the TME thus cumulates in effector T cell hyporesponsiveness. Mechanistically, low glucose levels in the TME reduce AKT activity and induce apoptosis in CTLs through the activation of proapoptotic B-cell lymphoma-2 (Bcl-2) family members (110, 111). The latter mechanism likely also applies to various CD4+ T cell populations in the TME, although direct evidence is missing so far. Reduced glucose levels also decrease the levels of the intermediate phosphoenolpyruvate in T cells, which impairs calcium flux and nuclear factor of activated T cells (NFAT) signaling (112). In addition, high lactate in the TME further impairs NFAT activation and its translocation to the nucleus (113). As calcium-mediated NFAT signals control metabolic reprogramming of T cells by regulating gene expression of several glycolytic enzymes (114), T cells in the TME show impaired activation, proliferation and effector function against neoplastic cells. Importantly, acidification of the TME through high lactate concentrations impairs effector T cell function stronger than the function of Tregs. This likely occurs as Tregs also use fatty acid oxidation and might even use lactate as fuel (115–117). In view of the fact that also tissue Th2 cells seem to use lipid metabolism preferentially, it is tempting to speculate that also Th2 cells could be more resistant to high lactate concentrations and a low pH within the TME.

In addition to low glucose concentrations within tumors, the TME is also depleted of specific amino acids including glutamine, alanine, tryptophan, arginine, cysteine and ornithine, some of which were shown to be important for T cell proliferation and effector function (118–120). Importantly, upon T cell activation several genes e.g. those encoding for amino acid transporters are upregulated (121), which indicates a high demand for the exchange of amino acids for clonal expansion of T cells following antigen encounter.

While many studies have focused on glucose and amino acid metabolism, less studies report on lipid metabolism in the TME. Generally, lipids play a significant role in cancer progression (122, 123). Cancer cells are capable of inducing lipolysis in adjacent adipocytes and fatty acid synthesis in cancer associated fibroblasts. This has been demonstrated for melanoma (124, 125), breast cancer (126, 127), ovarian cancer (128), prostate cancer (129) and pancreatic cancer (130).

Another characteristic of especially necrotic tumors is that the TME consist of a specific ion composition that is characterized by high potassium levels due to necrotic cell lysis (131). Increased potassium concentrations in the extracellular fluid of mouse and human tumors suppress CD8+ CTL function, while overexpression of the voltage-gated potassium channel K+1.3 (that transports potassium outside the cell) improved CTL effector function and survival of melanoma bearing mice (131). Importantly, preventing calcium influx through genetic deletion of components of the calcium release-activated calcium channel (CRAC) pathway impairs CD8+ CTL effector function and antitumor immunity in mouse models for melanoma and colon carcinoma (132). In addition to calcium also sodium was shown to regulate T cell function, more precisely, the effector function of Th17 cells (133–136). However, the role of sodium on effector T cell function within the TME is elusive. The above studies (131, 132) show that ions have significant impact on effector T cell function against tumors. However, despite these studies the impact of ions on adaptive and innate immune cells in the TME but also in other tissues is still largely neglected and not well understood.

Hypoxia is another prominent feature of the TME (137). The high metabolic rate of tumor cells in combination with an insufficient vascularization especially of large solid tumors leads to a TME that is characterized by reduced oxygen levels. Hypoxia within the TME was on the one hand reported to increase CTL-mediated tumor cell killing through increasing the packaging of granzyme B. This was associated with prolonged survival in the B16-OVA melanoma mouse model (138). In contrast, others have shown that T cells in fact avoid areas of hypoxia and have reported an immunosuppressive function of hypoxia on effector T cells in the TME (109, 139, 140). In that context, the oxygen-sensing prolyl-hydroxylase (PHD) was reported to limit Th1 and CTL function, while PHD promoted Treg differentiation following tumor colonization in the lung (141). HIF-1α, an important transcription factor in sensing oxygen levels, was shown to positively control PD-L1.
expression in myeloid derived suppressor cells (MDSCs). This induced T cell exhaustion but promoted generation of Tregs (142, 143). Of note, deletion of HIF-1α increased fatty acid catabolism (oxidation) and improves PPAR-α signaling in CD8+ CTLs (144). As HIF-1α negatively regulates fatty acid oxidation and tissue Th2 cells predominantly use lipid metabolism, this could have important mechanistic implications how hypoxic TME regulate Th2 cell metabolism and function.

In addition to the above discussed evasion mechanisms, neoplastic cells also produce several metabolic intermediates, which affect the functions of various immune cells including T cells within the TME. In malignant cells Indoleamine 2,3-dioxygenase (IDO) is upregulated (145). IDO degrades tryptophan to kynurenine, which inhibits effector T cells and promotes Treg differentiation within tumors (104). Importantly, mass spectroscopy of tumor fluid from tumor bearing mice has already in part allowed characterizing metabolite composition within the TME of a handful of tumors (107).

**DISCUSSION**

**Interactions of Th2 Cell Metabolism, TME, and Potential Therapeutic Strategies**

Current evidence indicates that Th2 cell-mediated type 2 immune responses can contribute to anti-tumor immunity, although for some tumors Th2 cells and/or cytokines have also been shown to promote tumor growth and metastasis.

One way how tumors can influence Th2 cell-mediated immunity to neoplastic cells is by consuming nutrients and thereby starving Th2 effectors. This mechanism was meanwhile indicated for several immune cells within the TME including macrophages, CD8+ T cells, dendritic cells (DCs), and natural killer cells but not yet for Th2 cells (130, 146–149). Tumors consume high levels of glucose to perform glycolysis. Glucose is on the other hand essential for metabolic reprogramming of naïve T cells when becoming effector T cells (19–23). While tissue Th2 cells in the allergic lung were dependent on lipid metabolism, also pharmacological inhibition of glycolysis by the glucose analogue 2-DG attenuated asthmatic airway inflammation by interfering with Th2 cytokine production (30). This indicates that also in the TME Th2 cells likely could be affected by low glucose levels (Figure 1). However, direct evidence whether and how reduced glucose concentrations within the TME affect Th2 cells is so far elusive.

In recent literature, a Th2 cell-specific utilization of lipid metabolism pathways has been described (29–31, 150). In this context, tissue Th2 cell activation was shown to involve PPAR-γ activation (31, 43). PPAR-γ, in turn, controlled Th2 cell gene expression and the expression of genes associated with lipid metabolism (29, 30, 39). Of note, Coquet and colleagues reported reduced T cell numbers in the bronchoalveolar lavage following house dust mite-induced asthmatic airway inflammation after in vivo administration of orlistat or etomoxir, which block fatty acid synthesis and uptake or fatty acid oxidation, respectively (30). It is of note, that these drugs also inhibited ILC2s, which resulted in elevated helminth burden after infection with *Trichuris muris* (151). This dependency on lipid metabolism could mean a significant advantage for Th2 cells (and ILC2) in the TME for at least two reasons: First, availability of lipids within the TME might be even higher than in healthy tissues. In addition, as Th2
cells are capable of utilizing lipids in the TME, this could maintain their function even when being exposed to low glucose environments (Figure 1).

Given this evidence, therapy regimens that involve the modulation of the Th2 cell metabolism are thinkable. One potential molecular target could be indeed the transcription factor PPAR-γ, as it facilitates lipid metabolism of Th2 cells. Thiazolidinediones (TZDs), a group of diabetes drugs that activate PPAR-γ, have already been shown to be associated with a lower risk for cancer (152, 153). While this might be mediated by the antidiabetic effects of TZDs, there is also evidence for TZDs directly inhibiting growth of established tumors. Moreover, TZDs are in fact discussed for cancer mediated by the antidiabetic effects of TZDs, there is also plausible to target the metabolism of tumor cells could lead to a net pro-tumor effect of TZDs.

Discussed in recent years (109, 157, 158). First, disturbing dependent (156). If this mechanism also applies to the TME, this metabolite is shown to be important mainly for Th17, but not for Th1 and Th2 differentiation (35, 38). Others, however, reported mTORC1 to be important for Th2- and mTORC2 for Th1 differentiation (40, 47). While mTORC1 has been shown to respond to various metabolic conditions like low energy supply and hypoxia (37, 41), mTORC2 has been shown to be regulated by metabolic cues such as glucose availability (41, 42). Moreover, mTORC2 is discussed to act as a sensor for Acetyl-CoA and NAD⁺ levels and therefore to detect the overall energy status of cells (36).

In principle, Th2 cells may be used for advanced adoptive cell transfer therapies. So far, CAR T cell therapies have been (often) unsuccessful for treatment of solid tumors as the latter possess several mechanisms to escape immune responses (166, 167). In addition, there are only a few studies so far investigating Th2 cell adoptive cell transfer to treat tumors in mice (49, 56, 61).

For tumor cells a high IDO expression was reported (145). Importantly, IDO is also expressed by innate immune cells such as DCs that take part in anti-tumor immunity (168). CD4⁺ T cells co-cultured with IDO-deficient lung DCs produced less Th2 cytokines. High IDO activity in tumors and DCs could thus secondarily amplify Th2 cell responses against tumors. However, this assumption is complicated by the fact that there also exists evidence that kynurenine metabolites can negatively regulate T cell function by inducing apoptosis (169). In addition, studies have shown that genetic or pharmacological deletion of IDO restores anti-tumor immunity (170). This is the case as IDO is involved in the generation of Tregs and other effector cells within the TME (105, 171). In line with this observation studies reported that kynurenine induces the transcription factor aryl hydrocarbon receptor (AHR) that is important for differentiation of naïve T cells into Tregs (172, 173).

As IDO inhibitors are currently in clinical trials for different cancer types including bladder cancer, endometrial cancer or head and neck squamous cell carcinoma (174) it would be of great interest to characterize the immune cell repertoire in the TME upon IDO inhibition.

Another tissue factor that influences T cell function in the TME is the ion composition and concentration. As calcium signaling plays a role in metabolic reprogramming of T cells, an effect of ions in the TME on T cell metabolism seems plausible. However, while there is clear and strong evidence that calcium and potassium regulates the function of CTLs (132, 175, 176), there is a gap in our understanding how ions influence the function of Th2 cells in tumors.

**CONCLUSIONS**

To develop tailor-made cancer therapies that target specific immune cell populations such as Th2 cells by modulating their metabolism, a detailed understanding of the TME of various tumor subtypes is needed, and still some challenges have to be
overcome. One important question is whether Th2 cells, based on their metabolic profile, are able to function in the glucose and amino acid and oxygen depleted TME.

Despite great advances in the field, a lot of evidence for the metabolic regulation of various Th cells still is based on experiments using in vitro culture systems and artificial media. To overcome this, some strategies were recently discussed by Jones and colleagues (108). First, the design of physiologic media resembling the specific metabolite (and at best also ion-) composition of different compartments can help in elucidating the relationship of immune cells and their surrounding environment. Second, tumor spheroids and organoid models and the detailed characterization of the TME in vivo will help to understand the complex relationship and metabolic interdependency between tumors and immune cells better.

Furthermore, a detailed understanding of the TME of various tumor subtypes is needed to identify tumors with a Th2 advantageous TME. The decision whether Th2 cells and type 2 immunity provides pro- or anti-tumor immune responses is strongly dependent on the type and stage of the individual tumor. Considering the utilization of lipid metabolism pathways by Th2 cells and the capability of tumors to induce lipolysis, especially tumors with adjacent adipose tissue could be of significant advantage. Especially melanoma might be promising for two reasons: First, melanoma are close to a source of lipids, namely the subcutaneous adipose tissue and have been shown to induce lipolysis in adjacent adipocytes (124, 125). Second, adoptive cell therapy by using Th2 cells has already been shown to be effective in melanoma animal models (49).

In conclusion, the special metabolic characteristics of Th2 cells might prove advantageous when therapeutically modulating the TME to treat cancer. Especially Th2 cell utilization of lipids might be useful. In future, a precise characterization of the TME in different tumors, a specification of the role of lipid metabolism in tissue Th2 cells and a more direct observation of Th2 cells in the TME in vivo or during experiments with artificial environments and a defined nutrient composition in vitro are needed. Of note, in tumors where Th2 cells exert pro-tumor effects, an inhibition of metabolic pathways used by Th2 cells is thinkable, vice versa.

**AUTHOR CONTRIBUTIONS**

SS and SK drafted the manuscript. All authors contributed to the article and approved the submitted version.

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