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Hypoxia-inducible factor 1
A link between metabolism and T cell differentiation and a potential therapeutic target

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Naïve T cells activated by antigen-presenting cells (APC) can be differentiated into at least four major types of T-helper (T_H) cells: T_H1, T_H2, T_H17 and inducible regulatory T cells (iTreg) based on their unique cytokine production profiles and characteristic functions.[1] T_H1 produce interferon-γ (IFNγ) and are important for protective immune responses to intracellular viral, bacterial and parasitic infection. T_H2 cells produce interleukin-4 (IL-4), IL-5, IL-23 and are critical for controlling extracellular parasites such as helminthes. T_H17 cells are responsible for expelling extracellular bacteria and fungi through secretion of IL-17a, IL-17f and IL-22.[2] These cells however are perhaps better known for their propensity to drive autoimmune responses. Tregs including naturally occurring regulatory T cells (nTreg) play important roles in the suppressive control of both innate and adaptive immunity in vivo.[3,4]

Introduction

In this review, we discuss a number of recent studies suggesting crucial roles for metabolic sensor molecules in the regulation of the balance between these opposing, yet developmentally linked T-cell subpopulations. Understanding the factors impacting the generation of these cells is of considerable importance. An imbalance between T_H17 and Treg cell function may result in some inflammation mediated diseases (such as IBD), autoimmune diseases and cancer.

The Mammalian Target of Rapamycin (mTOR)/Hypoxia-Inducible Factor 1 (HIF-1) Axis, as an Environmental Sensor, Plays an Important Role in T-Cell Fate Determination

Rapamycin was originally identified as an antifungal compound derived from *Streptomyces hygroscopicus*, found in soil samples collected from Easter Island. A potent immunosuppressive drug with a target, which was identified a decade ago as FKBP-rapamycin-associated protein (FRAP, mTOR), a serine-threonine protein kinase. mTOR integrates environmental cues as a means of regulating cellular size, growth, proliferation, survival and metabolism. Its activity can be regulated by diverse stimuli such as amino acid availability, oxygen tension, energy status and growth factors.[5] The role of mTOR in cancer and T cell biology has been comprehensively reviewed recently.[6] Work from Powell and colleagues found that mTOR plays a significant role in the generation of effector T cells. They discovered that in the absence of mTOR, naïve $CD4^+$ T cells differentiate preferentially into $Foxp3^+$ Tregs. Mechanistically, the inability to become effector cells in mTOR null T-cell mice was associated with a failure to upregulate appropriate T helper subset-specific transcription factors (such as Tbet for T_H1 cells). These mice also displayed decreased STAT activation in response to various skewing cytokines. Along these lines, it has been shown that STAT3-deficient T cell are incapable of becoming T_H17 cells. In this way, mTOR, a central regulator of cellular metabolism and protein translation, integrates various extracellular and intracellular signals to promote effector but not regulatory T-cell differentiation.[7]

Recently, another study identified mTOR, and particularly elements downstream in its signaling as being crucial to T effector cell differentiation.[8] However, they found this signaling axis to be indispensible for one particular lineage. Combining pharmacological and genetic approaches, Shi et al. demonstrated elegantly that the basic metabolic machinery in different subsets of T cells is actively regulated and involved in T-cell fate determination. These authors report that T_H17 and Treg cells have marked differences in their glycolytic activity and expression of glycolytic enzymes. They also found that glycolysis serves as a key metabolic checkpoint to direct the cell fate determination between these lineages. Specifically, the glucose analog 2-deoxyglucose (2-DG), a prototypical inhibitor of the glycolytic pathway, dampened the development of naïve precursors into T_H17 cells while promoting Treg cell generation. Additionally, deficiency in the transcription factor hypoxia-inducible factor 1α (HIF1α)—which is downstream of mTOR signaling—in T cells diminished expression of the glycolytic molecules and skewed the dichotomy between the T_H17 and Treg lineages in agreement with studies from our own group that will be discussed below. These findings demonstrate that HIF1α-induced metabolic reprogramming orchestrates lineage differentiation of T cells. In the following sections we will discuss more studies concerning

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this metabolically important regulator that expand upon its role in T-cell differentiation and disease.

Hypoxia Inducible Factor (HIF)-1, a Major Oxygen Sensor and Metabolic Regulatory Transcription Factor, is Involved in the Regulation of the Balance between Treg and T_H17 Cell Differentiation

HIF-1 is a heterodimeric transcription factor consisting of a highly regulated oxygen sensitive HIF-1α subunit and a constitutively present β subunit (termed HIF-1β or ARNT, which interestingly is also the non-ligand binding subunit of the AHR). HIF-1α was originally discovered by Semenza and colleagues as a hypoxia responsive factor activating erythropoietin transcription. Since its discovery, the expanded role of HIF-1 as a central regulator of metabolic programs has been delineated. As a sequence-specific DNA-binding transcription factor for 100–200 genes that regulate adaptation to hypoxia, HIF-1 has attracted considerable attention in fields ranging from ischemia to cancer.[9] As part of its role in the hypoxia response, HIF-1 also regulates multiple metabolic genes including those involved in glucose transport and glycolysis.

Sensing of oxygen tension occurs at the level of HIF-1α protein stability. Under normoxic conditions HIF-1α degradation is initiated through hydroxylation by the Phd family of 2-oxoglutarate- and iron-dependent dioxygenases. Further metabolic regulation of Phd activity comes from the capacity of various species such as ROS and succinate to compete with 2-oxoglutarate for Phd binding. Elevated reactive oxygen species (ROS) can also affect HIF-1 levels via inactivation of Phds through oxidation of the ferrous ion at the active site. Hydroxylation of HIF-1α at a specific proline (402 in murine HIF-1α) by Phd recruits the Von Hippel Lindau (VHL) and an E3 Ub ligase (along with the associated catalytic complex containing elongin B/C, RBX1 and cullin2) and ubiquitinated HIF-1α is degraded by the proteosome. Oxygen is not the only regulator of HIF-1 levels. It is transcriptionally activated by a number of signaling pathways important in immune responses, notably those of NFκB and STAT3. Not surprisingly, the HIF-1 pathway interacts with other pathways that regulate metabolism such as mTOR signaling. For example, mTOR regulates translation of HIF-1α mRNA whereas certain HIF-1 activated genes, such as BNIP3 and REDD1, encode proteins that feedback inhibits mTOR activity (**Fig. 1**).

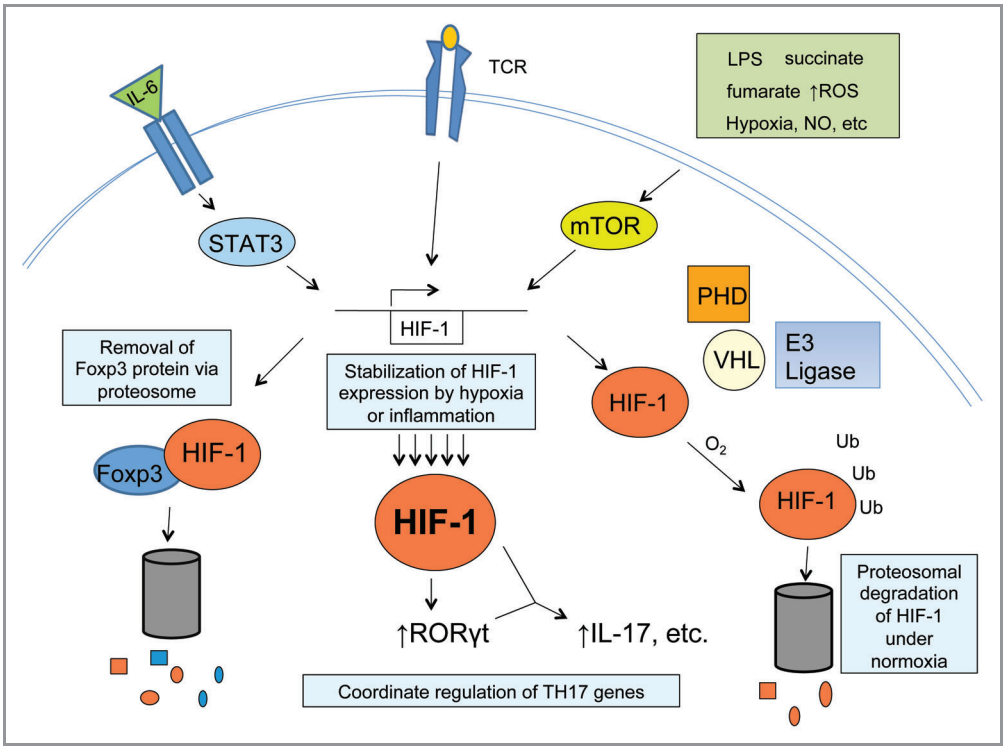

Figure 1. HIF-1's regulation and its role in driving the T_H17 genetic program. In $CD4^+$ T cells, under normoxic conditions, HIF-1 is generated and promptly marked for proteasomal degradation. This is accomplished by proline hydroxylation at a specific proline residue by the PHD dioxygenases—an event that recruits the Von Hippel Lindau (VHL) and an E3 ligase that polyubiquitinates the HIF-1 molecule. Under hypoxia, the degradation machinery is inactive and HIF-1 protein accumulates. Under normoxia, however, HIF-1 expression can also be dramatically upregulated by a number of stimuli including TCR signaling and proinflammatory cytokines (such as IL-6 which activates the STAT3 signaling cascade). This expanded pool of HIF-1 protein activates expression of the T_H17-associated transcription factor, RORγt which in turn complexes with HIF-1 and other factors to spur on transcription at the IL-17 gene as well as other T_H17 loci. Additionally, HIF-1 binds to Foxp3 and mediates its co-degradation via the proteasome favoring the generation of IL-17 producing T cells over that of iTreg.

How HIF-1 and hypoxia impact the immune system is no trivial matter as oxygen levels at sites of infection, inflammation or injury can approach or reach hypoxic levels.[10] Tumors are notorious for their hypoxic or even anoxic regions. Given the likelihood of immune cells encountering low oxygen levels as they execute their various functions in the periphery, how hypoxia and elements of the hypoxic response (such as HIF-1) impact immune cell function is a highly relevant topic. As interest in understanding the complex metabolic regulation of immune responses grows, study of the role of hypoxia-sensing and the HIF-1 pathway in the innate immune response has intensified.[11] The role of HIF-1 in adaptive immunity, however has only recently begun to be elucidated. Recently, we and others reported that HIF-1 during oxygen scarcity in fact regulates the T_H17/Treg balance in a multifaceted manner.[8,12] Specifically, we have discovered that HIF-1 promotes T_H17 differentiation by directly inducing RORγt transcription and subsequently collaborating with RORγt to regulate downstream T_H17 genes. In addition, HIF-1 inhibits Treg differentiation through an active process that targets Foxp3 protein for degradation. Our study sheds light on how the balance between these highly plastic differentiation programs can be subject to metabolic regulation and suggests new strategies to manipulate these cell lineage decisions in order to treat diseases associated with a T_H17/Treg imbalance. As previously mentioned, Shi et al. have found that HIF-1 is necessary for optimal T_H17 differention in vitro and in vivo. Interestingly, this study, also done in the murine system attributed HIF-1's role in T_H17 generation to be that of an inducer of glycolytic genes needed for T_H17 lineage commitment suggesting another possible mechanism for HIF-1 in the process besides or in addition to its direct role in regulating T_H17-associated loci. An additional dimension of HIF-1's involvement in T_H17 biology was recently suggested by Kryczek et al. Using a HIF-1 inhibitor and shRNA mediated knockdown, they found that HIF-1 was necessary for preventing apoptosis of human T_H17 cells by inducing several survival promoting genes. The results of this study suggest that HIF-1 may allow for the persistence of T_H17 cells[13]

HIF-1 as a Therapeutic Target in Inflammation Diseases, Autoimmune Diseases and Cancer

The role of HIF-1 as a positive regulator of the T_H17 response has been established by the work of several groups including our own.[8,12,13] Studies using cell lineage specific HIF-1 deficient mice or T cells from these animals have been central to these discoveries. Genetic ablation of HIF-1 function, however does not speak to the suitability of HIF-1 modulation as a therapy to counter undesirable T_H17 responses. Work concerning HIF-1's role in cancer biology, however does suggest that the downstream effects of HIF-1 signaling can be modulated with inhibitor compounds.

HIF-1 is known to play a major role regulating several aspects of cancer cell biology. HIF-1 targets include genes crucial for cell immortalization, vascularization and glyolytic metabolism. Since hypoxia is a common element of the tumor microenvironment, and pronounced HIF-1 expression during cancer has been linked to poorer prognoses and patient survival, it is not surprising that efforts to identify inhibitors of HIF-1 function have been taken up in earnest by cancer biologists. Indeed, a number of inhibitors with diverse mechanisms of action have been identified and tested in vitro and in vivo for their effectiveness at counteracting HIF-1 mediated tumor processes.[14] Among the compounds shown to have potent HIF-1 antagonizing properties is a drug known as, digoxin. This cardiac glycoside was identified by the Semenza group to be a potent inhibitor of HIF-1 function.[15] Recently, the Littman group found that this compound and its derivatives were also potent antagonists of T_H17 responses.[16] Specifically, treatment of mice with digoxin inhibited the generation of a T_H17 response in mice subjected to EAE. As a result, these mice were protected from the immune mediated neuropathology seen in this model of human MS. While the authors attribute the action of digoxin to inhibition of RORγt, a key regulator of T_H17 development, it is reasonable to suspect that the drug may have impacted HIF-1 levels, as has been previously reported. It is also noteworthy that the Treg/T_H17 imbalance seen in digoxin treated cells mirrors that seen upon genetic ablation of HIF-1.[12] Other characterized HIF-1 inhibitors include a range of agents with distinct modes of action.[14] Unpublished findings from our group corroborate those of the aforementioned drug study and suggest that using other HIF-1 inhibitors can also suppress in vivo T_H17 mediated pathology as well (FP and DP unpublished results). These findings strongly suggest that such molecules, due to their ability to dramatically reduce the severity of T_H17 responses, are a pool of drugs with a great deal of potential as treatments for inappropriate or excessive T-cell responses of this kind.

While the effectiveness of HIF-1 inhibition as a therapy for autoimmune diseases has been demonstrated (at least in animal models), it remains to be determined which consequence of HIF-1 functional ablation is chiefly responsible for this protection from autoimmune disease; the reduced T_H17 response or the enhanced presence of Treg cells. The findings of Korn et al. that antigen specific Tregs accumulating in the CNS are insufficient to control EAE suggest that reducing the development of a robust T_H17 response in the first place may be more beneficial in EAE.[17] Indeed, further study may shed light on this question. The treatment of other autoimmune diseases having a strong IL-17 component may benefit from including HIF-1 inhibition in the treatment arsenal. It is reasonable to expect that inflammatory bowel disease (IBD) may also be ameliorated upon HIF-1 inhibition since the balance between T_H17 and Tregs has been shown to impact disease severity. Of course, future work is will be needed to validate this notion. While it seems likely that HIF-1 inhibition is well suited as an anti-autoimmune intervention, the setting of cancer, however, presents a more complicated scenario in regards to the suitability of HIF-1 targeting as a treatment method.

In the marshalling of an effective anti-tumor response, the proinflammatory, T_H1-associated cytokines IFNγ and IL-12 play an undeniable role in promoting the killing of cancer cells. $CD8^+$ cytotoxic T lymphocytes also are important for the destruction of tumor cells. On the other hand, the action of Tregs in the anti-tumor response has been shown repeatedly to be negatively

associated with the effectiveness of the response and overall disease outcome.[18] Tregs are known to accumulate in tumor tissues and depleting them or inhibiting their suppressive function increases the effectiveness of certain cancer vaccines. For this reason, the sabotaging of Tregs has become an aim of many developing immunotherapy approaches.

The impact of T_H17 cells in the tumor setting is less cut-and-dry. While they have been observed to accumulate in many cancer patients often along side Tregs, their contributions to either tumor progression or tumor eradication is the subject of some debate. T_H17 cells have been reported by some to be efficient participants in the anti-tumor response.[19] Furthermore, in a recent study, adoptive transfer T_H17 cells slowed the growth of established ovarian tumors in immunodeficient mice. Co-transfer of these cells with tumor antigen specific $CD8^+$ T cells had an even greater effect on tumor growth.[13] Not only does this study suggest that, at least after tumor initiation, T_H17 cells have anti-tumor capacities, it also raises the possibility that cooperation with other effector T cells may be key for this function. On the other hand, mounting numbers of studies suggest that IL-17 and the cells producing it promote tumor growth and progression. In particular, T_H17 and IL-17 producing T cells have been linked to poorer prognoses in cancer patients or numerous types.[20] IL-17 more clearly contributes to the progression of inflammation associated tumors. In colorectal cancer, IL-17 producing $Foxp3^+$ are thought to be important instigators of disease—suggesting that Treg cells may play a more active role in tumor progression, beyond dampening a desirable anti-tumor response. Moreover it was found that exposure to hypoxia could bring about IL-17 expression by Treg cells showing that this condition, which almost certainly involves upregulation of HIF-1, can also drive Treg cells, under the right conditions, to become active participants in an IL-17 driven response. Another strong link between T_H17 cells and tumor progression was seen in a model of colon cancer induced by a wide spread human commensal organism. Experimental colonization of mice predisposed to intestinal tumors with an enterotoxigenic strain of *Bacteriodes fragilis* results in the aggressive development of large bowel tumors.[21] In these studies, deletion of STAT3 in the $CD4^+$ compartment or anti-IL-17 antibody treatment greatly reduced cancer severity providing another example of IL-17's tumor promoting capacity.

The underlying mechanisms by which IL-17 and the cells that produce it influence tumor formation and progression remain to be completely defined. However, recently, several studies have linked T_H17 cells or the cytokines they are known to produce to the promotion of angiogenesis- a process both characteristic and necessary for tumor development. In gastric cancers, vascularization of tumors is positively correlated with the levels of IL-17 and T_H17 associated cytokine mRNA in the tumor tissue.[22] IL-17 producing cells which are enriched in colorectal cancer (CRC) tumor tissues are associated with poor prognosis at least in part due to the induction of the infamous pro-angiogenic factor, VEGF in the cancer cells. Indeed, HIF-1 within the cancer cell itself has been clearly shown to be important for regulating genes important for angiogenesis.[9] All the same, the possibility that IL-17 producing T cells influence their intra-tumor neighbors should be considered. Interestingly, Hot and Miossec have reported that the T_H17-associated cytokines can induce the expression of genes linked to the hypoxic response[23] suggesting that T_H17 responses may be subject to positive feed back loop regulation. Therefore, one wonders if tumor infiltrating $IL\text{-}17^+$ T cells might perpetuate a pro-angiogenic chain reaction through interaction with other cells of the tumor microenvironment. In addition to an apparent pro-angiogenic role of T_H17 associated cytokines, some reports suggest that they play a role in cancer spread as well. Recently, Li et al. reported that IL-17A can promote hepatocellular carcinoma metastasis through the regulation of metalloprotease expression.[24] In addition to promoting cytokines with tumor promoting capacities, HIF-1's regulation of glycolysis-associated genes in cancer cells is considered a major contribution to the progression of tumors. Specifically, HIF is important for the establishment of the Warburg effect. In this metabolic shift from aerobic respiration, the machinery of glycolysis is upregulated in cancer cells, giving them a metabolic advantage for surviving and thriving in the oxygen poor microenvironment of the tumor. It is likely that HIF-1 inhibitors will rob the tumor cells of needed vascularization, a chance to spread and the metabolic edge imparted by their glycolytic lifestyle.

In all it stands to reason that targeting HIF-1 in the tumor microenvironment should prove an effective, multiple pronged anti-cancer treatment strategy for a variety of cancers. Since as mentioned above, certain effects of the T_H17 response may promote tumor development, growth and spread in some cancer models and given HIF-1's importance in the cancer cell itself, well characterized HIF-1 inhibitors make tempting potential therapeutic tools. Indeed pharmacological inhibition of HIF-1 in tumor models has yielded promising, yet preliminary findings. Specifically, Semenza and colleagues report that treatment of mice with subcuteanous tumors with digoxin or acriflavine (inhibitors of HIF-1 expression and function, respectively) limits tumor growth.[15] In these and other studies, a major effect of general HIF-1 inhibition was a reduction in neovascularization (process of angiogenesis) and the switch to glycolytic metabolism. Neither of these studies addressed how these inhibitors were impacting the T cell response to the tumor and it remains to be seen how much of the tumor growth suppressing effect of these compounds is actually attributable to the presumed inhibition of the T_H17 response.

While chemical targeting HIF-1 appears to be a highly viable anti-cancer strategy with multiple potential benefits, studies using mice with HIF-1 deficient T cells sound a note of caution when considering HIF-1 inhibition as monotherapy cancer treatment. While HIF-1 inhibitors can interfere with the tumor-promoting processes of angiogenesis and the favoring of glycolytic metabolism, they may, as suggested by the previous work of our group and others, also elevate the frequency of immune suppressive Treg cells. These cells are known to stymie anti-tumor immune response by promoting immune tolerance—a state permissive to cancer persistence and progression. Nevertheless, it is still likely that HIF-1 inhibition may yet prove particularly advantageous in the treatment of cancer. It may be prudent or necessary to evaluate the efficacy of HIF-1 inhibition as a cancer therapy

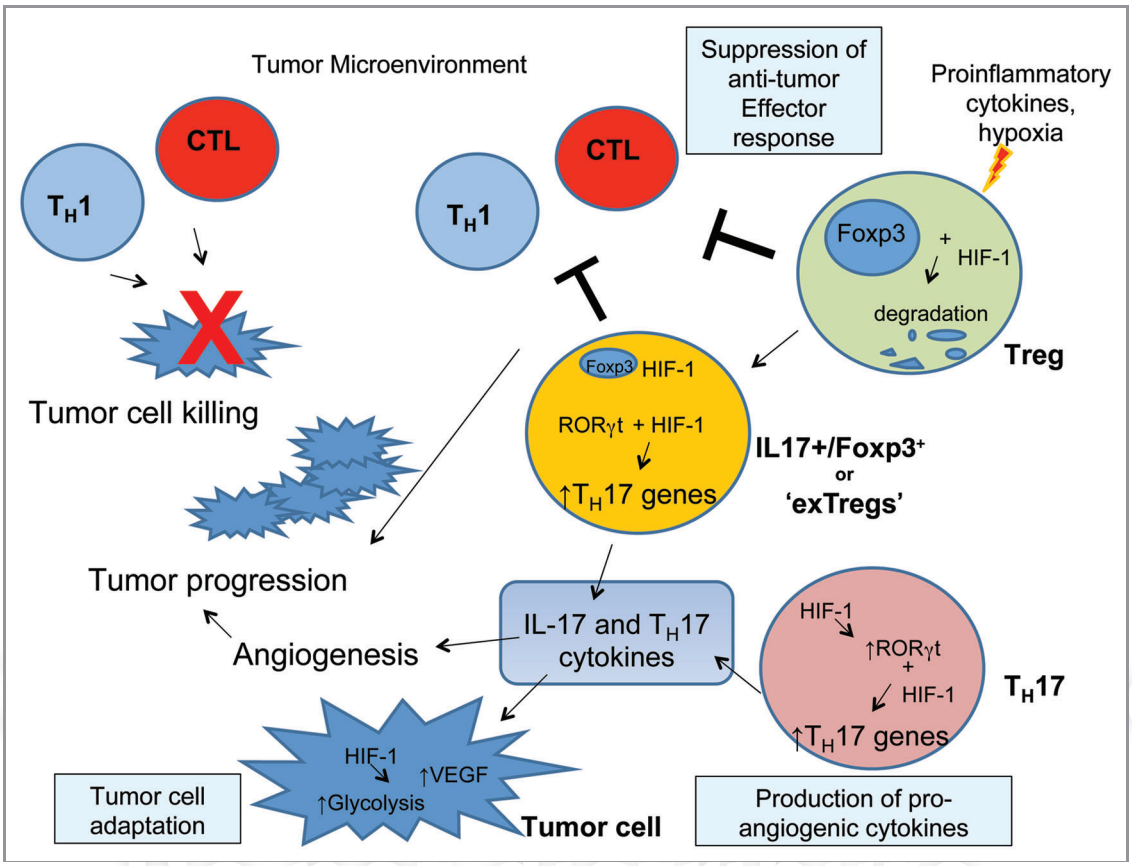

Figure 2. HIF-1 contributes to the production of IL-17 and in the tumor microenvironment may promote cancer progression through multiple mechanisms. In the tumor microenvironment, Tregs and T_H17 cells accumulate. The former population suppresses the action of T effector cells capable of cancer cell eradication (T_H1, CTL) while the exact role of the latter is the subject of some debate. Recent findings suggest that despite a strong reputation as a pro-inflammatory subset, T_H17 cells by virtue of the angiogenesis-promoting effect of their signature cytokines, may promote tumor development. In the hypoxic tumor microenvironment, Foxp3$^+$ Tregs can be induced to produce IL-17 as well. It is probable that HIF-1, induced by hypoxia or the cytokine milieu of the tumor microenvironment is central for the elevation of angiogenesis-promoting cytokines. In addition to this potential contribution to tumor progression HIF-1 has well documented roles in cancer cell metabolism and other processes as well. HIF-1 targeting should therefore be explored as a cancer strategy with the potential for sabotaging tumor promoting processes at multiple levels.

in combination with other agents aimed at counteracting the potential increases in suppressor cell generation such as the drugs used to deplete Treg cells. Such a combinational approach, should in theory, simultaneously neutralize two tumor-promoting T-cell populations. Additionally, since some studies suggest that in the latter stages of tumor development, T_H17 cells have anti-tumor effects, restricting the therapeutic window of HIF-1 inhibition to early developing tumors may prove more effective as a treatment strategy.

Concluding Remarks

While it is well appreciated that during T-helper cell differentiation from naïve precursors, ultimate lineage choice is heavily swayed by cytokine initiated signaling pathways, other sources of environmental input that also influence T-cell lineage choice are just being brought to light or still remain known. Recent findings strongly suggest that metabolic cues can significantly affect T-cell lineage choice. mTOR, a molecule involved in the sensing numerous indicators of metabolic state, is important for differentiation of naïve T cells into effector lineages.[7] Another metabolic sensor heavily involved in steering T-cell differentiation is HIF-1. This molecule, known to be an important regulator of the cellular response to low oxygen level has been the topic of several recent studies sharing a complimentary theme. Either as a key inducer of the glycolysis dominated metabolic shift necessary for T_H17 development under the control of mTOR signaling[8,12] (a regulator of and cooperative partner with the T_H17 transcription factor RORγt that interestingly sabotages the protein level of the antagonistic Treg regulator, Foxp3) or as a promoter of differentiated T_H17 cell persistence HIF-1 is a major regulator of the T_H17 response. Additionally, reports of the T_H17 suppressing properties of the HIF-1 inhibitor digoxin appear to bolster this notion.[16] Future work should evaluate the potential of HIF-1 inhibitors as autoimmune disease remedies and (with concurrent management of Treg levels) anti-cancer agents. For the latter, however, the above studies suggest that further work should be taken on to rule out or compensate for possible Treg elevation and inadvertent negation of potentially beneficial anti-tumor actions that T_H17 cells may have in some established tumors.

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