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Unravelling the Vital Role of T-Follicular Helper Cells in Cancer & Autoimmunity: A Functional Background and Overview

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Abstract

T-helper ($CD4^+$) cell assistance is required to activate B cells, induce somatic hypermutation, switch between isotypes, and produce them. Tfh cells (a specialized subset of $CD4^+$ T cells) have been linked to a better prognosis in a variety of human cancers, but the mechanism governing their prognostic function is still unknown. Data demonstrate a critical relationship between increased TIL (Tumor infiltrating lymphocyte) concentrations and improved clinical outcomes across the majority of solid tumour types. Anti-PD-1/PD-L1 inhibitors are effective in treating certain patients with tumour cells that do not express PD-L1, suggesting that their ability to respond to cells' interconnection may be a key factor. Antigen presentation, T cell activation, cytokine secretion, complement activation, antibody-mediated tumour cell phagocytosis, antibody-dependent cell cytotoxicity, stimulation of T cells, and direct cancer eradication by TIL are important anti-tumour effector activities.

CXCL13/CXCR5 is a signaling axis in the tumour microenvironment that promotes Tfh recruitment at the tumour site and preserves T cell activity. Epitope spreading is one proposed mechanism that might aid in the emergence of autoimmunity when ICI therapy is used. Anti-CTLA-4 therapy encourages T cell growth, including tumor-reactive T cells. B lymphocytes in tumour tissue, such as organized tertiary lymphoid structures (TLS), are correlated with survival and a positive response to cancer immunotherapy. T_{reg} cells, which contain the transcription factor FOXP3, are essential for maintaining immunological homeostasis. Follicular regulatory T (Tfr) cells are thought to play a crucial role in optimizing protective reactions and suppressing the formation of antibodies to self-antigens & allergens.

Keywords: Tfh cells; Tumor infiltrating lymphocyte (TIL); CXCL13/CXCR5; Tertiary Lymphoid Structures (TLS); Tumour microenvironment; ICI therapy; Tfr cells

Abbreviations: TIL: Tumor Infiltrating Lymphocyte; TLS: Tertiary Lymphoid Structures; Tfr cells: Follicular Regulatory T; Tfh cells: T Follicular Helper Cells; NSCLC: Non-Small-Cell Lung Cancer; irAEs: Immune-Related Adverse Events; ICI: Immune Checkpoint Inhibitor; AIRE: Autoimmune Regulator; ACT: Adoptive Cell Transfer Therapy; DCs: Dendritic Cells; CAR T: Chimeric Antigen Receptor T

Introduction

$CD4^+$ T cell assistance is necessary to activate B cells, cause somatic hypermutation, switch between isotypes, and generate them. [1,2] Following CD40 activation, B cells proliferate and go towards the germinal centre where they go through somatic hypermutation, aiding in the development of diverse antibodies with different affinities. T cells can also go into the germinal center, where they can continue to engage in interactions with B cells and contribute to the development of plasma cells and memory B cells [3].

T follicular helper cells (Tfh), a distinct $CD4^+$ T lymphocyte fraction which serves this purpose, have been identified (Figure 1). Tfh cells are identified through the membrane markers description like Chemokine receptor 5 with the C-X-C motif (CXCR5) and receptor of chemokine (C-X-C motif) ligand 13 (CXCL13), both of which are necessary for their movement toward the germinal center, additionally, through B cell lymphoma 6 (BCL6), Interleukin (IL-21), PD-1, ICOS, and AchaeteScute family member transcription factor 2 [4]. Here the substances are demonstrated as crucial because they control growth of Tfh, emigration as well as obligation. Majorly Tfh cells (a distinct independent T helper cell subtypes) which differs from Th1, Th2, Treg, and Th17 can be reliably identified by robust expression of PD-1 in combination with CXCR5.

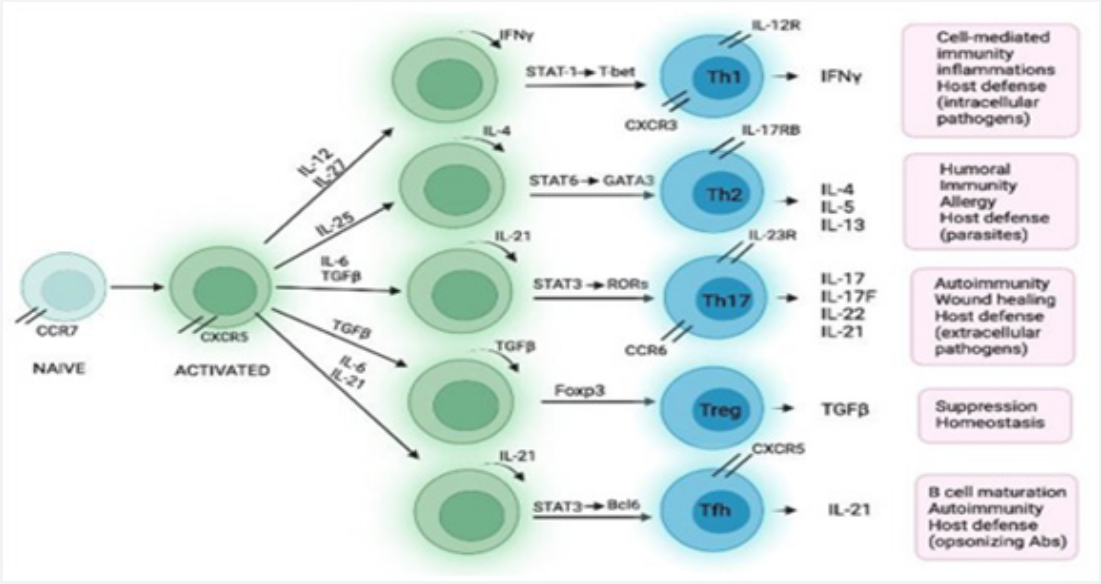

Figure 1: Differentiation and development of different lineages of T-Helper cell & growth of T-Follicular Helper cell with their brief functional aspects.

Tfh cells have been linked to a better prognosis in a variety of human cancers, including colorectal, non-small-cell lung cancer (NSCLC), and breast cancer [5-8]. However, the mechanism governing their prognostic function is still unknown. In mouse models, TGF-β dependent CXCL13 production by intratumor $CD8^+$ T cells was necessary for the Tfh anticancer effect, and anti-PD-1 treatment was ineffective unless Tfh cells were present. This suggests that Tfh cells may be responsible for the anticancer effect of anti-PD-1 treatment [9-14].

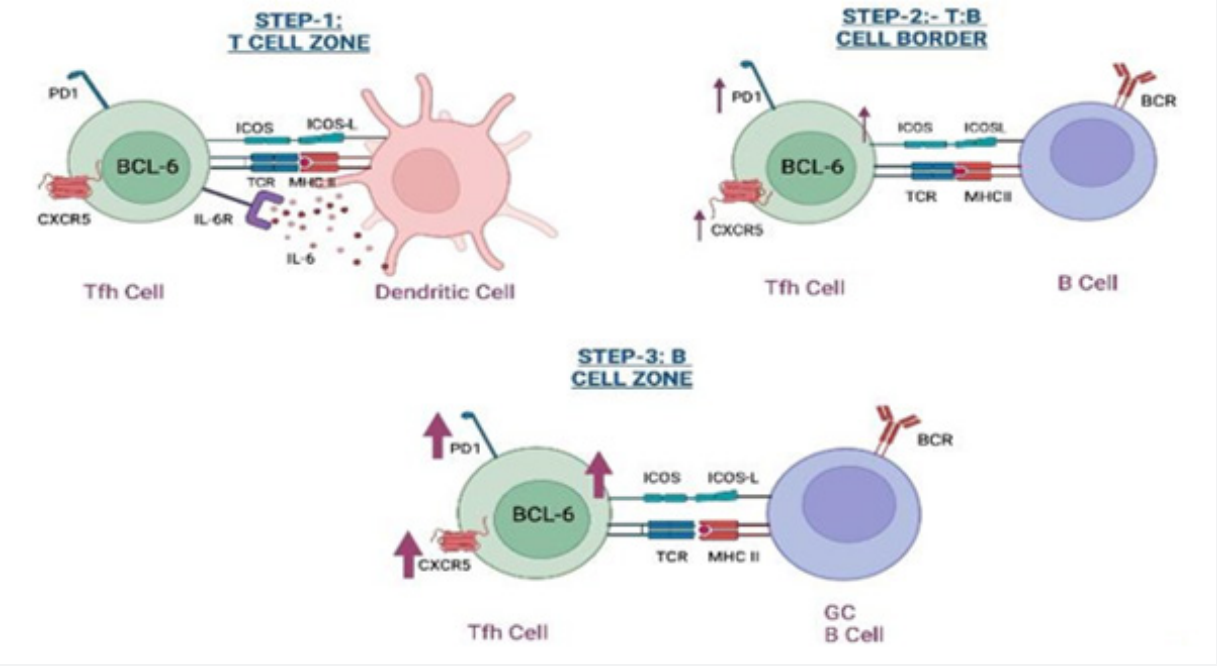

Figure 2: Presence of unique T cell zone and B cell zone in mature tertiary lymphoid organs (TLSs). The T cell zone is a region where T cells are activated & undergo clonal expansion in response to antigenic stimulation. The B cell zone is a region where B cells undergo activation, Proliferation and Differentiation into antibody secreting plasma cells in response to antigenic stimulation.

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Significance of TIL & role of TLS composition

Data demonstrate a critical relationship between increased TIL (Tumor infiltrating lymphocyte) concentrations and improved clinical outcomes across most solid tumour types, but the size and equilibrium between immune cell subpopulations vary [15-17]. TILs are present in the tumour microenvironment and have an architecture resembling secondary lymphoid organs. Different maturation stages in human malignancies are reported, with dense lymphocytic aggregates being the source of TLS. Mature TLS is composed of Tfh cells, mature DC, lymphatic arteries, a segregated T cell zone, B cell follicle, GC B cells, follicular DC, and macrophages [18] (Figure 2). Some TLSs are defective or attenuated and have larger concentrations of regulatory cells. Tumor-infiltrating B cells (TIL-B) are linked to improved clinical outcomes and TLS [19].

The GC works in secondary lymphoid organs to create affinity-matured and class-switched B lymphocytes that recognise cognate antigens and develop both humoral immunity and memory B cells. Global TIL, such as Tfh TIL, $CD4^+$ TIL with a Th1 orientation, and TIL-B that secretes antibodies, are closely connected with GC B Cells [20]. Tfh TIL are quickly identified with in germinal center due to elevated expression of PD-1. Active TLS can also be identified by their functioning PD-1hi Th1-oriented Tfh TILs that express IFN, IL-21, and CXCL136 [21,6,22].

Role of anti PD-1/PD-L1 inhibition in clinical investigation

Anti-PD-1/PD-L1 inhibitors are effective in treating certain patients with tumour cells that do not express PD-L1, suggesting that their ability to respond to cells interconnection may be a key factor [23]. These findings suggest that elevated surface PD-1 on TLS-resident Tfh TIL can be more related to modifying their functions and activities than fatigue. Antigen presentation, T cell activation, cytokine secretion, complement activation, antibody-mediated tumour cell phagocytosis, antibody-dependent cell cytotoxicity, stimulation of T cells, and direct cancer eradication by TIL are important anti-tumour effector activities [24,25].

Infiltration of Tfh cells and formation of TLS

It has been observed that TIL density is associated with improved clinical outcomes in $HER2^+$ and TN breast cancer. TIL is composed of both innate and adaptive immune cells, with T cells often holding a predominance [26,27]. TIL accumulations, such as aggregates or tertiary lymphoid structures (TLS), are typically found in the stroma. Tfh cells can direct migration and encourage GC production. The CD4+CXCR5-BC TIL (TfhX13) is the main source of CXCL13 and is present in normal human tonsils and patients with rheumatoid arthritis [17,28-30]. CXCR5-TfhX13 TIL has an impact on TIL recruitment and TLS induction in BC and is capable of assisting T-dependent B cells and producing IFN-γ. Functional Th1-oriented Tfh TIL, a greater level of TLS activity, and a balance between active and inactive TLS are markers for tumours [19,31,32].

CXCL13/CXCR5 Signaling axis in tumour microenvironment

CXCL13/CXCR5 is a signaling axis in the tumour microenvironment that promotes Tfh recruitment at the tumour site and preserves T cell activity. It has a direct antitumor effect and is crucial for immune cell trafficking in the tumour microenvironment. Tfh and CXCR5+B cells are made to migrate to the tumour as a result of CXCL13, forming TLS [33-35]. The exact mechanism underlying CXCL13 and Tfh's beneficial effects is not yet known, but other research suggests that Tfh may have a detrimental role. Therefore, the CXCL13/CXCR5 axis may afterwards aid in the escape of cancerous cells [36,37] (Figure 3).

Discussion

Emergence of immune-related adverse events (irAEs)

The emergence of immune-related adverse events (irAEs) is often associated with the effectiveness of immune checkpoint inhibitor (ICI) therapy. However, there is still a great deal of mystery around the underlying mechanisms that cause irAEs to be induced. Tfh and Tfh-like cells are significant members to take into account when attempting to connect the extremely effective ICI cancer treatment with the occurrence of irAEs. Epitope spreading is one proposed mechanism that might aid in the emergence of autoimmunity when ICI therapy is used. This idea proposes that during cytotoxic tumour cell killing, self-antigens are released by dead bystander cells and picked up by dendritic cells (DCs) and B cells, which upon movement to the draining lymph nodes stimulate extra self-reactive $CD8^+$ and $CD4^+$ T cells & (auto) antibody generating B lymphocytes [38,9].

ICI therapies for PD-1 or its ligand PD-L1 act on the antitumor immune response at various phases (Figure 4). Anti-CTLA-4 therapy encourages T cell growth, including tumor-reactive T cells. B lymphocytes in tumour tissue, such as organized tertiary lymphoid structures (TLS), are correlated with survival and a positive response to cancer immunotherapy. CXCR5 expressing T-Follicular Helper cells support the development of antibodies with great affinity and formation of memory B cells and effector B-cells by expressing co-stimulatory molecules, co-inhibitory receptors, and producing IL-21 and IL-4. A tiny population of Tfh cells, also known as circulating Tfh cells, are also present in the circulation and are more prevalent in autoimmune diseases [39,40].

Immune checkpoint inhibitor (ICI) treatments

Immune checkpoint inhibitor (ICI) treatments can activate cells that express high levels of CD40L, ICOS and other co-stimulatory molecules and increase the likelihood of cancer. In patients with lung cancer, Tfh cell signatures were associated with GCs and longer survival, and neoantigen-driven B cell and Tfh cell cooperation was recently found to produce powerful

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antitumor $CD8^+$ T cell responses [41-43]. Anti-PD-1 therapy may also have an impact on both CTL-mediated immune responses against autoantigens and humoral immunological responses. T cell-specific PD-1 impairment led to aberrant GC responses and enhanced Tfh cell population in SLOs. Generally, Tfh cell responses are controlled by regulatory T (T_{reg}) cells and T follicular regulatory (Tfr) cells [44,45].

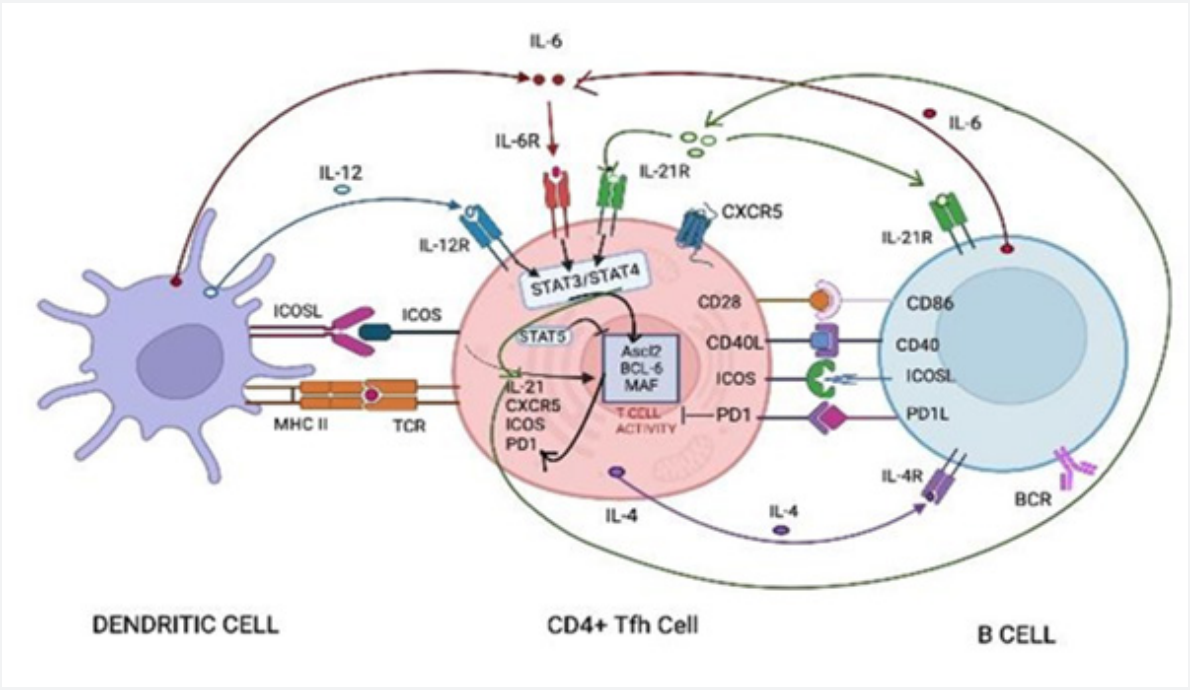

Figure 3: connections between dendritic cells (DCs), T follicular helper cells (Tfh), and B cells in germinal centres (GCs) on a cellular and molecular level. Tfh cells also interact with B cells directly by recognizing the antigen displayed on B cell receptors (BCRs) and providing necessary co-stimulatory signals. This interaction leads to the formation of specialized structures within GCs called germinal centers reactions, where B cells undergo somatic hypermutation and class-switch recombination to generate high-affinity and class-switched antibodies. Molecularly, the interaction between Tfh cells and B cells is mediated by various cell surface molecules and soluble factors such as CD40L, ICOS, IL-21, and IL-4. These molecules provide necessary co-stimulatory signals and cytokines for B cell activation and differentiation. Overall, the interaction between DCs, Tfh cells, and B cells in GCs is a tightly regulated process that is critical for the generation of effective humoral immune responses.

Common pathways regulate T-follicular helper cells

Differentiation & Autoimmunity

The development of Tfh cells and their assistance to B cells is a carefully regulated process. Because T cell development is more tightly regulated than B cell development, B cell tolerance heavily relies on limiting T cell assistance. Naive T cells are evaluated against self-antigens during their development, and transcription factors like autoimmune regulator (AIRE) represent several peripheral self-antigens. It has been shown that 20% of mature naive B cells exhibit low levels of self-reactivity [46], although peripheral self-antigens may be less accessible to bone marrow-derived B cells. Additionally open to variation within GCs, B cell antigen specificity outweighs any developmental limitations on self-reactivity. Therefore, it is vital to deny T lymphocytes assistance to self-reactive B cells in order to stop the onset of potentially harmful autoimmune reactions. For optimum protective immunity, it's crucial to ensure that T cell-B cell cooperation is well managed. When analyzing the mechanisms regulating differentiation of Tfh cell, three fundamental and interrelated pathways involving regulatory T (T_{reg}) cells, cytotoxic T lymphocyte antigen 4 (CTLA4), and IL-2 emerge.

Treg cell-mediated control of Tfh cells

Treg cells, which contain the transcription factor FOXP3, are essential for maintaining immunological homeostasis. Short-term reduction of regulatory T cells promotes the production of T-Follicular Helper cells specific to antigens in response to immunization. CTLA4 is constitutively expressed by Treg cells, and loss of CTLA4 expression can reproduce increased Tfh cell differentiation [47-50]. Down regulation of CD25 (IL-2R) expression is required to produce BCL-6, which is antagonistic to BLIMP1 expression driven by IL-2. Follicular regulatory T (Tfr) cells are thought to play a crucial role in optimizing protective reactions and suppressing the formation of antibodies to self-antigens & allergens [51,52].

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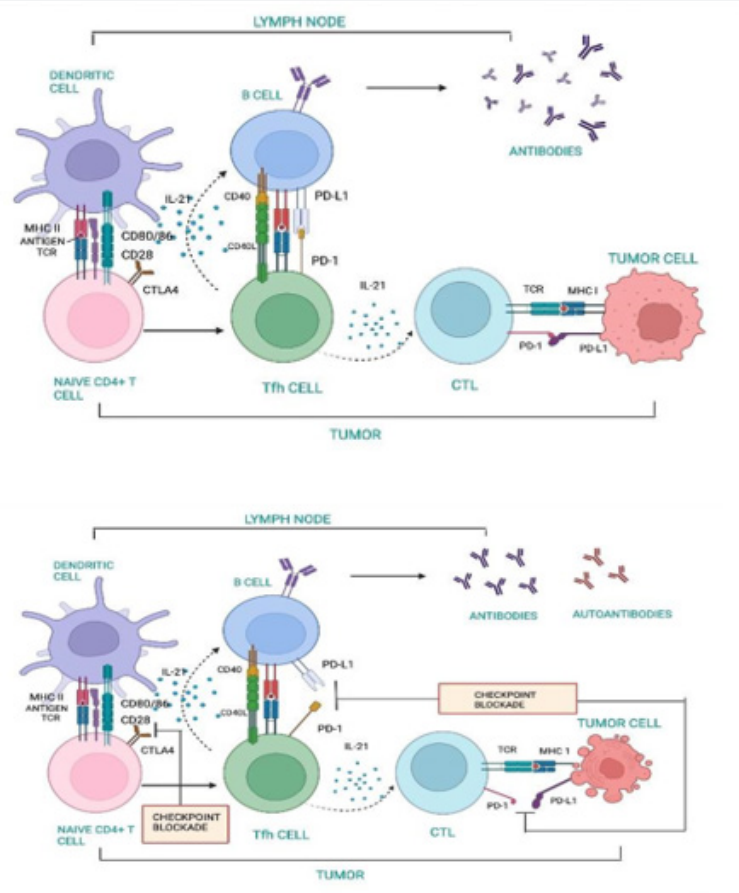

Figure 4: Possible effects of immune checkpoint inhibitor (ICI) on Tfh cell responses. One of the primary inhibitory signals in Tfh cells is the programmed cell death protein 1 (PD-1) receptor and its ligand, PD-L1, which are often upregulated in the tumor microenvironment to evade immune surveillance. ICI treatment, such as anti-PD-1 or anti-PD-L1 antibodies, blocks the interaction between PD-1 and PD-L1, leading to the reactivation of Tfh cells and the promotion of germinal center reactions. In terms of T follicular helper (Tfh) cell responses, CTLA-4 has been shown to play a critical role in regulating the germinal center reaction and antibody production. Studies have shown that CTLA-4 deficiency or blockade can enhance Tfh cell activation, leading to increased germinal center reactions and antibody production. Specifically, CTLA-4 has been shown to regulate Tfh cell differentiation and function by modulating the expression of co-stimulatory molecules on APCs, such as CD80 and CD86. By binding to CD80/CD86, CTLA-4 inhibits the co-stimulatory signals required for Tfh cell activation and germinal center formation. In the context of ICI treatment, CTLA-4 blockade by ipilimumab can enhance Tfh cell responses by relieving the inhibitory signals that limit their activation, leading to increased germinal center reactions and antibody production. This, in turn, can promote the generation of tumor-specific antibodies and improve anti-tumor immunity.

However, selective depletion of Tfr cells leads to only minor or temporary increases in Tfh cells. Tfr cells may use additional suppressive strategies along the T cell-B cell border and inside the follicle, such as production of neuropeptide neuritin or targeting of B lymphocytes metabolic pathways [48, 53-56].

Therapeutic Approach

Exhausted $CD8^+$ T cells can be revitalized by antibodies targeting PD-1 or PD-L1, but the degree of early activation determines how effective they are. IL-21 and T-Follicular Helper cells may be useful tools for preserving $CD8^+$ T lymphocytes activities and enhancing the effectiveness of immune checkpoint inhibitors in malignancies. CXCL13 intratumor production is sufficient to promote Tfh recruitment. New methods for ensuring the effectiveness of checkpoint inhibitors include adoptive transfer of non-specific Tfh cells and $CD4^+$ Chimeric Antigen Receptor T (CAR T) cells developed into Tfh-like cells. These findings suggest that TGF-β creates a significant immunological loop where $CD8^+$ T lymphocytes attract Tfh cells, which subsequently maintains $CD8^+$ T lymphocyte activity, induces their division, and prevents these cells from dying [57].

These findings have a few ramifications, such as preventing $CD8^+$ T cell depletion in the tumour and overriding resistance to

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anti-PD-1 therapy. Additionally, Tfh and worn-out $CD8^+$ cells may help predict the effectiveness of checkpoint inhibitors in patients receiving anti-PD-1/PD-L1 monotherapy and serve as a new predictive biomarker [58,59].

Conclusion

$CD4^+$ T cell support plays a pivotal role in various processes such as activation of B lymphocytes, somatic hypermutation & isotype switching etc. T-Follicular Helper cells (Tfh) are identified by the expression of CXCR5 and CXCL13 and have been linked with better prognosis of different cancer types. A significant increase of Tfh levels is correlated with an increase in different cell types such as interferon γ (IFN-γ) producing Th1 cells, $CD8^+$T and B lymphocytes. But Tfh-like cells found within tumor show an immunosuppressive mechanism & interrupts the functions of $CD8^+$ and Th1 cells. Global TIL, which includes Th1-oriented $CD4^+$ TIL, T-Follicular Helper (Tfh) TIL, TIL-B which secrets antibodies, and greater survival have been closely connected with GC B cells. Higher concentrations of tumor-infiltrating lymphocytes (TIL) are associated with improved clinical outcomes across a wide range of tumour types, with T cells often holding predominance. Tfh activity dysregulation can, in fact, cause the formation of pathogenic autoantibodies and has been linked to a number of autoimmune disorders.

Treg cells, which contain the transcription factor FOXP3, are essential for maintaining immunological homeostasis and are significantly more prevalent in secondary lymphoid organs in scurfy mice. Tfr cells are thought to optimise protective antibodies. TLS deactivation or dormancy may occur as immune responses progress. PD-L1 occupancy by CD80/PD-L1 silence on nearby antigen-presenting DC or B cells could explain why PD-1 does not activate in these circumstances. New methods for ensuring the effectiveness of checkpoint inhibitors include adoptive cell transfer therapy (ACT) such as transfer of Tfh cells or injection of IL-21, and CXCL13 intratumor production is sufficient to promote Tfh recruitment. This suggests that Tfh cell adoption or intratumor IL-21 injection therapy may be used to address anti-PD-1 medication resistance and may also serve as a new predictive biomarker. TIL levels were elevated in tumour tissues, promoting Tfh-induced B cell responses that aided the immune system's ability to fight the tumour.

Future work

Further research into the detailed beneficence and development of Tfh cells and tumour-associated Tfh-like cells, as well as their function in the generation of irAEs, is justified given their involvement in both humoral and cellular antitumor immunity. For the present initiatives in personalized medicine, this is especially crucial. Only a small percentage of patients treated with immune-checkpoint inhibitors (ICIs) experience subordinate autoimmunity, raising the idea that ICI therapies could highlight or worsen the consequences of prior mutations in other pathways that have not yet manifested as vital illness. It would be advantageous for patients and the healthcare system if these processes were better understood because it would open up new possibilities for improving the effectiveness of ICI treatments as well as lowering the possibility of side effects. Epitope spreading is one proposed mechanism that might aid in the emergence of autoimmunity when ICI therapy is used. This idea proposes that during cytotoxic tumour cell killing, self-antigens are released by dead bystander cells. These self-antigens are picked up by dendritic cells (DCs) and B cells, which upon movement to the draining lymph nodes stimulate extra self-reactive $CD8^+$ and $CD4^+$ T cells & (auto) antibody generating B lymphocytes (Figure 4). Autoimmunity might subsequently develop as a result of these cells returning to the tumour microenvironment and destroying new tumour cells or unrelated non-malignant self-tissues. ICI therapies for PD-1 or its ligand PD-L1 act on the antitumor immune response at various phases.

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