Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 7
MISBP 2024

The Specific Mechanism of Th1Th2 Balance in Tumor Immunity

Zaixi Li*

Beijing No.159 High School, Beijing, China

*Corresponding author: jeanneli@lgy.edu.rs

Abstract. With the development of modern science, tumor immune microenvironment (TME) has become the mainstream of research. There are many related studies on Th1/Th2, so it is important to bring together such studies. At present, the research on Th1/Th2 mainly focuses on the following aspects: the mechanism of Th1/Th2 cells in TME, the inhibitory effect of Th1 cells in tumor tissues, and the related therapies for Th1/Th2 cell balance. However, there are few studies that summarize the above research directions. In this paper, the interaction between Th1 and Th2 was elaborated and found that Th2 interfered with the normal anti-tumor function of Th1 inhibition in TME, and MDSC was produced and accumulated in tumor tissues, resulting in the increase of MDSC. MDSCs can show effective immunosuppressive and tumor-promoting functions in TME through a variety of mechanisms, and together with M2 macrophages, they can assist Th2 to exert inhibitory effects on Th1 and CD8+ T cells. Saikosaponin A and xanthohumol can effectively balance Th1/Th2 to achieve the effect of treating tumors. This study reveals the specific interaction mechanism of Th2 and Th1 in TME, elucidates the inhibitory role of Th1 cells in tumor tissues, and summarizes the research results in related fields in recent years, as well as the current research progress in related fields.

Keywords: T helper cells, tumor immunity, immune mechanisms, tumor microenvironment (TME), Th1/Th2 ratio.

1. Introduction

The function of T helper (Th) cells in tumor immunity is crucial, and can exert their biological effects through a variety of cytokines. The mutual inhibition of Th1 and Th2 will inevitably lead to a significant decrease in the ability of Th cells to fight tumor immunity. CD30 is expressed only in Th2 cells, but not in Th1 cells. The chemokine receptors CCR5 and CCR3 are important taxonomic markers for human Th1 cells and Th2 cells, respectively [1].

By producing inflammatory cytokines, Th1 cells primarily mediate cellular immunity and delayed hypersensitivity inflammation, IFN-g can promote the synthesis of antibodies by B cells to convert to IgG2a and IgG3, Th2 cells mainly mediate humoral immune responses by secreting Th2 cytokines (IL-4, etc.), for example, promoting B cell activation; Promote the conversion of antibodies synthesized by B cells to IgE and IgG4; Chemoattractant B cells, eosinophils, basophils, etc., play a crucial part in preventing helminth infections and bacilli [2]. Th1 cells can contribute to tumor immunity by preventing the development and multiplication of tumors by secreting cytokines like IL-1, whereas Th2 cells contribute to tumor immunity by secreting cytokines like IL-2. Furthermore, the Th1/Th2 ratio and the cancer stage are highly correlated. As a result, the transition of Th1 to Th2 type T cell responses may be crucial for the initiation and spread of cancer. Immune homeostasis is largely dependent on the balanced production of Th1 and Th2 cytokines. The etiology and pathophysiology of cancer as well as transplant rejection are significantly influenced by the disproportion between these two immune regimes. Understanding the mechanisms that cause this dysregulation in Th1/Th2 displacement can improve immunotherapy and outcomes in cancer and transplant patients [3].

To explore the specific effects of the cytokine network produced by Th1 and Th2 cells, to clarify the specific mechanism of cell differentiation of Th1 and Th2 in TME, to review the research results in recent years, and to summarize the conclusions and experiences of each experiment. Feasible ideas for tumor treatment were also proposed.

2. Mechanism of action of Th1/Th2 cells in TME

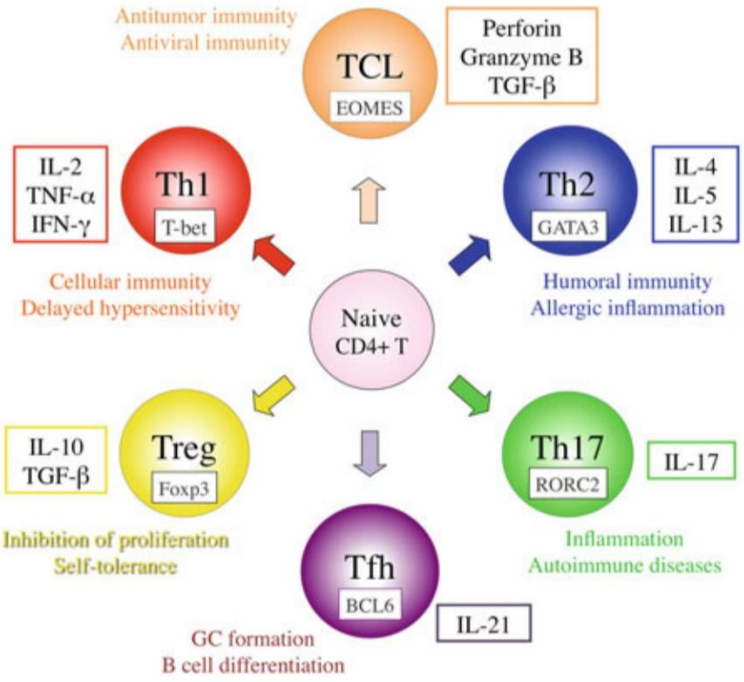

Fig. 1 Th cell typing [4].

Ghosh et al. examined mouse colon adenocarcinoma and renal cell carcinoma (RCC) models in mice and discovered that as tumors become larger, the Th2 cytokine profile rises and the Th1 population eventually disappears [1]. Consequently, a number of studies conducted on laboratory animals suggest that the transition from Th1 to Th2 type T cell responses may be crucial to the initiation and spread of cancer. Analyzed in human oncological illnesses, the idea that tumor growth may be associated to qualitative variations in cytokine-induced immune responses has been documented in many kinds of malignancies (Figure 1).

The majority of clinical investigations back up the finding that cancer patients have an aberrant Th1/Th2 ratio. Peripheral blood mononuclear cells (PBMCs) flow cytometry study of PBMC subsets from patients with advanced cancer showed an imbalance between Thl and Th2 in terms of both frequency and cytokine production capability. For instance, patients with non-small cell lung cancer had high amounts of IL-10 and IL-4, but not IL-2, expressed by their tumor-infiltrating lymphocytes (TILs). Put differently, Th1 cells exhibit very little expression activity. The same patients' PBMCs also showed significant levels of IL-10 mRNA expression, which is generated by ribosomes, the Golgi apparatus, and the reticulum endoplasmic. In nearly all cancer patients tested, alterations in the Th1 or Th2 cytokine profile have been reported. These include glioblastoma, Other tumor types include lung cancer, non-Hodgkin's lymphoma, cancers of the breast, bladder, kidney, and prostate, malignancies of the head and neck, cutaneous T-cell lymphomas, and basal cell carcinomas. These changes are frequently characterized by a reduced Th 1/Th2 ratio. B-cell chronic lymphocytic leukemia (CLL) patients have also been shown to produce more IL-4 when a particular subset of "Th2-like" cells proliferate [2].

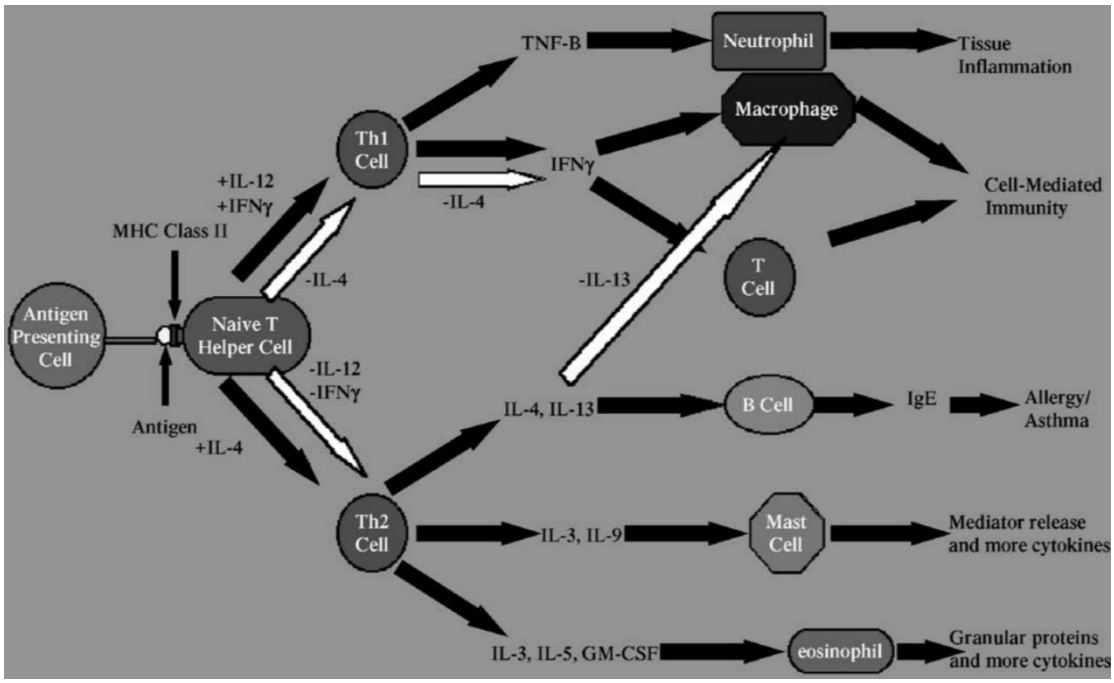

Fig. 2 T cell differentiation pathway [5].

Studies have shown that local and peripheral Th2 cytokine patterns are present in most of the cancer patients studied. A typical characteristic of malignant processes in cancer patients is changes in the Th1/Th2 ratio, which can be brought on by either Th1 cell malfunction, Th2 lymphocyte activation, or a combination of the two [3]. The process of Th1 dysfunction will be thoroughly explained in the next section (Figure 2).

3. Inhibition of Th1 cells in tumor tissues

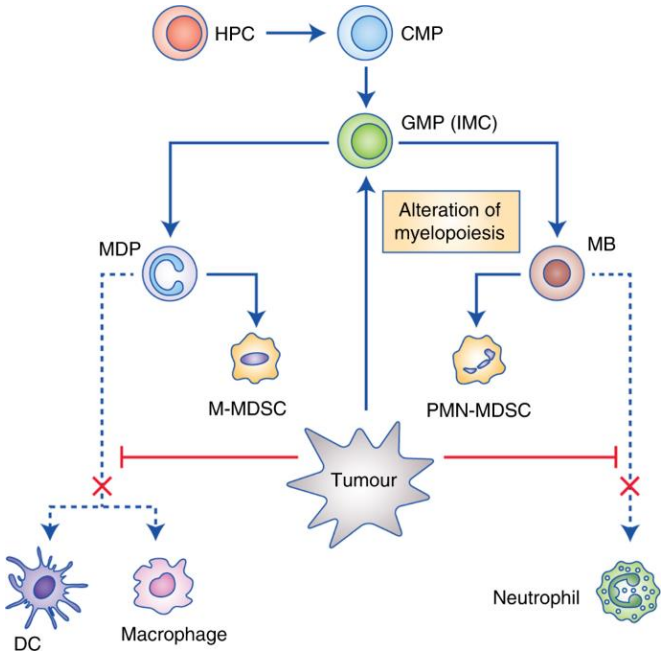

Fig. 3 Mechanism of production of myeloid-derived suppressor cells [6].

In cancer, myeloid-derived suppressor cells (MDSCs) are key players in inhibiting immune responses. Chronic inflammation triggers abnormal myelopoiesis, disrupting the differentiation of HPCs. Under normal conditions, hematopoietic progenitors typically evolve from CMPs into GMPs. These IMCs then either develop into MDPs or MBs, which subsequently mature into dendritic cells, macrophages, or neutrophils. However, in cancer, the tumor microenvironment interferes with myelopoiesis,

impeding normal progenitor development and causing an abnormal rise in monocytic MDSCs. The expansion of these cells in tumors amplifies immune suppression, facilitating tumor progression [6]. However, in cancer, the environment around the tumor interferes with this natural process, leading to an increase in MDSCs that haven't fully matured. This rise in MDSCs weakens the immune system's ability to fight the tumor, which allows the cancer to grow and spread. Understanding this process is crucial, as it highlights how tumors exploit the body's own mechanisms to protect themselves, revealing potential areas for therapeutic intervention (Figure 3).

Through a variety of ways, MDSCs are essential to the TME's immunosuppressive and tumor-promoting environment. They do this by producing reactive oxygen and nitrogen species, inducing other immunosuppressive cells, blocking lymphocyte homing, lowering essential metabolites required for T cell function, modifying adenosine metabolism through the release of extracellular enzymes, and expressing immune checkpoint molecules that suppress immune responses. Together, these actions strengthen the TME's immunosuppressive milieu and promote tumor growth. Research has demonstrated that MDSCs can stimulate the formation of Tregs through specific signaling molecules, further compromising the immune system's ability to respond. MDSCs promote the generation of Treg cells via pathways involving IFN-γ and IL-10. In liver cancer patients, certain MDSC subtypes are capable of inducing Treg differentiation through interactions with T cells. Additionally, studies utilizing melanoma mouse models have shown that Treg cells amplify the suppressive function of MDSCs by activating specific immune regulatory proteins, such as B7-H1 (PD-L1) and B7-H4, while concurrently increasing the secretion of IL-10, which further dampens the immune system's anti-tumor response. Notably, Treg cells are recruited into the tumor microenvironment via chemokine signals, which reinforces the immunosuppressive actions of MDSCs. These findings highlight the intricate crosstalk between Treg cells and MDSCs as a key mechanism by which tumors evade immune detection, offering new potential therapeutic targets for cancer treatment [7].

Immune cells in the TME are divided into two major categories, one is the effector cells responsible for attacking tumors, and the other is the protective cells that help tumors evade the immune system. Current immunotherapy mainly focuses on enhancing the activity of effector cells, such as T cells and NK cells. Although this can improve the attack on tumors to a certain extent, due to the presence of a large number of protective cells around the tumor, such as MDSCs and Tregs, they form an immunosuppressive barrier that offsets the effect of effector cells. Therefore, therapies that rely solely on enhancing effector cells are often not enough to eliminate tumors [8]. By simultaneously reducing the activity of protective cells, combination therapy can break this barrier, thereby more effectively enhancing the immune system's ability to fight tumors. This shows that the dual strategy can not only improve the treatment effect, but also increase the overall response rate of patients to immunotherapy (Figure 4).

In summary, tumors can protect themselves by affecting the function of certain immune cells in the body, thereby suppressing the body's immune response and promoting tumor growth. Most current treatments focus only on enhancing immune cells that fight tumors, but because there is a type of cell that helps tumors evade the immune system, this approach alone is often of limited effectiveness. Therefore, combining the two strategies, both enhancing the function of immune cells and reducing cells that protect tumors can more effectively improve treatment outcomes and help the body better fight tumors. This dual approach shows greater potential in immunotherapy. The immune system's balance between fighting cancer and being suppressed by the tumor environment is crucial. MDSCs play a significant role in helping tumors evade the immune system by suppressing the activity of cells that could otherwise fight the cancer. They not only promote the growth of tumors by weakening immune responses but also contribute to creating a protective shield around the tumor that makes treatments less effective.

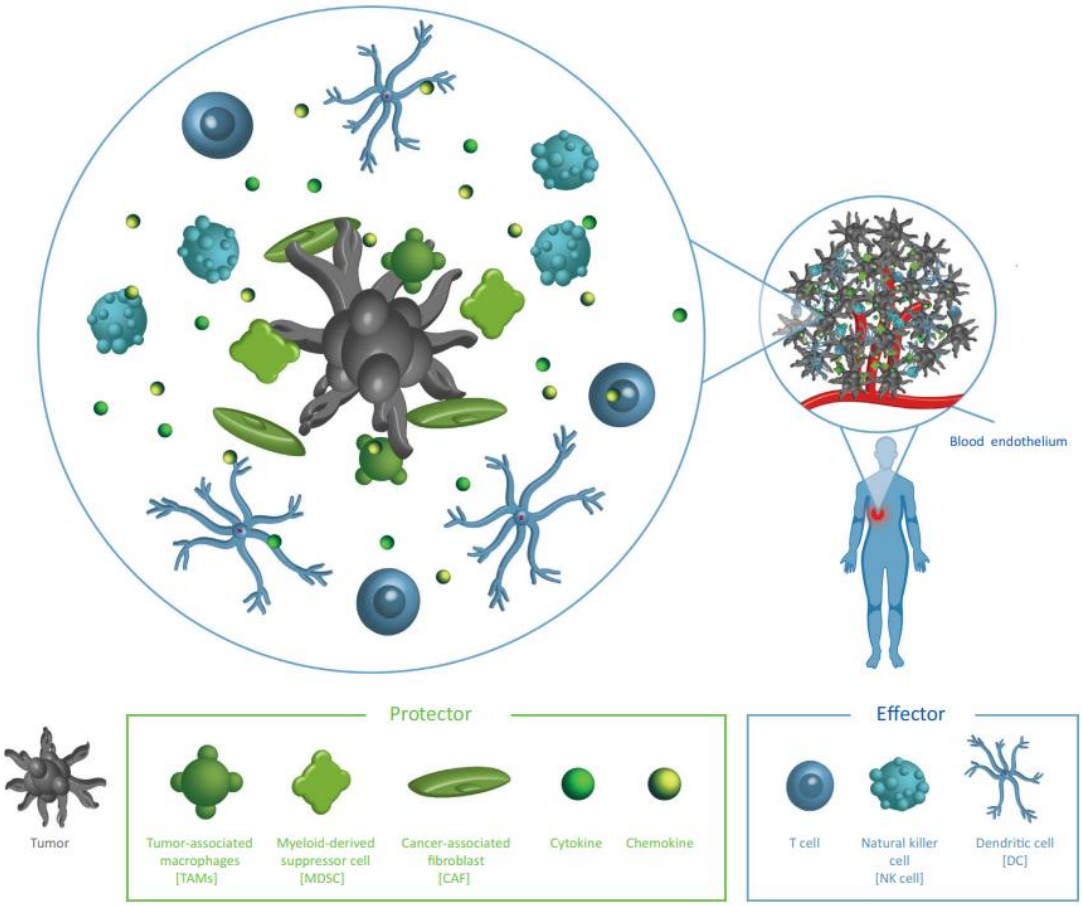

Fig. 4 Cellular composition within TME [8].

4. For Th1/Th2 cell balance

The tumor cell proliferation marker Ki-67 is associated with a poor prognosis for patients with breast cancer (BC). The Th1/Th2 balance is regulated by saikosaponin A (SSa), which is useful in BC treatment. Tumor tissue was stained with ki-67 using immunohistochemistry. Ki-67 was mostly expressed in the tumor cells' nuclei in the control group, and the staining was intense. Compared to the control group (A), both treatment groups were weaker. The morphological findings showed that, in comparison to the control group, there was a substantial decrease in Ki-67 positive stained tumor cells after TAM or SSa therapy.

The experiment demonstrated the use of CD8 and CD4 IHC labeling to detect CD8+ and CD4+ T cells that had infiltrated the tumor. According to the morphological findings, there were more CD8 cells in the SSa group than in the control group ($P < 0.01$). The control and TAM groups did not differ significantly from one another. T cell membranes are the primary site of CD4 positive staining. The morphological findings demonstrated that there were much more CD4 cells entering the SSa group than the control group. The control and TAM groups did not differ significantly from one another. These findings imply that SSa enhances CD8+ and CD4+ T cell infiltration within tumors [9].

BC is one of the most frequent cancers and the second leading cause of cancer-related deaths among women. Many of the contemporary methods used to treat BC, including hormone therapy, surgery, chemotherapy, radiation therapy, and complementary therapies, can have negative side effects in addition to not always being effective in curing the illness. Natural products, on the other hand, have immunomodulatory properties and are less harmful than chemicals.

Research have demonstrated the regulatory roles that natural products play in tumor immunity, including the activation of T cells, the enhancement of CTL function, and the secretion of cytokines by NK cells, specifically xanthohumol (XN). In a mouse model, XN inhibits the expression of CA15-

3 and Ki-67. Antigen Ki-67 and CA15-3 are the most widely used indicators for BC. IHC examination revealed that following therapy, there was a substantial inhibition of Ki-67 expression in tumor tissues. A mouse CA15-3 ELISA kit is used to measure the amount of CA15-3 in serum at the same time. The CA15-3 level in the control group was considerably greater than in the other groups, according to the results. These findings imply that XN stops BC cells from growing in a mouse model [10].

5. Conclusion

Th2 interferes with the normal anti-tumor function of Th1 inhibition in TME, and MDSC is produced and accumulated in tumor tissues, resulting in the increase of MDSC.

MDSCs can show effective immunosuppressive and tumor-promoting functions in TME through a variety of mechanisms, and together with M2 macrophages, they can assist Th2 to exert inhibitory effects on Th1 and CD8+ T cells. Saikosaponin A and xanthohumol can effectively balance Th1/Th2 to achieve the effect of treating tumors. This study reveals the specific interaction mechanism of Th2 and Th1 in TME, elucidates the inhibitory role of Th1 cells in tumor tissues, and summarizes the research results in related fields in recent years, as well as the current research progress in related fields. However, the specific treatment is still unclear.

References

[1] Ghosh P, Komschlies KL, Cippitelli M, Longo DL, Subleski J, Ye J, Sica A, Young HA, Wiltrout RH, Ochoa AC. Gradual loss of T-helper i populations in spleen of mice during progressive tumor growth. J Natl Cancer Inst, 1995, 87: 1478.

[2] Basu A, Ramamoorthi G, Albert G, Gallen C, Beyer A, Snyder C, Koski G, Disis ML, Czerniecki BJ, Kodumudi K. Differentiation and regulation of TH cells: A balancing act for cancer immunotherapy. Front Immunol, 2021, 12: 669474.

[3] Shurin MR, Lu L, Kalinski P, Stewart-Akers AM, Lotze MT. Th1/Th2 balance in cancer, transplantation and pregnancy. Springer Semin Immunopathol, 1999, 21: 339-359.

[4] Moriyama M, Nakamura S. Th1/Th2 immune balance and other T helper subsets in IgG4-related disease. Curr Top Microbiol Immunol, 2017, 401: 75-83.

[5] Packard KA, Khan MM. Effects of histamine on Th1/Th2 cytokine balance. Int Immunopharmacol, 2003, 3(7): 909-920.

[6] Murakami H, Ogawara H, Hiroshi H. Th1/Th2 cells in patients with multiple myeloma. Hematology, 2004, 9: 41-45.

[7] Groth C, Hu X, Weber R, Fleming V, Altevogt P, Utikal J, Umansky V. Immunosuppression mediated by myeloid-derived suppressor cells (MDSCs) during tumour progression. Br J Cancer, 2019, 120: 16-25.

[8] Zhao X, Liu J, Ge S, Chen C, Li S, Wu X, Feng X, Wang Y, Cai D. Saikosaponin A inhibits breast cancer by regulating Th1/Th2 balance. Front Pharmacol, 2019, 10: 624.

[9] Tesi RJ. MDSC; the most important cell you have never heard of. Trends Pharmacol Sci, 2019, 40: 4-7.

[10] Zhang W, Pan Y, Gou P, Zhou C, Ma L, Liu Q, Du Y, Yang J, Wang Q. Effect of xanthohumol on Th1/Th2 balance in a breast cancer mouse model. Oncol Rep, 2018, 39: 280-288.