

CD8 T Cell Exhaustion in Cancers And IBD

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Abstract. People are increasingly at risk of inflammatory bowel disease and tumours due to diet and lifestyle. CD8T cells are immune cells, but they are frequently depleted. So far, the relationship between CD8T exhaustion and disease is unclear, and the relationship needs to be sought for further treatment. In the study, changes in glutamine levels in CD8T cells and hepatocellular carcinoma cells were found to influence CD8T cell depletion and replicative expression in hepatocellular carcinoma. Regarding the pathogenic factors of IBD, the depletion of CD8T cells has been found to be associated with the pathogenic factors of IBD. Tumours are favoured by changes in cholesterol levels in the tumour microenvironment. In this study, we investigated the mechanism of CD8T cell depletion in inflammation and tumors.

Keywords: CD8T cells, glutamine, hepatocellular carcinoma, IBD, cholesterol.

1. Introduction

Inflammatory bowel disease (IBD) is a kind of chronic gastrointestinal inflammatory diseases of unknown cause, including ulcerative colitis (UC), Crohn's disease (CD) and indeterminate colitis (IC). IBD has become more and more common in recent years, but its pathogenesis is still not completely understood. Currently it is recognized as a multifactorial disease that may be related to genetic, environmental, immune and other factors. IBD is most common in children. It can have serious nutritional, developmental and psychological effects. The cancer presented in this article is specifically liver cancer, and the development of liver cancer is also multifactorial, influenced by both environmental and dietary factors. Early-stage liver cancer is asymptomatic, with many symptoms appearing in the middle and late stages. CD8T cells are a subset of leukocytes that have a lethal effect on viruses and cancers. It is an important line of defense for anti-tumour immunity. Exhaustion of CD8T results in its inability to function properly, reducing the collective ability to fight tumours and viruses. Preventing or reducing exhaustion may make it more likely that treatment will work

2. Glutamine metabolism in CD8T cells in killing cancer cells

CD8T subpopulation is a key lymphocyte with anti-tumour effects on the immune microenvironment of HCC and can be targeted to kill cancer cells, and previous studies have argued that high glucose metabolism in tumour cells remodels the metabolic networks and holds CD8T cells from exhibiting anti-tumour capabilities. In 2021, it was firstly found that CD8T cells are not glucose-deficient, so it is possible that high glucose metabolism is not the most important factor. In contrast, the uptake of glutamine in cancer cells is four times higher than in CD8T cells, and glutamine, which is known as an immune fuel, plays multiple roles in the immune process, including DNA and RNA synthesis. protein degradation, so it is possible that we are underestimating the role of glutamine in the fight against tumours [1].

2.1. CD8 T Cell exhaustion Turns Chronic Infections into Cancer

The exhaustion of T-cell is a general term for a phenomenon first observed in human immunodeficiency virus (HIV) patients, T-cell exhaustion leads to unsuccessful elimination of therapeutic threats. CD8T cells are a group of crucial population in cancer with the characteristic of exhaustion. In addition, it has become hypo-responsive to tumour cells. After infection with the virus,

naive CD8T cells can either further develop into short-lived effector cells (SLEC) or memory progenitor effector cells (MPEC); SLEC die while fighting the infection, while MPEC can live to develop memory for long-time immunological protects. In one experiment, mice were exposed to acute (Armstrong and WE) strains and chronic (Clone 13 and DOCILE) strains of lymphocytic choriomeningitis virus (LCMV), a rodent-borne negative-stranded RNA arenavirus. The mice were infected for more than 200 days, the T-cell receptor collapsed and CD8T cells collapsed and disappeared without memory.

2.2. High scores in genes related to glutamine metabolism are an independent risk factor in patients with HCC

Based on the TCGA sequence, 363 patients were scored for genes related to glutamine metabolism in cancer cells, which were divided into high and low expression using the median value as a cut-off, and it can be seen that the one-, three- and five- year survival rates of those with high expression were lower than those with low expression (high: 78%, 60% and 38% low: 88%, 66% and 57%), indicating that there is an association between glutamine metabolism and anti-tumour expression [2].

2.3. Analysis based on differences in glutamine metabolism

Cancerous cells and CD8T cells from the patients were extracted via glutamine metabolism related genes, the gene expression was analyzed, and results concluded that glutamine expression of cancer cells is a lot greater than that in CD8T group, so further analysis, due to the significant changes in the metabolism of glutamine between the CD8T cells, and therefore divided into different groups for observation of the experiments, it was concluded that it is the dominant occurrence of the difference in the metabolism of glutamine between the cancerous and the CD8T cells.

3. CD8 T in IBD

IBD is a type of chronic gastric disorder majorly affecting intestines and exhibits characteristics of wide-ranging effects attributed to the environment, defects in the immune system and alterations in gut microbiology in genetically predisposed individuals. It includes two major types: UC and CD, and is relevant to a large subpopulation of CD8 T cells.

3.1. Pathogenesis of IBD

Genetic, environmental and immune mechanisms are involved. Autophagy is an important part of the immune response in IBD. Firstly, genetically, NOD2 was discovered in 2001 [3], initially thought to be an intracellular receptor that recognizes the cell wall dipeptide (MDP), which regulates not only innate immunity but also adaptive immune system. IBD is associated with the IL23R gene [4], which encodes the inflammatory cytokine IL-23. In conclusion, the increased number of susceptibility loci for IBD suggests a role for both genetics and the environment, which plays an important role in regulating IBD, including smoking; smoking is negatively correlated with UC, and the application of non-steroidal anti-inflammatory drugs (NSAIDs) especially for a long-term show ability to increase the number of UC patients with IBD [5]. Innate immunity is generally unspecific and is generally triggered by recognition of biotic antigens, epithelial barrier defects and increased intestinal permeability can be observed in patients with IBD, leading to adherence of the first layer of mucosa by foreign mediators. Second, adaptive immunity, this immunity is specific in nature and Th17 cells are a group of magical population in the development of IBD.

3.2. Mechanisms of CD8T action in the intestine

It is well known that T cells have the ability to recognize specific types of CD8 T cells. Antigen presenting cells (APCs) present the information to naive T cells, which can further proliferate and differentiate into target as well as memory cells. In our gut, macrophages take antigens from the microbiome into the intestinal tissue, where they recognize them and don't attack us. CX3R1

macrophages acquire antigens by stepping up and also apoptotic intestinal epithelial cells are similar, this homeostasis is impaired and the regulation of CD8T cells in IBD has still been controversial, for example in some researches. The transcription of circulating CD8T cells in pediatric patients with active IBD was found to be independent of DNA methylation profiles. CD8T subpopulations were also found in the epithelial and lamina propria compartments [6]. In CD patients there was a decrease in CD8T in inflamed sites and an increase in non-inflamed sites. It has been suggested that CD8 Trm may be involved in UC, and also that TNF α CD8T cells have been related with fistula development in CD patients [7]. There is also an interpretation that CD8T subpopulations are divided into a number of subtypes, with regular cytotoxic CTLs, CD8 Treg, as well as Tc2, IL, Tc9 and Tc17. In the colon of IBD patients, CD8T populations have been identified exhibiting varying degrees of commitment. There is another study suggesting an association with grade, with two types of CD8T cells being clearly expressed in adult patients, but no clear expression in pediatric patients [8].

4. Cholesterol induces the exhaustion of CD8 T cell in tumour microenvironment (TME)

CD8T cells are often depleted, but the mechanisms involved are not understood, and from the report it was found that cholesterol induces CD8T cell expression and exhaustion, and tumour-infiltrated CD8T is cholesterol-rich, so cholesterol levels may affect CD8T cell exhaustion. It can be controlled by cholesterol levels. The level of inhibitory molecules including PD-1, LAG-1, 2B4, etc. Depleted CD8T cells are known be increased. In addition, cholesterol is a essential part of the membrane lipid plasma [9], and in early studies it was found that the reason for the inferior anti-tumour ability of Tc9 versus IL-8 was due to its high cholesterol content [10], and in one study it was found that cholesterol was enriched in the TME.

4.1. Cholesterol accumulation is related to CD8 T cell exhaustion in TME

In one study, the level of immune checkpoint expression in CD8T cells was positively related to the total cellular cholesterol, and the cells were classified and analyzed for apoptosis, cytotoxicity and proliferation. The results showed that CD8T cells with high PD-1 were the most exhausted, demonstrating the inhibitory response of cholesterol on CD8 cells in the TME. To determine if this is related to cancer in humans, cancer cells from patients with colorectal cancer and myeloma were extracted and analyzed, and PD-1-high CD8T cells showed the top level of apoptosis rate, and to sum up, low cholesterol levels contribute to CD8T expression.

4.2. Cholesterols accumulation and exhaustion of CD8 T cells in TME

The expression level of immunological checkpoints (eg. CD8T,1B8) of CD8T cells was positively related to cholesterol accumulation. One study showed that tumour-infiltrating metastatic (Pmel-8 CD16 T) CD8T cells underwent more apoptosis and had increased apoptosis expression compared to splenic T cells, and both models showed increased PD-1 and 2B4 expression in tumour-infiltrating metastatic CD8T cells compared to the other. Experiments in human cancers were also consistent with mice, and these results suggest that CD8T exhaustion after homing. High cholesterol content of tumour tissue leads to T-cell failure.

4.3. Cholesterol levels in the tumour microenvironment leads to CD8T cell exhaustion

In the study, the level of cholesterol were much higher in tumour tissues tissues. The depletion of CD8T cells was also higher. This indirectly suggests that high cholesterol content induces the expression of immune checkpoints on CD8T cell depletion. Two immune checkpoints PD-1 and 2B4. Both checkpoints were induced to be expressed at elevated levels in the high cholesterol environment.

5. Conclusion

The mechanism of action of CD8T cells remains controversial. And the pathogenesis of IBD and hepatocellular carcinoma is not clear, but the effect of glutamine and cholesterol on CD8T in IBD and hepatocellular carcinoma can be found from this, according to the TGGGA sequence can be concluded that there is a relationship between the expression of glutamine and the depletion of CD8T, and glutamine and the content of CD8T cells showed a negative relationship in the content of CD8T cells. The B16 metastatic lung tumour model was observed in the tumour environment. Metastatic tumours had much higher cholesterol levels than normal tumours and other models. The results suggest that cholesterol is enriched in tumour tissue. In IBD, depending on the stimulation of cytokines, co-stimulatory molecules and the TCR intensity, CD8T cells acquire various phenotypes. And there are highly distinct cell populations in IBD patients. In conclusion, the mechanisms of CD8T depletion and its own mechanisms of action on tumours and inflammation need to be investigated.

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