해부 · 생물인류학 제 36 권 제 2 호
Anat Biol Anthropol Vol. 36, No. 2 (2023) pp. 43~50
https://doi.org/10.11637/aba.2023.36.2.43

Review Article

Chronic Disease with the Immune System in Internal Organs

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Abstract : The emergence and spread of unknown pathogens, such as COVID-19, have become a major concern in recent years due to their potential to cause pandemics and threaten our quality of life. Many pathogens can trigger chronic inflammation in various organs, which is a long-term and uncontrolled immune response that can develop many other diseases, such as cancer, cardiovascular disease, ocular disease, pulmonary disease, metabolic syndrome and autoimmune disease. Immune cells, particularly macrophages and T lymphocytes, exhibit complex phenotypes in chronic inflammation, highlighting the need for the development of safe drugs or treatments that are based on a better understanding of the exact mechanisms and related immune systems involved. This review provides a brief overview of the inflammatory response and associated diseases in several organs, with the ultimate goal of aiding the development of effective strategies for managing chronic inflammatory diseases and emerging pathogens.

Keywords : Chronic disease, Immune cells, Inflammation, Autoimmune disease, Pathogens

INTRODUCTION

Inflammation is the defense mechanism in response to invading pathogens or endogenous signals, such as viruses and bacterium [1,2]. The immune system recognizes and responds to these stimuli, aiming to remove and clear them from the body [3,4]. Acute inflammation is a rapid response and is essential for tissue repair and homeostasis [5]. Unlike acute inflammation, chronic inflammation has been regarded as one of the hallmarks of cancer [6,7]. Approximately 20% of human cancers are associated with chronic inflammation, promoting tumor progression and gene mutation [8-11]. Chronic inflammation resembles and promotes the immunosuppressive environment of cancer, so it is highly related to the efficacy of immunotherapy [11,12]. Therefore, it is crucial to understand how the immune response is regulated in chronic inflammation, particularly in diseases such as pancreatitis, cirrhosis and chronic obstructive pulmonary disease (COPD).

Many immune cells are involved in chronic inflammation [13-15], which produce cytokines upon exposure to pathogens or signals, leading to an immune response [16,17]. However, the excessive inflammatory response by immune cells can result in chronic inflammation, hence requiring proper response regulation [18,19]. Among them, the regulatory T cell (Treg) is responsible for maintaining immune tolerance to prevent exaggerated immune responses [20-22]. Dysregulation or depletion of Treg can lead to severe autoimmune diseases, such as rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) [23-25]. Treg blocks and regulates other immune cells by producing immunosuppressive cytokines including, TGF-β, Interleukin (IL)-10 and IL-35, or expressing the inhibitory receptor, cytotoxic

The author(s) agree to abide by the good publication practice guideline for medical journals.
The author(s) declare that there are no conflicts of interest.
Received: May 30, 2023; **Revised:** June 14, 2023;
Accepted: June 21, 2023
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ISSN 2671-566X (Online)

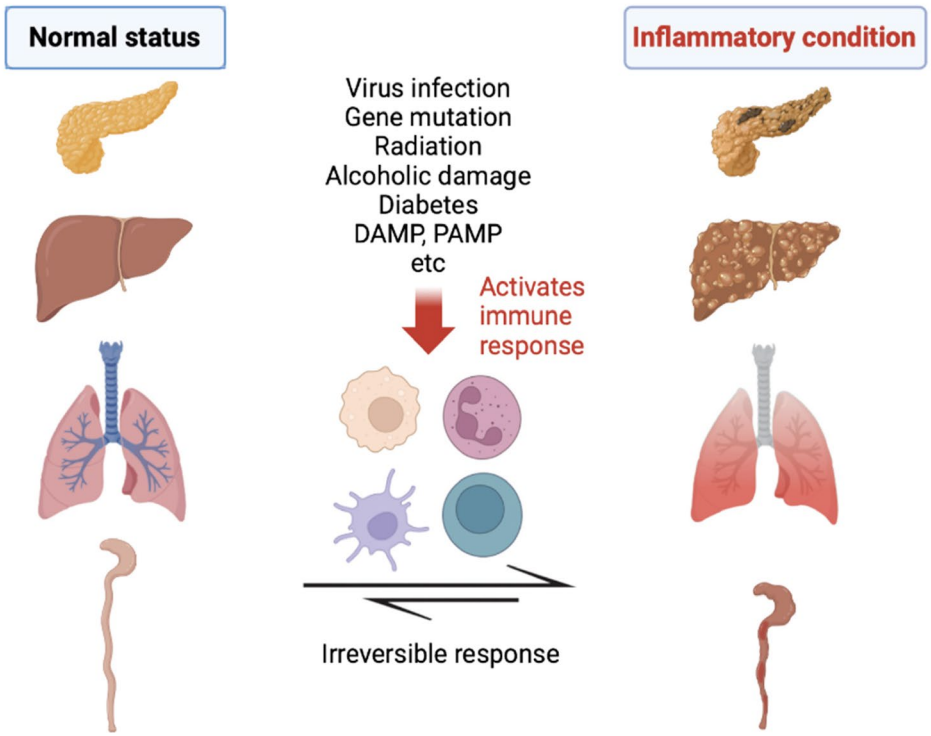

Fig. 1. Risk factors for the inflammatory response in each organ.

T lymphocyte antigen (CTLA)-4 [26,27]. However, not only Treg, the other immune cells, such as macrophages, NK cells and T cells have specific roles in the regulation of inflammatory response [28-30]. Thus, tight regulation and control of immune response are pivotal in resolving chronic inflammation. This review provides an overview of the disease with the immune system in internal organs, such as the pancreas, liver, lung and colon.

PANCREATITIS

Pancreatitis is a pathological condition characterized by irreversible fibrotic changes in the pancreas [31]. Heavy drinking, smoking and metabolic abnormalities are the main risk factors for pancreatitis (Fig. 1) [32]. Alcohol abuse is the most common cause of pancreatitis and meta-analysis provides a strong relationship between these two [33]. The main symptoms of pancreatitis, abdominal pain, nausea, fever and vomiting are not specific therefore, diagnostic tests are required to confirm the diagnosis [31]. Pancreas has both endocrine and digesting functions [34]. The main hormones secreted by the endocrine glands of the pancreas are insulin and glucagon, which regulate glucose homeostasis in the blood [35]. Pancreatitis can lead to the loss of these functions, therefore blocking and preventing pancreatitis is urgently needed.

1. The immune system in Pancreatitis

Pancreatitis involves the activation of several immune cells (Table 1). Chronic pancreatitis (CP) in both mice and humans exhibits a marked increase in CD68+ macrophages [29], whereas hereditary CP shows a high frequency of CD3+ T cells [36]. In particular, macrophages play a key role in developing pancreatitis by producing pro-inflammatory cytokines, including TNF-α, IL-1β and IL6, etc [37-39]. Interestingly, the CD4 T cell depletion model in pancreatitis reduces the severity of pancreatitis, but not the CD8 T cell depletion [28,40]. A study has shown that Treg inhibits CP by regulating the type 2 immune response, and their depletion promotes pancreas remodeling during chronic inflammation [41]. The role of natural Killer (NK) cells in pancreatitis is not yet fully studied, however, their population positively correlates with pancreatitis-related diagnostic indicators including, amylase and lipase [42].

Table 1. List of immune cells and cytokines in each organ disease

Disease	Immune cell	Secreted cytokine
Pancreatitis	Macrophage	IL-1β, IL-6, TNFα
	CD4	IL-6, TNFα
	Treg	IL-4, IL-10
Liver disease	Kupffer cell	IL-1β, TNFα, Perforin
	CD8	IL-2, IFNγ
	Treg	TGF-β
	NK cell	IFNγ, Perforin, Granzyme
COPD	Macrophage	IL-6, TNFα, GM-CSF, MMP
	CD8	IFNγ, TNFα, Perforin
	Treg	IL-10, TGF-β
	Th17	IL-17
Colitis	CD8	IL-10, IL-26, IFNγ
	Treg	IL-10, TGF-β
	Th2	IL-5, IL-13, IFNγ
	ILC2	IL-5, IL-13
	NK cell	IL-4, IFNγ

LIVER DISEASE

The liver is an important and complex organ with multiple functions for sustaining life [43]. One of its primary roles is storing glycogen as an energy source, but it also produces bile to aid in the digestion of fats and help process and eliminate alcohol from the body [44]. However, several common risk factors can lead to liver diseases, such as hepatitis viruses and excessive alcohol consumption [45]. Chronic hepatitis viruses infection can lead to severe hepatitis. Moreover, heavy alcohol intake or excessive fat accumulation can result in cirrhosis (especially, non-alcoholic steatohepatitis, NASH) (Fig. 1). Symptoms of liver diseases may include dark urine, yellow skin and eyes, weight loss and itchy skin [46]. Having this kind of liver disease for an extended period increases the risk of developing liver cancer, such as hepatocellular carcinoma (HCC) [47]. Liver cancer is the fifth most common leading cause of cancer deaths worldwide [48]. Therefore, preventing liver disease is a crucial strategy to prevent the development of HCC.

1. The immune system in hepatitis virus disease

CD8 T cell has been known as the main effector T cell responsible for viral clearance in the acute virus infection [49]. However, in chronic HBV infection, co-inhibitory receptors, such as programmed death (PD)-1 and CTLA-4, with CD8 T cell blocks the function of their cytotoxicity [50,51]. Additionally, Treg has been found to play a diverse role in hepatitis with Tregs from HBV patients being unable to expand and regulate other immune cells [52]. Conversely, other studies have shown that number of Treg is significantly increased in virus-infected patients and these cells promote virus infection and cancer progression [53,54]. Kupffer cells (KC) which are liver-resident macrophages have cytotoxic functions such as, expressed perforin and Fas-ligand [55]. Furthermore, recent research has suggested macrophages can suppress HBV replication with IL-1β secretion [56] (Table 1).

2. The immune system in cirrhosis

Immune response to cirrhosis differs from the response observed in virus-mediated hepatitis. In liver fibrosis, CD8 T cell has been found to play a promoting role by increasing the expression of the fibrotic gene and promoting fibrosis through the induction of apoptosis in hepatic stellate cells (HSCs) [30,57]. KC is also known to be pro-fibrotic effector cells by producing TNF-α and collagen 1 and its activity is correlated with attenuated fibrosis [58,59]. Treg, the main source of TGF-β cytokine, has a diverse role in fibrosis with both pro-and anti-fibrotic functions. In the CCl4 injection model, Treg regulates the immune system to protect against liver fibrosis [60]. Another study suggests that Treg expansion by rapamycin blocked HSCs activation in the CCl4-induced fibrosis model [61]. Conversely, HSCs promote Treg expansion by IL-2 dependent manner [62] and Treg protects HSCs from NK cell degranulation with TGF-β cytokine [63]. The other immune cells, NK cell acts as anti-fibrotic effector cells in liver fibrosis with NKG2D and NKp46 receptors being activated by their ligand from HSCs and inhibiting disease progression [64,65] (Table 1).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

The lungs are a pair of fresh air-filled organs located on the side of the chest to provide oxygen to the blood [66,67]. The right and left lungs are similar but asymmetrical and divided into different numbers of lobes [67]. The lobes are

further divided into specific bronchi and then into smaller branches called bronchioles [66], ultimately leading to alveoli [68]. Therefore, viruses or other pathogens can easily attack the lungs through the air passages that lead to bronchi and alveoli. COPD is an inflammatory disease caused by damage to the airway or alveolar [69]. Considering the deterioration of air pollution, there are many risk factors for COPD or other lung-related diseases [70]. According to the Global Burden of Disease (GBD), COPD is currently the third leading cause of death, and it is predicted to continue for a few more years [71]. Unfortunately, there is no drug to reduce the risk of developing COPD, making it crucial to understand the mechanism of this disease [72].

1. The immune system in COPD

Nowadays, T helper (Th) 17 and Treg are considered as key players in COPD (Table 1). COPD patients have shown high expression of Th17-related cytokines, such as IL-17. [73,74]. Moreover, there is a negative correlation between Th17 and Treg in cigarette smoke-exposed mouse model [75] and Th17/Treg imbalance is also observed in both COPD patients and healthy individuals due to decreased Treg numbers [76,77]. Macrophages also contribute to inflammation by releasing pro-inflammatory cytokines, such as IL-6, TNF-α and GM-CSF in COPD [78]. These cells also can produce metalloproteinase (MMP) which can induce an inflammatory environment [79,80]. Lastly, several studies have shown an increased number of CD8 T cells in human and mouse models of COPD with cytotoxicity [81-84].

COLITIS

The colon, also known as the large bowel or large intestine [85], is part of the digestive system that follows the small intestine [86]. Nowadays, there is a growing interest in the gut microbiota, which are permanent residents in the human intestine [87]. There are many studies about gut microbiota in an intestine, which play a crucial role in immune and metabolic homeostasis to protect against pathogens [88]. Colitis is a chronic inflammatory disease that affects the mucosal lining and is part of the group of inflammatory bowel diseases (IBDs), including Crohn's disease [89]. However, the exact causes or risk factors of colitis remain unknown. One of the most significant possible causes is an abnormal and excessive immune response [90]. Moreover, colitis is a well-known risk factor for colorectal cancer, making it essential to understand the immune system's role in colitis.

1. The immune system in colitis

Some specific interleukins, such as IL-33, are upregulated in the colitis [91-94]. IL-33 is an alarmin cytokine, which is released from mainly epithelial and endothelial cells upon cellular damage [95-98]. IL-33 can induce a pro-inflammatory response and regulate many other immune cells, including Th 2 cell, innate lymphoid cell (ILC) 2, CD8 and Treg [99-102]. IL-33 can bind to specific receptor Il1rl1 (also known as ST2), a Toll-like receptor superfamily member [103]. ST2 is mainly expressed in Th2 and Tregs compared to other immune cells [104]. IL-33 can induce GATA3 expression which is a marker and transcription factor of Th2 cells and amplify Th2 type responses [99,100]. ST2-positive Tregs are enriched in colon tissues and these Tregs promote colitis-mediated colorectal cancer development [105]. IL-33 regulates the numbers and expansion of Tregs in colon tissues, but the function of Tregs is diverse [106,107]. Therefore, further studies are urgently needed to understand the immune cells and immune responses in colitis (Table 1).

CONCLUSION

Multiple risk factors are still increasing and the etiology of several diseases continues to remain unknown. Moreover, immune cells, such as macrophages and Treg, have a controversial role in pro- or anti-inflammatory responses in different diseases. The same cytokine can trigger a different response on target immune cells because its receptor is expressed on different immune cells. The complexity of the immune response to pathogens makes drug discovery a challenging endeavor. Therefore, a deeper understanding of the mechanisms and processes by which immune cells are related to various diseases will lead to innovative ideas for developing effective therapeutic drugs to prevent and treat severe illnesses.

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