

Immune Communication between the Kidneys and Adipose Tissue

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Abstract. Traditionally, the kidneys and adipose tissue have been regarded as relatively independent organs, mainly responsible for filtration, excretion and energy storage respectively. However, with the development of modern biology, adipose tissue has been redefined as the active endocrine and the immune organ, and the kidneys are far from being merely a filter. The two are in close "dialogue" through a series of complex signal molecules. This thesis aims to systematically expound the cutting-edge scientific topic of "immune communication between renal cells and adipose tissue". First, summarize the immunological characteristics of kidney cells and adipose tissue. Under pathological conditions, obesity triggers chronic low-grade inflammation, disrupts the immune homeostasis of the kidneys, and jointly accelerates the progression of chronic kidney disease. Conversely, the uremic environment and local inflammation in the state of kidney disease can also remotely affect the function of adipose tissue, forming a vicious cycle. An in-depth understanding of kidney- adipose tissue immune communication will provide a crucial theoretical basis for recognizing metabolic kidney diseases and developing new intervention methods.

Keywords: Kidney; Adipose tissue; Immunity.

1. Introduction

The kidneys and adipose tissue are two core organs that maintain the homeostasis of the body. Kidney plays an important role in oxygen perception and other aspects by precisely regulating water, electrolytes and acid-base balance, excreting metabolic wastes and secreting hormones such as renin and erythropoietin. Adipose tissue has long been regarded as a passive energy storage reservoir. However, since the discovery of leptin in 1994, through a large number of animal experiments and clinical studies, it has been found that adipose tissue is also an endocrine organ that can secrete numerous adipokines such as leptin and adiponectin. These adipokines not only regulate appetite and energy metabolism, but also profoundly influence the immune and inflammatory states throughout the body [1-3].

At the same time, the kidneys are not immune-exempt organs. They contain resident immune cells (such as macrophages and dendritic cells), and kidney intrinsic cells (such as podocytes and renal tubular epithelial cells) themselves also have strong immune response capabilities, can express pattern recognition receptors, and produce a large number of chemokines, cytokines and adhesion molecules under stress. Actively participate in the local and systemic inflammatory processes.

Previous studies using *Drosophila* as a model have explored the immune communication mechanisms between renal cells and the fat body. By employing *sns-Gal4* and *Yp1-Gal4* drivers to target renal cells and the fat body, respectively, and crossing them with a series of RNAi lines of immune-related genes, significant bidirectional interactions between the two were observed. The loss of key immune genes in either tissue led to notable structural abnormalities in the other organ, such as cell shrinkage, disorganized arrangement, or fragmentation of the fat body. These findings collectively reveal a close functional connection between these two distal organs mediated through immune signaling pathways.

From a human perspective, under physiological conditions, renal cells and adipose tissue maintain a delicate balance through a series of signaling molecules. However, under pathological conditions of nutrient excess, obesity-related chronic inflammation may target the kidneys, disrupting their normal immune homeostasis. Meanwhile, renal cells are not merely passive victims; they can actively

respond to these inflammatory signals and, in turn, secrete immune mediators that further amplify local and systemic inflammatory responses, creating a vicious cycle [4].

Therefore, the "immune communication between renal cells and adipose tissue" constitutes a pivotal bridge connecting metabolic disorders and organ damage. This not only holds significant theoretical value but will also provide a critical theoretical foundation for developing the novel diagnostic and also the therapeutic strategies.

2. The Immune Function of the Kidneys and Related Cells

The kidneys have a complex immune microenvironment. It can also actively respond to abnormal signals and initiate new immune signals when damaged.

2.1. Macrophages

The role of macrophages in inflammatory responses is regulated by their polarization states. The dynamic balance between classically activated macrophages (M1) and alternatively activated macrophages (M2) is crucial for maintaining normal inflammatory reactions. When macrophages are activated, a shift from anti-inflammatory M2 to the pro-inflammatory M1 phenotypes occurs. M1 macrophages drive renal inflammatory responses, oxidative stress, and cell apoptosis by releasing factors such as the IL-6 and TNF- α . They also promote the activation of myofibroblasts, leading to renal interstitial fibrosis and sclerosis. Additionally, while phagocytosing pathogens and cellular debris to clear foreign substances, they can simultaneously exacerbate tissue damage. Previous studies have shown that inhibiting macrophage recruitment or activation through pharmacological means (e.g., mycophenolate mofetil) or genetic approaches (e.g., Op/Op mice) significantly alleviates renal injury [5].

2.2. Renal Tubular Epithelial Cells

Studies have reported that renal tubular epithelial cells are highly susceptible to damage under various pathological conditions, such as the oxidative stress, secretion of inflammatory mediators and soon. Damaged renal tubular epithelial cells can release various cytokines (such as TNF- α , TGF- β 1, uromodulin, Wnt ligands, etc.) to promote inflammatory responses and even lead to cell death. For instance, TNF- α increases in the early stages of inflammation, stimulating the secretion of leukocyte adhesion molecules, increasing the expression of IL-6, stimulating renal mesangial cells to produce oxygen free radicals, causing damage to the basement membrane, destroying glomerular mesangial cells, accelerating glomerulosclerosis, altering local microvascular permeability in the glomerulus, and increasing the production of proteinuria [6,7].

2.3. Podocytes

It is an important cell in the glomerulus of the kidney and an active participant in both innate and adaptive immunity within the kidney. In innate immunity, podocytes express various Toll-like receptors (such as TLR3, TLR4) and RIGI-like helicases, enabling them to directly sense pathogen-related molecular patterns, such as bacterial lipopolysaccharides or viral double-stranded RNA, thereby triggering pro-inflammatory signaling pathways, leading to cytoskeletal rearrangement and damage to the filtration barrier. In adaptive immunity, podocytes become the core targets due to the expression of unique autoantigens such as PLA2R1 and THSD7A on their surfaces. Autoantibodies in circulation bind to them to form in situ immune complexes, activate the complement system, and eventually form the membrane attack complex C5b-9, which inserts into the podocellular cell membrane, causing subsoluble injury, proteinuria and typical podocellular process fusion. In addition, podocytes can upregulate MHC Class II molecules under inflammatory conditions, possess potential antigen-presenting capabilities, and secrete chemokines (such as CXCL12) and cytokines, actively recruiting and regulating immune cells, thereby intensifying local inflammatory responses [8].

When kidney damage occurs, such as ischemia-hypoxia, it may lead to a rapid depletion of ATP, triggering mitochondrial damage and release of contents. This, in turn, cleaves and produces the mature pro-inflammatory factor IL-1 β , inducing tubular cells to secrete various chemokines. Secondly, the stable activation of hypoxia-inducible factor HIF-1, which typically acts as a transcription factor to directly upregulate the gene expression of various cytokines and chemokines. Furthermore, during reperfusion, oxygen free radicals (such as hydrogen peroxide) emerge as signaling molecules, activating the p38 MAPK signaling pathway. This, in turn, drives the activation of key transcription factors like NF- κ B and AP-1, ultimately promoting the large-scale production of chemokines. These three pathways collectively convert hypoxia stimuli into strong inflammatory signals, setting the stage for subsequent leukocyte infiltration and tissue damage (such as adipose tissue). Additionally, erythropoietin (EPO) not only promotes hematopoiesis but also has immunomodulatory effects. However, in CKD, EPO resistance and abnormal signaling may be involved in regulating immune cell function, potentially indirectly affecting adipose tissue [9].

3. Adipose Tissue Serves as an Immune Organ

3.1. Structure and Immunomodulatory Function of Adipose Tissue

Adipose tissue is a dynamic organ with a complex structure and active immune regulatory function. Traditionally, it is mainly classified into white adipose tissue and brown adipose tissue based on morphology and function. The latter is rich in mitochondria and is responsible for heat production and energy supply. In addition, there is beige fat transformed from white fat through cold exposure and other stimuli, as well as pink fat that is specific to the lactation period. In terms of cellular composition, adipose tissue is not solely composed of mature adipocytes that store lipids. Mature adipocytes account for only 15% to 30% of the total number, while the majority (70% to 85%) are vascular stromal components, which include preadipocytes, stem cells, endothelial cells, and a rich variety of immune cells. Immune cells include innate immune cells (such as TNF- α , TGF- β 1, uromodulin, Wnt ligands, etc.) and adaptive immune cells. In addition, adipose tissue also possesses unique immune structures, such as adipose-associated lymphocyte clusters [10-12].

Anti-inflammatory M2 macrophages help maintain insulin sensitivity and participate in tissue repair. Crown-like macrophages surrounding adipocytes are responsible for clearing apoptotic cell debris, thereby preventing inflammation. Sympathetic neuron-associated macrophages interact with nerve fibers and may be involved in regulating thermogenesis. Additionally, invariant natural killer T (iNKT) cells can bind to CD1d molecules on the surface of adipocytes, promoting the secretion of anti-inflammatory cytokines such as the IL-4/10, thereby fostering an anti-inflammatory milieu. Eosinophils and type 2 innate lymphoid cells are crucial regulators of adipose tissue homeostasis. The cytokines they secrete, including IL-4/13, are key signals that promote the transformation of macrophages to the M2 anti-inflammatory phenotype [11].

3.2. Adipose Tissue Inflammation Related to Obesity

Inflammation induced by obesity is fundamentally different from traditional inflammation and is not accompanied by typical clinical manifestations such as "redness, swelling, heat and pain", and thus is defined as "chronic low-grade inflammation", which is specifically manifested in the following three aspects:

Firstly, obese patients exhibit significant changes in serum adipocyte-derived inflammatory factors, manifested as increased levels of pro-inflammatory factors (such as the leptin, IL-1, and TNF- α) and significantly decreased the anti-inflammatory factor adiponectin [13]. Additionally, leptin, an informational peptide hormone encoded by the leptin gene and secreted by white adipose tissue, can suppress the appetite and also increase the energy expenditure. Leptin also participates in immune regulation of monocytes and macrophages (enhancing monocyte proliferation and macrophage phagocytosis, as well as the pro-inflammatory factors production and in the activation of T lymphocytes. When obesity occurs, the stimulatory effect of leptin on fat energy expenditure may be

limited, leading to increased levels of leptin in the body and triggering a series of inflammatory reactions [14,15]. Adiponectin is an endogenous bioactive polypeptide or protein secreted by adipocytes, closely related to energy metabolism and insulin resistance in the body, and has a protective effect on diseases such as inflammation and vascular sclerosis. Its levels are often lower in obese individuals, which may exacerbate inflammatory damage [16].

Secondly, when the volume of fat cells increases to a certain limit, they will undergo apoptosis due to the dual effects of mechanical stress from the extracellular matrix and local hypoxia. Macrophages in white adipose tissue can recognize and eliminate apoptotic adipocytes, forming what is called a "coronal structure", which is regarded as an important biological marker of adipose tissue inflammation [17]. However, in an obese state, the number of "M1-type" macrophages in the coronal structure relatively increases, while regulatory T cells and the anti-inflammatory factor interleukin-10 relatively decrease, thereby inducing chronic low-grade inflammation.

Thirdly, the elevated level of lipopolysaccharide (LPS) in obese patients can further promote the expression of inflammatory factors by activating nuclear transcription factor κ B (NF- κ B) and binding to Toll-like receptors (TLR). Meanwhile, visceral fat can prompt the inflammasome NLRP3 to release IL-1 β , and the increased free fatty acids activate signaling pathways such as Jun N-terminal kinase (JNK), inhibitory κ B kinase (IKK), and NF- κ B. Among them, the binding of long-chain fatty acids to TLR can further trigger inflammatory responses, while the activation of JNK and IKK will aggravate insulin resistance (IR), forming a vicious cycle and continuously worsening the inflammatory state [18].

In another animal experiment, an obese mouse model was established through high-fat diet induction. The study systematically compared the differences in gene expression related to inflammatory responses among three types of adipose tissues as well as the underlying mechanisms. The results indicated that the ITGAD gene (involved in regulating fat metabolism) was significantly upregulated in all three tissues, suggesting its potential central role in obesity-related inflammation [19].

4. The Immune Imbalance between Obesity and Kidneys is the Core Pathological Basis of Many Diseases

4.1. Obesity-related Nephropathy (ORG)

The obesity rate among patients with kidney diseases worldwide can reach 20% to 25% [20]. A large-scale cohort study has shown that ORG accounts for approximately 15% to 30% of chronic kidney diseases (CKD). In the early stage, the clinical manifestations are proteinuria of varying degrees, and in the late stage, it can be manifested as a decrease in the glomerular filtration rate until end-stage renal failure. Its pathological features are simple glomerular hypertrophy (O-GM) and/or focal stage glomerular sclerosis (O-FSGS). Obesity accompanied by increased leptin levels further enhances sympathetic nerve excitability, leading to increased vascular tension, sodium reabsorption, and high filtration in the kidneys. Additionally, elevated resistin levels also raise the levels of various inflammatory cytokines. In addition, obesity accelerates the senescence of adipose tissue cells, and the age-related secretory phenotype (SASP) it releases further amplifies local and systemic inflammation, directly damaging renal function [21,22].

4.2. Diabetic Nephropathy

Diabetic nephropathy is one of the major complications of diabetes, affecting approximately 33.3%-50% of diabetic patients, which has become one of the main causes of CKD and end-stage renal disease [23].

The abnormal metabolic changes caused by obesity are one of the core factors accelerating the progression of diabetic nephropathy. On the one hand, obesity can lead to insulin resistance, which promotes elevated blood glucose levels, further increasing the burden on the kidneys. On the other

hand, under obese conditions, the secretion of adipokines such as the leptin and TNF- α activates the renin-angiotensin-aldosterone system and sympathetic nerves, leading to glomerular hyperfiltration, insulin resistance, and oxidative stress, directly damaging glomerular endothelial and mesangial cells. Perirenal fat tightly surrounds the kidneys and its thickening not only increases renal interstitial pressure and affects renal blood flow through physical compression, but also exacerbates inflammation through local adipokine dysregulation (such as leptin promoting glomerular cell proliferation) and macrophage infiltration. Renal sinus fat accumulation directly compresses the intrarenal sinus vessels and collecting system, increases renal vascular resistance, alters renal hemodynamics [24].

Clinically, by improving the symptom characteristics and diabetes-related indicators of obese patients, the progression of diabetic nephropathy can be effectively delayed, and the clinical treatment effect can be enhanced.

4.3. Changes in Adipose Tissue Caused by Uremia

When CKD progresses to the uremia stage, the accumulated uremic toxins in the body inherently possess pro-inflammatory properties. They can remotely affect adipose tissue, further exacerbating its inflammatory state and insulin resistance. A clinical study, by comparing and analyzing the fat and muscle tissues of 18 patients with end-stage renal disease (ESRD) and 6 controls with normal renal function, showed that the infiltration of macrophages in the subcutaneous and visceral adipose tissues of ESRD patients was significantly increased, even in non-obese individuals, indicating that uremia itself can trigger adipose tissue inflammation independently of obesity. The primary reason is that the accumulation of uremic toxins directly activates the immune response, while the kidney's reduced ability to clear inflammatory factors. Furthermore, adipocytes in the uremic state secrete more pro-inflammatory factors and are in a state of oxidative stress, collectively creating a microenvironment that continuously recruits macrophages [25].

Meanwhile, another study explored the impact of uremia (advanced CKD) on the phenotype of human subcutaneous adipose tissue. Fat samples from 71 surgical patients were prospectively collected, and the levels of 10 biological mediators, including leptin, adiponectin and resistin, were evaluated through protein analysis. It was found that compared with non-uremic patients, the levels of leptin and adiponectin in the adipose tissue of uremic patients were significantly decreased (by 10% and 33.3% respectively), while resistin increased by three times. Multivariate regression analysis showed that uremia was the strongest predictor of changes in the levels of these three fat hormone. Histological examination also revealed structural changes such as fibrosis and increased microvessel density in adipose tissue of patients with uremia. Studies have shown that uremia directly disrupts the biology of adipose tissue, leading to abnormal hormone expression [26].

5. Conclusion

In a word, the immune communication between the kidney and adipose tissue constitutes a dynamic, bidirectional, and highly complex physiological and pathological network. It serves as a crucial bridge for maintaining metabolic-immune homeostasis in the body and is also an important hub for the development of diseases. Under physiological conditions, this dialogue may be involved in the fine regulation of energy metabolism, water-salt balance, and local immune surveillance. However, under metabolic stress such as obesity, dysfunctional adipose tissue continuously impacts the kidney by releasing excessive pro-inflammatory adipokines, cytokines, and other signals, activating its innate immune response, recruiting inflammatory cell infiltration, and impairing renal function. Simultaneously, the ensuing uremic environment and systemic inflammation caused by chronic kidney disease further adversely affect adipose tissue function, forming a vicious cycle that is difficult to break and accelerates organ functional decline. Although current research has outlined the core contours of this axis, it still faces many serious challenges: for example, most existing knowledge is derived from animal models, which have inherent limitations in perfectly simulating

the complexity of human diseases; the specific mechanisms of action of many molecules involved in communication, especially their precise functions in specific cell types, are still poorly understood; the evidence chain for the details of "reverse signaling" by which the kidney reversely affects the immune status of adipose tissue is still weak; in addition, translating basic research findings into clinically effective targeted therapeutic strategies, such as precisely regulating specific adipokines or avoiding systemic immunosuppression, remains a long way off. To break through these bottlenecks in the future, multidimensional efforts are urgently needed to deeply analyze the causal effects of key signaling molecules and verify their clinical relevance; actively seek specific biomarker combinations that can reflect the state of this communication axis for early warning and classification of diseases; and design and conduct targeted clinical trials to verify novel therapies targeting specific communication nodes, fundamentally interrupting this vicious cycle and opening up new and precise treatment pathways for the prevention and treatment of related diseases.

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