STAMP2 in Diabetes, Inflammatory Diseases and Cancers

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STAMP2 plays a pivotal role in the pathogenesis of type II diabetes, inflammation and cancers. The six transmembrane protein of prostate 2 (STAMP2), a metalloreductase involved in iron and copper homeostasis, is well known for its critical role in the coordination of glucose/lipid metabolism and inflammation in metabolic tissues. STAMP2 is a critical modulator for coordinating metabolism and inflammation. Although STAMP2 has been widely studied focusing on the inhibitory role in inflammation and metabolism, the underlying mechanism is not fully understood. In addition to its role in metabolism and inflammation, STAMP2 is also associated with tumorigenesis. For example, STAMP2 overexpression may increase ROS, which may contribute to increased mutational rates and further progression of prostate cancer.

Keywords: NAFLD ; STAMP2 ; metalloreductase ; iron homeostasis

1. STAMP2 and Type 2 Diabetes

Nonalcoholic fatty liver disease (NAFLD) is present in >70% of individuals with type 2 diabetes [1]. Impairment of glucose and lipid metabolism, which has been accelerated by the worldwide increase in the prevalence of obesity and type 2 diabetes, is most likely behind the increase in patients with NAFLD [2]. Insulin resistance underlies both obesity and type 2 diabetes. Insulin activates the PI3 K/Akt pathway, which is responsible for insulin-stimulated glucose uptake. In response to insulin, phosphatidylinositol 3-kinase (PI3 K) is activated, which leads to the phosphorylation of Akt. Phosphorylated Akt induces GLUT4 translocation to the plasma membrane, which directly increases glucose transport into cells [3]. Previous studies showed that STAMP2 affects insulin-stimulated GLUT4 translocation and glucose transport by targeting the PI3 K/Akt signaling pathway in human adipocytes [4][5]. Cheng et al. found that STAMP2 deficiency significantly reduced GLUT4 translocation, glucose uptake, and the phosphorylation levels of PI3 K (P85) and Akt [4]. A loss of function study using a STAMP2 antibody also showed a decrease in the insulin-stimulated tyrosine phosphorylation of the insulin receptor substrate (IRS)-1, phosphorylation of PI3 K (P85), and Akt [5]. JNK is an important mediator of insulin resistance too. Activation of JNK decreases insulin activity [3]. In diabetic ApoE-/-/LDLR-/- mice, the phospho-JNK/JNK ratio was increased in white adipose tissue (WAT) and BAT, but overexpression of STAMP2 significantly decreased the ratio of phospho-JNK/JNK [6]. In the previous study, while liver-specific knockdown of Stamp2 by in vivo siRNA delivery increased insulin resistance, overexpression of hepatic STAMP2 improved HFD-induced insulin resistance [7]. These results suggest that the STAMP2 gene is involved in the pathogenesis of type 2 diabetes.

2. STAMP2 and Inflammatory Diseases

Dysregulation of STAMP2 has been implicated in various inflammatory diseases, including obesity [8][9][10][11], rheumatoid arthritis (RA) [12][13][14], and atherosclerosis [15][16]. The expression of TNFα in the synovia correlates with the progression of joint swelling in both murine models and arthritis patients. STAMP2 expression is observed in the synovium of rheumatoid arthritis. STAMP2 is induced in synovia by TNFα [12][13][14]. In addition, RA-like pathology was observed in Stamp2 knockout mice [12]. A marked increase in atherosclerotic lesion area was demonstrated in the aortas of Stamp2-/-ApoE-/- mice, a model system to study atherosclerosis. Stamp2 is detected in mouse and human atherosclerotic plaques and its deficiency promotes atherosclerosis in mice. These findings suggest a role for STAMP2 in protecting against atherosclerosis [16]. STAMP2 expression was previously detected in circulating monocytes and its expression correlated with the macrophage marker CD68 [8]. Furthermore, adenoviral overexpression of Stamp2 in ApoE-/-LDLR-/- diabetic mice suppressed atherosclerosis by preventing macrophage apoptosis [15].

STAMP2 integrates inflammatory and nutritional signals with metabolism, which is supported by the loss of STAMP2 function, both in vitro and in vivo results, in elevated inflammatory markers, diminished insulin sensitivity, and dysfunctional glucose uptake. Stamp2 knockout mice also exhibit an increased number of macrophages [10][17][18].

STAMP2 may counter-regulate insulin resistance through regulating macrophage polarization in visceral adipose tissue (VAT) and BAT [6]. In contrast, STAMP2 overexpression actively protects adipocytes against inflammatory challenges. STAMP2 overexpression reduces rates of atherosclerosis and plaque formation in diabetic mice, while STAMP2 deficiency promotes atherosclerosis [15]. Similarly, STAMP2 overexpression reduces the migration of neutrophil-like HL60 cells [19] and reduces IL-6 and IL-8 cytokine expression, whereas siRNA knockdown of STAMP2 increases cytokine signaling in patients with rheumatoid arthritis (RA) [12], again, consistent with a role for STAMP2 in a negative feedback loop. These protective effects have also been observed at the systemic level. STAMP2 also exerts anti-inflammatory activity in other tissues, most notably, the liver. Hepatic STAMP2 appears to be a target of STAT3, which is known for negatively regulating hepatic gluconeogenic gene expression, thus, playing a protective role in hepatic insulin signaling [20][21]. This suggests that STAMP2 conducts protective activity in maintaining insulin signaling in the presence of obesity and inflammation signals. STAMP2 also controls macrophage inflammation by controlling NADPH homeostasis [16].

3. STAMP2 and Cancers

STAMP2 was originally identified as a gene that had sequence similarity to STAMP1 and high expression in the prostate. It was then found to be regulated by androgens, with increased mRNA levels in PCa cells compared with normal prostate cells [22]. Several studies revealed the association of STAMP2 with prostate cancer. STAMP2 overexpression induced an increase in number and size of the PC-3 cell line and increased growth of COS7 and DU145 cells [22]. STAMP2 knockdown induced apoptosis and cell cycle arrest and markedly inhibited the growth of PCa cell lines, including LNCaP, VCaP, and 22 Rv1, both in vitro and in vivo [23]. Additionally, another recent study suggested that STAMP2 knockdown inhibits the proliferation of prostate cancer cells through the activation of the cGMP-PKG pathway in an inflammatory microenvironment [24].

STAMP2 has been recently reported to be involved in other cancers as well. Wu et al. found in keratinocytes that STAMP2 expression is regulated by IL-17 to be known to promote cancer [25]. STAMP2 was critical for IL-17-induced proliferation in cultured keratinocytes. STAMP2 was required for IL-17-dependent sustained activation of the TRAF4-ERK5 axis for keratinocyte proliferation and tumor formation. Further work is needed to understand the details of how STAMP2 affects keratinocyte biology and tumorigenesis. Orfanou et al. found that STEAP4 expression was obvious only in malignant breast tissues, whereas all benign breast cases had no detectable levels. Furthermore, knockdown of STEAP4 also suppressed cell proliferation and enhanced the pharmacological effect of lapatinib (HER2 inhibitor) in HER2-overexpressing breast cancer [26], confirming its potential oncogenic role in breast cancer. These results in various cancers demonstrate that the growth-inducing and anti-apoptotic roles of STAMP2 are needed for carcinogenesis. On the other hand, another study investigated RNA-seq in hepatocellular carcinoma (HCC) between GSE54503 and TCGA datasets and showed that STAMP2 expression was reduced in HCC tissues and that STAMP2 inhibited the proliferation and metastasis of HCC cells. These findings indicate that STAMP2 functions as a tumor suppressor gene in HCC [27].

Therefore, the differential expression of STAMP2 in normal and cancer tissue makes STAMP2 a potential candidate as a biomarker or a therapeutic target for cancer

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