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Cellular Senescence, Insulin Resistance, and CDKN2B: An Intrinsic Connection in Metabolic Diseases

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Abstract: This review summarizes the pivotal roles of insulin resistance (IR) and cellular senescence in metabolic diseases, focusing on how adipocyte and hepatocyte senescence promote IR and the progression of type 2 diabetes through the senescence-associated secretory phenotype (SASP) and key signaling pathways (e.g., p53, Akt/FoxO1). The article further focuses on the cell cycle regulatory gene CDKN2B and its non-coding RNA (CDKN2B-AS), elucidating their expression alterations and genetic susceptibility in various metabolic diseases including atherosclerosis, coronary heart disease, polycystic ovary syndrome, and diabetes. Although the role of CDKN2B in aging and metabolic regulation remains unclear, existing evidence suggests it may exert complex and critical regulatory effects on the pathogenesis of metabolic diseases by influencing insulin resistance patterns and tissue-specific senescence phenotypes. Future research should further elucidate the functional differences of CDKN2B and its isoforms across various tissues and disease states.

Keywords: Insulin Resistance; Cellular Senescence; Adipocyte Aging; CDKN2B; CDKN2B-AS; Type 2 Diabetes; SASP; Metabolic Diseases.

1. Introduction

Insulin resistance (IR) is an extremely common clinical phenomenon and serves as the pathophysiological basis for chronic metabolic diseases such as Type 2 diabetes(T2D), Polycystic Ovary Syndrome (PCOS), Non-alcoholic Fatty Liver Disease (NAFLD), and Atherosclerotic Heart Disease (ASCVD). In China, the standardized prevalence of insulin resistance among adults aged 25 years and older is 29.22% [1]. Obesity and associated inflammation can exacerbate Insulin resistance, increasing the risk of chronic metabolic diseases [2], severely impacting public health and adding to the societal burden.

Cellular senescence is a multifaceted state in which cells cease division while maintaining metabolic activity, leading to altered cellular phenotypes [3]. Although senescence exerts beneficial effects in tissue development, repair, and tumor suppression [4], the accumulation of senescent cells exerts detrimental effects on tissue homeostasis and induces inflammatory responses [5]. Growing evidence indicates that senescent cell accumulation is closely linked to metabolic dysregulation. The senescence-associated secretory phenotype (SASP) correlates with elevated pro-inflammatory cytokines, extracellular matrix degrading enzymes, and certain metabolites. Through autocrine and paracrine mechanisms, SASP amplifies and propagates senescence, thereby promoting chronic inflammation.

2. Adipocyte Aging and IR

Adipose tissue is the largest and most active endocrine organ in the human body, playing a pivotal role in regulating energy balance and maintaining homeostasis in glucose and lipid metabolism. Aging adipose tissue exhibits impaired lipid processing capacity, inducing insulin resistance , reduced adaptive thermogenesis, and abnormal adipokine production. Concurrently, it disrupts the normal physiological functions of distant tissues or organs through the senescence-associated secretory pattern .

Significant increases in IL-1β expression, a SASP factor, are observed in adipose tissue of obese patients [6]. It is well established that elevated IL-1β levels can induce the development of insulin resistance (IR) [7]. Similar to normal human aging, aged adipocytes accumulate extensively in obese and diabetic mouse models as well as in humans [8, 9].In obese individuals, chronic inflammation, ectopic lipid accumulation, and cellular senescence all contribute to increased insulin resistance (IR) [10, 11]. IR is one consequence of adipose tissue senescence, particularly following p53 activation. Induced expression of p53 in adipose tissue of obese individuals promotes adipocyte senescence and is also associated with IR [8].Overexpression of p53 induces aging and insulin resistance (IR) in diabetic animal models, whereas suppression of p53 expression produces the opposite effect in these models [8, 12]. Significant accumulation of senescent cells is observed in the white adipose tissue of prematurely aging mice, obese mice [2], and elderly obese humans [9]. Interestingly, transplanting white adipose tissue from prematurely aging or obese mice into normal mice similarly induces insulin resistance and promotes diabetes, suggesting that adipose tissue senescence is a contributing factor to insulin resistance and diabetes [8].

3. Hepatocyte Senescence and IR

Under the influence of insulin, hepatocytes can absorb and convert glucose, storing it as glycogen or lipids while simultaneously inhibiting gluconeogenesis to regulate blood glucose homeostasis. Hepatocyte senescence is closely associated with increased physiological lipid deposition in liver cells, leading to lipid-induced toxic injury and impairing normal liver function. Aged hepatocytes play a crucial role in the pathogenesis of chronic liver diseases, with approximately 80% of hepatocytes exhibiting senescent phenotypes in such conditions [13]. Under normal circumstances, insulin

regulates glucose uptake and conversion by activating the PI3K/Akt signaling pathway, while simultaneously storing glucose as glycogen. Aged hepatocytes exhibit significantly higher Akt phosphorylation compared to normal hepatocytes, leading to reduced As160 phosphorylation and diminished GLUT4 translocation to the cell membrane, thereby impairing glucose uptake. Concurrently, aged hepatocytes show decreased FoxO1 phosphorylation, resulting in weakened nuclear exclusion of FoxO1 under insulin stimulation. This promotes the expression of gluconeogenic genes and increases gluconeogenesis [14]. Conversely, obesity, T2D, and even chronic hyperinsulinemia can accelerate hepatic cellular senescence [15, 16]. Thus, a bidirectional relationship between hepatic senescence and diabetes appears plausible, though the precise mechanisms remain unclear.

4. CDKN2B and Metabolic Diseases

The Ink4a/Arf/lNK4b locus contains cyclin-dependent kinase inhibitor 2A (CDKN2A, encoding tumor suppressor proteins p16INK4a and p14ARF) and cyclin-dependent kinase inhibitor 2B (CDKN2B, encoding tumor suppressor protein p15INK4b). Both p16INK4a and p15INK4b function as inhibitors of the cell cycle and are highly expressed in senescent cells [17]. While p16INK4a and p14ARF have been extensively studied in tumor and aging research, understanding of p15INK4b remains limited. Beyond tumor and aging research, current studies on CDKN2B primarily focus on atherosclerosis and cardiovascular/cerebrovascular diseases. CDKN2B is believed to regulate atherosclerosis [18]. Knockout of CDKN2B promotes atherosclerotic progression [19], and reduced CDKN2B expression is observed in atherosclerotic plaques [18]. In ischemic stroke patients, higher CDKN2B methylation correlates with more pronounced aortic arch calcification [20]. These findings collectively suggest that CDKN2B may influence the onset and progression of atherosclerosis. Individuals with high CDKN2A methylation exhibited a lower average age compared to those with low methylation. Conversely, individuals with high CDKN2B methylation demonstrated a significantly higher average age than those with low methylation. Additionally, CDKN2B methylation was higher in females than males, whereas CDKN2A methylation levels showed no gender difference. Gender is a critical variable requiring consideration in chronic disease research, including coronary heart disease. The prevalence and incidence rates of cardiovascular events differ between men and women [21]. A study reported that women with a low triglyceride/high-density lipoprotein cholesterol (TG/HDL) ratio exhibited a significantly lower incidence of CHD compared to men with a low TG/HDL ratio [22]. Furthermore, CDKN2B polymorphism is closely associated with an increased TG/HDL ratio [23]. Therefore, although the methylation levels of CDKN2A and CDKN2B are not correlated with the risk of CHD, the authors still believe that differences in CDKN2B methylation levels may be risk factors for CHD in the elderly and women [24].

The Ink4a/Arf/lNK4b locus also contains a long non-coding RNA, CDKN2B-AS (also known as ANRIL), which silences p15 transcription by mediating H3K27 trimethylation. Studies reveal significantly elevated CDKN2B-AS expression in atherosclerotic plaques, which accelerates lipid uptake and intracellular lipid deposition by suppressing CDKN2B expression, thereby promoting foam cell formation [25]. Concurrently, CDKN2B-AS has been found to be highly expressed in patients with polycystic ovary syndrome [26]. However, other studies have reported low expression of CDKN2B-AS in atherosclerotic plaques. We found that CDKN2B-AS binds to DNMT1 in the nucleus to increase methylation of the ADAM10 promoter, thereby suppressing inflammation. Decreased expression of CDKN2B-AS promotes inflammation and exacerbates atherosclerosis [27].

These findings suggest that decreased CDKN2B expression levels or transcriptional suppression are closely associated with coronary atherosclerotic disease. However, research outcomes regarding the role of CDKN2B antisense oligonucleotides (ASOs) in atherosclerotic diseases remain inconsistent. Studies have identified multiple subtypes of CDKN2B-AS [28], with circular CDKN2B-AS expression associated with antiproliferative effects and protection against cardiovascular events [29-31]. In an aging model induced by the oncogene RAF1, the regulation of CDKN2B transcription by circular CDKN2B-AS shifted from inhibition to activation [32]. Therefore, we hypothesize that the variability in CDKN2B-AS research outcomes in atherosclerosis may be related to its subtypes, as different CDKN2B-AS subtypes exert distinct regulatory effects on CDKN2B transcription.

Insulin resistance serves as a common pathogenic substrate for coronary heart disease, polycystic ovary syndrome, and diabetes. Research indicates that both adipocyte and hepatocyte senescence can lead to insulin resistance. However, CDKN2B expression is downregulated in atherosclerotic plaques and foam cells associated with coronary heart disease and ischemic stroke, as well as in granulosa cells from patients with polycystic ovary syndrome. These divergent findings suggest that aging phenotypes in diseased tissues/organs differ from normal human aging. The impact of CDKN2B expression variations across tissues on organ function and disease progression requires further experimental validation.

5. CDKN2B and IR

CDKN2B is one of the currently identified genetic susceptibility genes for diabetes [33], and different genetic polymorphisms of CDKN2B exhibit varying susceptibility effects in diabetes and insulin resistance. Cohort studies have identified CDKN2B genetic polymorphisms as high-risk factors for type 2 diabetes and hypertriglyceridemia [23, 34]. In patients with familial hyperlipidemia, significantly increased CDKN2B gene expression has also been observed [35], and CDKN2B variants correlate with HOMA-IR [36]. GWAS indicates that CDKN2B-AS is a genetic susceptibility locus for type 2 diabetes. Diabetes-associated risk variants in the 9p21 region (rs10811661-T and rs2383208-A) are closely associated with downregulation of CDKN2B-AS expression [37].

6. Conclusion

Although studies on the role of CDKN2B and CDKN2B-AS in insulin resistance (IR) remain limited, current research on the association between CDKN2B and diabetes, along with the role of CDKN2B-AS in atherosclerotic diseases, suggests that CDKN2B undoubtedly plays a crucial regulatory role in insulin resistance. Selective insulin resistance manifests as isolated hyperglycemia without hypertriglyceridemia. CDKN2B expression decreases or transcription is suppressed in atherosclerotic diseases.

Conversely, increased CDKN2B expression is observed in hyperlipidemic patients. Consequently, we hypothesize that CDKN2B's regulation of insulin resistance may influence its subtypes. Whether the relationship between CDKN2B and diabetes is linked to cellular senescence remains to be verified through further experimental studies.

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