

Cellular Senescence In White Adipose Tissue of Obese Mice

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Abstract: Obesity is defined as excessive fat accumulation that presents as risk factor for various chronic diseases such as diabetes, cardiovascular disease, hypertension, hyperlipidemia, and cancer. The number of obese population has reached 1 trillion people worldwide and is expected to increase at 42% of the world population until 2030. Excess calories in obesity increase the formation of Reactive Oxygen Species (ROS) that cause DNA damage. DNA damage results in inhibition of the cell cycle and lead to cellular senescence. The mechanism of cell senescence caused by cell cycle inhibition can occur through the cellular senescence pathway by p53/p21 WAF1/CIP1 and p16INK4A / pRB. White adipose tissue is an appropriate reservoir to study of cellular senescence. White adipose tissue of obese model mice showed that there was cellular senescence with marked increase in p21 and p16 gene expression in obese mice]

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Introduction

Obesity is a global health problem in the world. The population with obesity has increased significantly in the last decade. By 2030 it is estimated that 51% of the world's population will be obese, consisting of 42% of people who are overweight and 11% of people with severe obesity [1]. In Indonesia, the percentage of people who experience excess body fat has increased also in the poor population groups and households. It is known that 1 in 3 adults, 1 in 5 school-age children, and 1 in 7 adolescents aged 13-18 years are overweight and obese.

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This increase is associated with bad habit on diet, low activity level, easy and inexpensive access to high-fat, sugar, salt consumption and poor availability of quality active mobility infrastructure [2].

Obesity occurs when there is excessive accumulation of body fat caused by the amount of energy entering through food is greater than the energy used. Based on the Basal Metabolic Index (BMI), obesity is categorized into class I obesity if BMI is 30-34.9 kg/m², class II obesity if it is 35 - 39.9 kg/m², and class III obesity if > 40 kg/m² [3]. Obesity is associated with various health problems such as cardiovascular disorders, dyslipidemia, and insulin resistance which can then cause diabetes, stroke, gallbladder stones, fat accumulation in the liver, obesity-related hypoventilation syndrome, sleep disorders, cancer and impaired fertility [4]. In addition, in children, consumption of diet that contain high fat and sugar causes early diabetes, high blood pressure, psychosocial problems, and low learning achievement, as well as the risk of life-threatening non-communicable diseases when they become adults such as heart disease, stroke and cancer [2].

There is a correlation between obesity and cellular senescence. Obesity is proven to shorten a person's life by 7.1 years in women and 5.8 years in men. Excess calories increase the formation of reactive oxygen species (ROS) through excessive production of NADH and FADH₂ [7]. Increased oxidative stress and inflammation in obesity can induce DNA damage and inhibit cell cycle and DNA repair mechanisms, which can be seen from the activation of genes encoding tumor proteins 53 (p53) and p21. Increased accumulation of DNA damage in people with obesity (Obesity-associated DNA damage) can cause cancer as a result of excessive cell migration and proliferation as well as apoptosis resistance [8].

Cell Cycle

The cell cycle is a process of cell division that occurs in the multicellular life cycle and is controlled very tightly so that there are no errors in each phase of division. Inhibition of the cell cycle (cell cycle arrest) is an abnormal condition due to the presence of certain stressors. The cell cycle is divided into 2 phases; interphase and mitotic phase. In the mitotic phase, the cell divides into 2 daughter cells, including cell organelles, DNA and cytoplasm. The interphase phase is the interval between division phases where the process of preparing the cell for growth and DNA replication occurs. There are 3 phases of interphase including the G₁ phase (presynthesis), the S phase (DNA synthesis) and the G₂ phase (Post Duplicate DNA) [10]. The G₁ phase (presynthesis) occurs in the formation of the molecules needed for DNA duplication. In this phase, various proteins that act as transcription factors work to control the expression of protooncogenesis and result in cell division. S phase (DNA synthesis) is DNA replication forming two identical copies attached to the centromere. The centromere is also duplicated in

this phase which later functions as a tool for movement during the division process. In the G2 phase (post-duplication of DNA), the cell already has two normal DNA complements. In addition, the RNA and proteins needed for division will be synthesized, energy will be stored, tubulin synthesis and DNA analysis (check point) will occur [10].

Cellular Senescence

Cellular senescence is a phenomenon in which cells stop growing and dividing permanently which normally occur as a physiological process or as a result of changes in cell biology. Cellular senescence can be resulted in response to various factors such as changes in telomere structure, oncogene activation, radiation, genotoxic stress, oxidative stress, epigenetic changes, changes in chromatin structure, mitochondrial dysfunction, inflammation, tissue damage, influence of chemotherapeutic agents and nutritional disorders. Cell aging can be assessed from the cell cycle arrest pathway indicated by the p16 and p53-p21 proteins [5]. Experimental animals of wistar rats fed a high-fat diet for 2 to 4 months showed an increase in body fat weight followed by an increase in p16 and p21 mRNA expression in brain tissue [6]. DNA damage, mitochondrial damage, changes in chromatin structure and abnormalities in mitosis stimulate cell senescence. DNA damage itself can be triggered by telomere shortening, oxidative stress and genotoxic stress, and oncogene activation [11].

Mechanism of Cellular Senescence Mediated Cell Cycle Arrest

Cell Senescence Pathway by p53/p21 WAF1/CIP1

Protein 53 (p53), known as the "guardian of the genome", is the main protein that plays a role in cell aging. P53 is activated in DNA translation stages such as phosphorylation, methylation, acetylation, sumoylation, ubiquitination, and neddylation phases. DNA damage will activate p53 which will then directly affect the expression of the p21 gene [9]. Protein 21 (p21) is a 21 KDa protein encoded by the CDKN1A gene. Protein 21 is capable of inactivating protein cyclin dependent kinases (CDKs) thereby stopping the cell cycle. Interaction p21 with Cyl and Cy2 will inhibit the RB-E2F complex. In normal levels, p21 functions as a promoter of the cell cycle, but if p21 expression increases it can cause inhibition of the cell cycle resulting in cell aging [12]. Giving a high-fat diet to rats showed that there was an increase in the expression of mRNA p16 and p21 in the 4-month high-fat diet group compared to the 2-month group [6].

Cell Senescence Pathway by p16^{INK4A}/pRB

Protein 16 (p16) is a 16 KDa tumor suppressor protein that directly binds to CDK4/6 and inhibits the formation of the cyclin-CDk4/6 complex. RB protein (Retinoblastoma Protein)

is the main target of the Cyclin-CDK complex. Unphosphorylated Retinoblastoma-E2F complex will inhibit the transcription phase in the cell cycle [12]. Giving a high-fat diet to rats showed that there was an increase in the expression of mRNA p16 and p21 in the 4-month high-fat diet group compared to the 2-month group [6].

White Adiposa Tissue (WAT)

White adipose tissue (WAT) is one of the abundant and easily accessible sources of mesenchymal stem cells in experimental animals. Adipose tissue is involved in the mechanism of body fat storage, endocrine signaling and also the immune system so that it becomes an appropriate reservoir for studying cellular senescence [14]. White adipose tissue is also now known not only as an energy reservoir in the form of triglycerides, but also its functions as a heat loss mechanism and protects internal organs from physical trauma [15]. White adipose tissue is divided into 2 types, namely subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). In general, subcutaneous adipose tissue is found in the lower parts of the body such as in the hips, thighs and legs, while visceral adipose tissue is found around the internal organs and includes omentum, mesenteric, epididymis, perirenal, retroperitoneal, and epicardial. Visceral adipose tissue is more metabolically active than subcutaneous adipose tissue and is a good predictor of obesity-related disorders [16]. Visceral adipose tissue in obese mice exhibits cell cycle inhibition by p16 and p53/p21 activation [16]. The white adipose tissue of rats showed signs of cellular senescence after 2 weeks of being given a high-fat diet [17].

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