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SOD2: Cell Guard from Free Radicals in Humans and Fruit Flies

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ABSTRACT

Superoxide dismutase 2 (SOD2) gene encodes the enzyme manganese superoxide dismutase (Mn-SOD) which plays a critical role in maintaining cellular redox homeostasis by dismuting superoxide radicals into hydrogen peroxide and oxygen. Localized in mitochondria, this enzyme protects mitochondrial DNA from oxidative damage caused by Reactive Oxygen Species (ROS), which can trigger mutations and carcinogenesis. The expression and activity of antioxidant enzymes such as SOD, catalase, and glutathione peroxidase are critical for ROS detoxification and genome stability. The human SOD2 gene, located on chromosome 6q25.3, consists of five exons and four introns, and encodes a homo-tetrameric protein with Mn^{3+} cofactor. Genetic variations, such as Val9Ala and Val16Ala polymorphisms, affect the structure of the mitochondrial targeting sequence and potentially increase susceptibility to various diseases. The SOD2 protein structure includes two functional domains containing residues essential for enzymatic activity, allowing the enzyme to perform its function in cellular defense against oxidative stress.
Keywords: *SOD2* , Mn-SOD, Reactive Oxygen Species , Mitochondria

ABSTRACT

Gen Superoxide dismutase 2 (SOD2) mengkode enzim mangan superoksida dismutase (Mn-SOD) yang berperan penting dalam mempertahankan homeostasis redoks sel melalui dismutasi radikal superoksida menjadi hidrogen peroksida dan oksigen. Terlokalisasi di mitokondria, enzim ini melindungi DNA mitokondria dari kerusakan oksidatif yang disebabkan oleh Reactive Oxygen Species (ROS), yang dapat memicu mutasi dan karsinogenesis. Ekspresi dan aktivitas enzim antioksidan seperti SOD, katalase, dan glutathione peroksidase sangat penting dalam detoksifikasi ROS dan stabilitas genom. Gen SOD2 manusia, yang terletak di kromosom 6q25.3, terdiri dari lima ekson dan empat intron, dan mengkode protein homo-tetramerik dengan kofaktor Mn^{3+}. Variasi genetik, seperti polimorfisme Val9Ala dan Val16Ala, memengaruhi struktur urutan penargetan mitokondria dan berpotensi meningkatkan kerentanan terhadap berbagai penyakit. Struktur protein SOD2 mencakup dua domain fungsional yang mengandung residu penting untuk aktivitas enzimatik, yang memungkinkan enzim menjalankan fungsinya dalam pertahanan seluler terhadap stres oksidatif.
Keyword: *SOD2, Mn-SOD, Spesies Oksigen Reaktif, Mitokondria*

1. Introduction

Free radicals such as reactive oxygen species (ROS) are byproducts of normal metabolism, but their accumulation can cause significant cellular damage. One of the main defense systems against ROS is superoxide dismutase (SOD), with SOD2 as the mitochondrial isoform that converts superoxide anion to hydrogen peroxide [1] . SOD2 dysfunction can lead to chronic oxidative stress, which is closely linked to aging, cancer, and neurodegenerative diseases [2], [3] .

Reactive oxygen species (ROS) cause DNA damage, resulting in genetic aberrations and genomic instability, thus promoting mutagenesis and carcinogenesis [4] . Damage by ROS is usually reduced by the antioxidant action of non-enzymatic antioxidants or antioxidant enzymes, thereby reducing the possibility of mutations and the likelihood of oncogenic transformation. Alterations in the expression of antioxidant enzymes, such as catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD), can disrupt the regulation of enzymatic activity and modify ROS detoxification. [5] .

Given the central role of SOD2 in ROS protection mechanisms and the importance of redox balance in preventing cellular damage, a deeper understanding of the structure, regulation, and genetic variation of this gene has significant implications for the development of antioxidant-based therapeutic and diagnostic strategies.

2. Structure and Location of the SOD2 Gene in the Human and Drosophila Genomes

human SOD2 gene is located on chromosome 6q25.3 and consists of five exons encoding the SOD2 protein, a mitochondrial enzyme that functions as a first-line defense against reactive oxygen species (ROS) in mitochondria [6], [7] . The promoter of this gene contains important regulatory elements such as the antioxidant response element (ARE), NF-κB binding site , and GC-rich elements that allow transcriptional regulation by various redox-sensitive transcription factors, including Nrf2 and Sp1 [7] . The resulting protein has a manganese ion-binding domain and a mitochondrial targeting signal at the N-terminal end, which are essential for its localization and function in mitochondria [8] .

In Drosophila melanogaster , the SOD2 homologous gene is found on chromosome 3L, genetic position approximately 75B1-75B2, and consists of three exons [8] . The structure of this gene is relatively simpler compared to humans, but still encodes a functional and structurally homologous SOD2 enzyme. The similarity of the amino acid sequence and manganese-binding domain shows high evolutionary conservation, indicating that the basic function of SOD2 has been maintained throughout evolution from insects to mammals [8] , [9] .

The differences in gene structure and length between humans and Drosophila reflect the higher regulatory complexity in mammals. The human SOD2 gene has more complex cis-regulatory elements, as well as longer inter-exon and intron spacing, which play a role in regulating tissue-specific expression and stress responses [7] . In contrast, the Drosophila SOD2 gene is more concise and tends to be constitutively expressed in mitochondria-rich tissues such as muscle and neurons [8] .

Despite differences in genomic structure, both humans and Drosophila show SOD2 expression that is induced by oxidative stress and aging. Regulation of this expression in both is controlled by conservative transcription factors such as dNrf2 (CncC in Drosophila) and other redox factors [8] , [9] . Therefore, understanding the structure and location of the SOD2 gene across species enriches insights into how cells maintain redox homeostasis and informs antioxidant-based therapeutic strategies [9] .

3. Regulation of SOD2 Gene Transcription in Response to Oxidative Stress

SOD2 gene transcription is highly dependent on oxidative stress-sensitive transcription factors. One of the major factors regulating SOD2 expression is Nrf2 (Nuclear factor erythroid 2-related factor 2), which functions to activate various antioxidant genes in response to increased levels of reactive oxygen species (ROS). Under oxidative stress conditions, Nrf2 is released from its binding to Keap1 (Kelch-like ECH-associated protein 1), which causes Nrf2 to translocate to the cell nucleus and bind to the antioxidant response element (ARE) in the SOD2 gene promoter , which increases the expression of the gene [10], [11] .

SOD2 transcription is also influenced by post-translational changes in the transcription factors involved. Modifications such as phosphorylation, acetylation, and methylation can alter the activity of Nrf2 and other transcription factors, as well as affect their binding to regulatory elements in the SOD2 promoter . Further research is ongoing to understand in depth how these post-translational modifications contribute to the regulation of SOD2 gene expression in various pathological conditions involving oxidative stress, such as aging and neurodegenerative diseases [12] , [13] .

In addition to Nrf2, other transcription factors such as Sp1 (Specificity Protein 1) and NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells) are also involved in the regulation of SOD2 transcription. Sp1 binds to the GC-rich element in the SOD2 promoter to facilitate basal transcription, while NF-κB plays a role in inducing SOD2 expression in response to inflammation and oxidative stress [14] . The combination of these factors ensures that SOD2 expression can be rapidly increased in situations requiring protection against oxidative damage.

Nuclear factor-kappa B (NF-κB) is one of the transcription factors in the regulation of SOD2 expression during oxidative stress. NF-κB activation promotes SOD2 transcription through direct binding to

regulatory sequences in the promoter of this gene, accelerating the cellular antioxidant response to ROS accumulation [15] . Studies have shown that NF-κB activation is triggered by ROS itself, creating a feedback loop in which increased ROS induces SOD2 expression to further reduce oxidative stress [16] .

SOD2 transcriptional regulation can vary, depending on the transduction signals received by the cell. For example, in muscle cells, transcription factors such as PGC-1α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha) can increase SOD2 expression to counteract the increased ROS generated during physical activity [17] . In addition, environmental influences can also modulate SOD2 expression , as seen in radiation exposure or hypoxic conditions, both of which can stimulate increased activity of transcription regulatory factors involved in the response to oxidative stress [18] .

In addition to NF-κB, the transcription factor forkhead box O3 (FOXO3) plays a key role in inducing SOD2 expression. FOXO3 activation occurs via the redox-sensitive PI3K/Akt pathway, where inactivation of Akt allows FOXO3 to translocate to the nucleus and bind to the SOD2 promoter, thereby increasing its expression [19] . This FOXO3 activity is important in maintaining cell viability and preventing apoptosis due to severe oxidative stress.

Epigenetic modifications play a major role in regulating SOD2 expression. Methylation of CpG islands in the promoter region can suppress SOD2 expression, while demethylation increases its transcription [20] . Various diseases such as cancer and neurodegenerative diseases show changes in methylation patterns in the SOD2 promoter that are associated with changes in the cell's ability to deal with oxidative stress. In addition to methylation, histone acetylation also plays a role in regulating SOD2 expression. Histone acetylation generally opens up the chromatin structure, making it easier for transcription factors to access DNA, increasing gene transcription including SOD2 [6] , [20] . Excessive histone deacetylase (HDAC) activity can actually suppress SOD2 expression, worsening oxidative stress.

Interactions between transcription factors and post-translational modifications of proteins are crucial for SOD2 regulation. For example, FOXO3 can be acetylated, reducing its ability to activate SOD2 expression. Deacetylation by enzymes such as SIRT3 restores FOXO3 activity and increases SOD2 transcription in the face of mitochondrial stress [21] . Another signaling pathway that influences SOD2 expression is the mitogen-activated protein kinase (MAPK) pathway. Oxidative stress can activate p38 MAPK and JNK, which then modulate the activity of transcription factors such as NF-κB and AP-1, ultimately altering SOD2 expression levels [22] . This suggests that SOD2 regulation is multifactorial and highly coordinated.

Crosstalk between ROS and transcriptional regulator signaling pathways is also an important mechanism in SOD2 regulation. For example, ROS at certain concentrations can activate the Nrf2, NF-κB, and FOXO3 pathways simultaneously, resulting in synergistic SOD2 expression to control excessive ROS levels [23] . This mechanism is important for maintaining a healthy redox balance in cells. In the context of stem cell biology, SOD2 expression is of particular importance. Stem cells rely on a strong antioxidant defense system to maintain their proliferative capacity and prevent premature differentiation due to oxidative stress [24] . Dysregulation of SOD2 expression in stem cells can lead to loss of regenerative potential or even cell death.

In pathological conditions such as cancer, SOD2 regulation is paradoxical. Some cancer cells show increased SOD2 expression as a survival strategy in ROS-rich environments, while in other cases, decreased SOD2 expression facilitates proliferation through increased ROS signaling as a tumor-promoting factor [25] . This suggests that SOD2 expression is contextually regulated depending on cellular needs. MicroRNAs also play a role in the regulation of SOD2 expression. MiR-21 and miR-146a have been identified to target SOD2 mRNA for degradation, decreasing the production of this enzyme under certain conditions [26] . These interactions add a new layer of complexity to controlling the cellular response to oxidative stress through post-transcriptional regulation.

Therapeutic strategies based on modulation of SOD2 expression are beginning to be developed, either by stimulating expression for neurodegenerative therapy or suppressing it for certain cancer therapies. This approach relies on a detailed understanding of how SOD2 transcription is regulated in various pathological contexts [27] . Overall, the regulation of SOD2 transcription in response to oxidative stress involves a complex network of transcription factors, epigenetic modifications, signaling pathway influences, and control by microRNAs. A deeper understanding of this regulation offers great opportunities in the development of therapeutic strategies based on modulation of oxidative stress.

4. SOD2 Genetic Polymorphisms and Their Relation to Disease Susceptibility

Genetic polymorphisms in the SOD2 gene can affect the activity of the SOD2 enzyme, which serves as a primary defense against oxidative damage in mitochondria. One of the most studied polymorphisms is the A16V variant, which replaces the amino acid alanine (Ala) with valine (Val) at position 16 of the protein. This

polymorphism has been associated with decreased SOD2 enzymatic activity, which may increase oxidative damage to cells and contribute to the development of various diseases [28] . Several studies have suggested that individuals with the Val allele are more susceptible to cardiovascular and neurodegenerative diseases due to their lower ability to handle oxidative stress [29] .

In addition to A16V, other polymorphisms such as T-9C in the SOD2 gene promoter also have a significant impact on the expression of this gene. The T-9C variation affects the transcription level of the SOD2 gene , with the C allele tending to reduce the expression of the gene, potentially increasing oxidative damage and influencing the development of chronic inflammatory diseases and some types of cancer. Decreased SOD2 expression due to this polymorphism has been shown to increase susceptibility to diseases associated with oxidative stress, such as type 2 diabetes and cancer [30], [31] .

Genetic polymorphisms of SOD2 have also been associated with susceptibility to neurodegenerative diseases, such as Parkinson's and Alzheimer's diseases. Decreased SOD2 activity caused by certain genetic variants can increase the accumulation of ROS in neuronal cells, which accelerates the process of neurodegeneration. Several studies have found an association between certain alleles of SOD2 polymorphisms and cognitive decline in the elderly, highlighting the important role of this gene in brain aging and neurological health [32] . Therefore, understanding these genetic polymorphisms is important for the development of more targeted therapies.

In addition, studies have shown that SOD2 polymorphisms can modulate the body's response to certain medications and therapies. For example, in cancer patients, SOD2 genetic variants can influence the response to chemotherapy that induces oxidative stress, with some genetic variants increasing susceptibility to the side effects of therapy. This opens up the potential use of SOD2 polymorphisms as biomarkers for predicting response to treatment as well as disease risk in individuals [33], [34] . Further research is needed to understand the interactions between these genetic polymorphisms and environmental factors in determining susceptibility to various diseases.

5. SOD2 Gene Mutations: Impact on Mitochondrial Function and Cell Viability

Mutations in the SOD2 gene can cause serious mitochondrial dysfunction due to reduced ability to cope with oxidative damage in the organelle. The SOD2 enzyme plays a key role in detoxifying reactive oxygen species (ROS) produced during mitochondrial cellular respiration. Mutations in SOD2 can reduce enzyme activity, increase ROS levels, and worsen oxidative damage to mitochondria, which in turn affects cellular energy function and can lead to impaired cell viability [1] . Several genetic mutations are known to worsen this condition, such as the A16V mutation which can decrease protein stability and lead to lower antioxidant activity [35] .

Mitochondrial dysfunction due to SOD2 mutations is associated with a variety of physiological and pathological disorders, including increased apoptosis (programmed cell death) and cardiac dysfunction. Decreased ROS detoxification capacity can lead to oxidation of mitochondrial components, including mitochondrial DNA, proteins, and lipids. This contributes to further mutations and damage to mitochondria, leading to tissue damage, impaired organ function, and decreased cell viability [36] . Studies in mouse models with SOD2 mutations have shown that mitochondria exposed to excessive ROS are prone to dysfunction, including impaired ATP production and increased mitochondrial membrane permeability, which facilitates the release of pro-apoptotic factors [37]–[39] .

In addition, SOD2 mutations may also affect cellular function at a broader level. For example, in the context of neurodegeneration, mutations in SOD2 may disrupt energy metabolism in the brain, leading to the inability of cells to maintain proper redox homeostasis. Decreased SOD2 activity in neurons may exacerbate ROS accumulation, which increases damage to cellular structures, including the accumulation of amyloid-beta protein in Alzheimer's disease and the formation of harmful protein aggregates in Parkinson's disease [40], [41] . Mitochondrial damage caused by SOD2 mutations may accelerate neuronal degeneration and affect long-term neuronal viability.

SOD2 mutations may also play a role in susceptibility to ischemic heart disease and cardiomyopathy. The mitochondrial dysfunction caused by these mutations may result in the heart's inability to cope with oxidative stress during ischemia or hypoxia. The decreased ability of the heart to produce sufficient energy may contribute to impaired cardiac contractility, which in turn reduces cardiac cell viability and increases the risk of heart failure [42], [43] . Further research into the impact of SOD2 mutations in the context of heart disease is essential to develop therapies that can correct or compensate for mitochondrial antioxidant deficiencies.

6. Conclusion

Superoxide dismutase 2 (SOD2) is a key antioxidant enzyme that plays a critical role in maintaining cellular redox balance by eliminating reactive oxygen species (ROS) in mitochondria. In both humans and

Drosophila melanogaster, the SOD2 gene shows strong structural and functional conservation, indicating its essential role in the evolution of cell defense systems. Its complex transcriptional regulation involves multiple transcription factors such as Nrf2, NF-κB, and FOXO3, as well as epigenetic and microRNA influences, allowing cells to respond to oxidative stress dynamically and efficiently. Polymorphisms and mutations in the SOD2 gene have been shown to significantly impact individual susceptibility to various chronic diseases such as cancer, neurodegenerative diseases, and metabolic disorders, mainly through impaired mitochondrial function and increased ROS accumulation. A deeper understanding of the regulatory mechanisms and genetic variations of SOD2 opens up great opportunities for the development of diagnostic and therapeutic strategies based on modulation of oxidative stress, both at the molecular and clinical levels.

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