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İÇİNDEKİLER

ALZHEIMER'S DISEASE AND NEUROINFLAMMATION

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1. INTRODUCTION

Alzheimer's disease is indeed the leading cause of cognitive impairment and dementia, currently impacting around 50 million people worldwide. As the populations age, estimates suggest that this number could triple by mid-century ("2023 Alzheimer's disease facts and figures," 2023; Scheltens et al., 2016). It is stated that the number of patients with Alzheimer's Disease (AD) standardized by age worldwide is 1.7 times higher in women than in men, and the probability of developing Alzheimer's in people aged 65 is 21.2% in women and 11.6% in men ("2020 Alzheimer's disease facts and figures," 2020; Aggarwal & Mielke, 2023). In addition to hormonal factors, behavioral, psychosocial, genetic and medical factors may also influence the risk and progression of AD differently in women compared to men (Aggarwal & Mielke, 2023). The basic neuropathological changes and main features of AD include increased levels of both amyloid-β (Aβ), which is formed by extracellular senile plaques, and hyperphosphorylated tau (p-tau), which accumulates as neurofibrillary tangles (NFTs) within the cell. The accumulation of Aβ plaques and NFTs causes neurodegeneration by preventing intercellular communication in synapses. Increased cellular debris as a result of neurodegeneration activates immune cells called microglia.

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Microglia phagocytose and cleanse the exogenous or endogenous debris in the environment. Chronic inflammation is thought to occur when microglia cannot keep up with the changes in the environment after the damage.

2. PATHOLOGICAL MECHANISM OF ALZHEIMER'S DISEASE

AD is described with the pathological accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs, resulting from tau hyperphosphorylation). This leads to extensive neuronal loss in the brain, and with disease progression, significant declines in cognitive functions are observed (Galimberti & Scarpini, 2012). These pathological changes are accompanied by early synaptic losses, impaired innate immune response, increased reactive astrocytes, decreased cerebral blood flow and neurovascular dysfunction, as well as damage to the blood-brain barrier and brain atrophy. As a result, these changes manifest themselves clinically as progressive cognitive decline and lead to significant losses in daily life functions of patients with the progression of AD (Mrdjen et al., 2019). Although the pathophysiology of AD is still a controversial area, many researchers believe that the "Aβ cascade" hypothesis explains the basic mechanisms of the disease (Hodson, 2018). The "amyloid cascade hypothesis" proposes that amyloid plaques and their main component, Aβ-peptides, are involved in the progressive neurodegeneration of AD (Hardy & Selkoe, 2002). Aβ is formed by the cleavage of β-amyloid precursor protein (APP) by β-secretase (BACE1) and subsequently γ-secretase (Haass, Kaether, Thinakaran, & Sisodia, 2012). BACE1 cleaves the N-terminus of APP, releasing APP-β and the membrane-bound C99 fragment (Deng et al., 2013). Then the γ-secretase complex, consisting of four

protein subunits, presenilin (PSEN), presenilin enhancer (PEN), APH and Nicastrin, cleaves C99 and produces Aβ peptides of 38, 40 or 42 amino acids in length (Voytyuk, De Strooper, & Chavez-Gutierrez, 2018; Zhou et al., 2019). Aβ is produced predominantly in endosomes and its release from neurons is modulated by activity at synapses, both pre-synaptically and post-synaptically (Long & Holtzman, 2019). Aβ peptides tend to accumulate in β-sheet conformations in AD, and this is considered an initiating factor in the pathogenesis of the disease. Aβ is thought to be associated with processes such as hyperphosphorylation of tau protein, oxidative stress, inflammatory response and synaptic dysfunction. These mechanisms draw a neuron-centric model as a set of causal factors that ultimately lead to dementia. However, the linearity of the amyloid cascade hypothesis in this relationship is debatable. Studies aimed at understanding the direct link between Aβ and neurotoxicity reveal the role of complex molecular mechanisms and receptors, which questions the simplicity of the hypothesis. Therefore, the pathophysiology of AD remains an area that needs to be thoroughly investigated (De Strooper & Karran, 2016).

Another factor that plays an important role in the pathology of AD is the hyperphosphorylated tau protein. Although tau is a critical component of the neural cytoskeleton, its specific functions within the Central Nervous System (CNS) are not fully understood. Many studies have been conducted to elucidate this issue. These studies have revealed that tau proteins are phosphorylated by tau kinases and that they play an important role in the stabilization of the cytoskeleton by supporting neuronal transport in this process (Dixit, Ross, Goldman, & Holzbaur, 2008; Weingarten, Lockwood, Hwo, & Kirschner, 1975). Abnormally phosphorylated tau proteins detach from microtubules and assemble into paired helical

filaments (oligomers), which accumulate as fibrils in neurons. Tau protein undergoes many post-translational modifications, containing methylation, acetylation, and ubiquitination (Marcelli et al., 2018). Pathological types and patterns of tau, which can be phosphorylated at 85 different sites, can emerge even before NFT formation (Guo, Noble, & Hanger, 2017). Several studies have shown that abnormal phosphorylation of tau results in reduced ability to bind to microtubules (Biernat, Gustke, Drewes, & Mandelkow, 1993; Mandelkow, Von Bergen, Biernat, & Mandelkow, 2007). This is thought to be a mechanism that increases tau protein aggregation and fibrillation. Furthermore, post-translational modifications on tau may have different effects on the pathology of AD (Cook et al., 2014; Min et al., 2010; Ryan et al., 2019). Various tau kinases such as glycogen synthase kinase 3 (GSK-3), cAMP-dependent protein kinase A (PKA), cyclin-dependent kinase-5 (Cdk5), calcium/calmodulin-dependent protein kinase II (CaMKII) and mitogen-activated protein kinase (MAPK) play a role in tau phosphorylation and stand out as important drug targets in the treatment of AD. Targeting these kinases offers potential strategies for the management of tau pathology (Guo et al., 2017).

Apart from Aβ plaques and NFTs, another cause of AD pathology is thought to be inflammation. Although inflammation is generally intended to be protective, prolonged release of inflammatory cytokines (chronic inflammation) causes damage to the brain and results in impaired brain function (Lyman, Lloyd, Ji, Vizcaychipi, & Ma, 2014). There is evidence that prolonged proinflammatory cytokine secretion causes neuroinflammation and contributes to the pathology of many neurodegenerative diseases, including AD. (Cao, Hou, Ping, & Cai, 2018).

3. NEUROINFLAMMATION

Neuroinflammation is a complex and often detrimental response in CNS that can result from a variety of endogenous and exogenous pathological conditions, such as ischemia, trauma, infection, and toxins. The neuroinflammatory response is a multifaceted process involving primarily glial cells, astrocytes and various other cell types within the CNS (Calsolaro & Edison, 2016; Morales, Guzmán-Martínez, Cerda-Troncoso, Farías, & Maccioni, 2014). The neuroinflammation is a process in which the production of proinflammatory cytokines, chemokines, reactive oxygen species (ROS) and small molecular messengers by microglia and astrocytes in the CNS play a leading role and are shaped by the mechanical and chemical damage exposure of endothelial and blood cells. (Heneka et al., 2015; Leng & Edison, 2021).

Neuroinflammation is indeed a significant contributor to the pathology of various neurodegenerative diseases, including Parkinson's disease, Huntington's disease, Spinal Muscular Atrophy, prion diseases, and AD (Kinney et al., 2018). According to the data obtained from the literature, it has been stated that pro-inflammatory cytokine levels increase in the brains of patients with Alzheimer's Disease (AD), and this increase causes synaptic dysfunction, inhibiting neurogenesis and even leading to neuronal death (Calsolaro & Edison, 2016; Lyman et al., 2014). In particular, Il-1β promotes synaptic loss by increasing presynaptic glutamate release and triggering prostaglandin E2 production (Mishra, Kim, Shin, & Thayer, 2012). TNF, on the other hand, activates caspase 8 when the TNF receptor 1 (TNFR1) and nuclear factor-κB (NF-κB) pathway are inhibited, leading to neuronal death (Micheau & Tschopp, 2003). Pro-inflammatory cytokine release increases microglia and astrocyte activation, leading to Aβ accumulation. This accumulation results in microglia inappropriately pruning

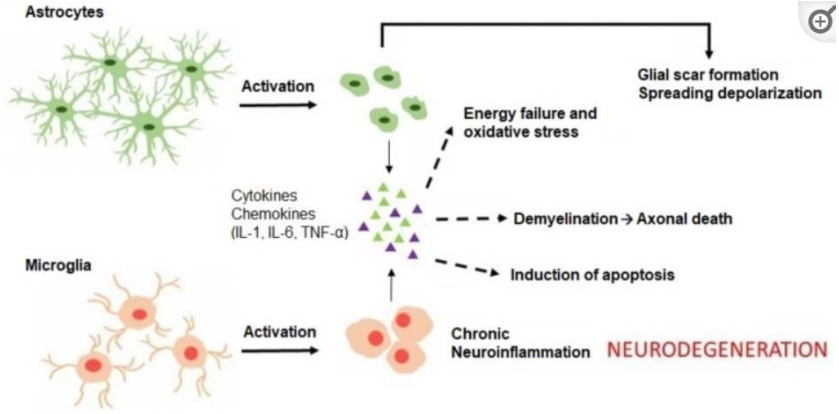
synapses (Hong et al., 2016; Taipa et al., 2019). Cytokines and chemokines induce chemotaxis in the brain, causing neuronal loss. The release of chemokines directs microglia to neuroinflammation, which triggers local inflammation (Taipa et al., 2019). Anti-inflammatory cytokines (such as IL-4, IL-10, IL-11) are also produced in the neuroinflammatory process and may be part of a complex mechanism to reduce neuroinflammation in this process (Fig. 1). However, in neurodegenerative diseases, neuroinflammation often becomes a chronic process that cannot be resolved and is considered a pathological factor of the disease (Leng & Edison, 2021).

3.1.Microglial Cells

3.1.1. Development and Functions of Microglial Cells

Microglial cells are resident cells of myeloid origin found in the CNS parenchyma, constituting 0.5% to 16% of glial cells in the human brain (Gomez-Nicola & Perry, 2015; Mittelbronn, Dietz, Schluesener, & Meyermann, 2001; Tay, Carrier, & Tremblay, 2019). While previous knowledge suggested that microglia are derived from hematopoietic stem cells, recent studies have shown that these cells are derived from the yolk sac and colonize the neuroepithelium in early embryogenesis (Ginhoux et al., 2010). Microglia, as they are called "macrophages of the brain," play critical roles in the normal development, function, and repair of the CNS (Hanisch & Kettenmann, 2007). These cells actively monitor abnormalities in their microenvironment and orchestrate a diverse spectrum of reactions to maintain tissue homeostasis (Paolicelli et al., 2011; Sierra et al., 2010).

Figure 1. Detrimental effects of glial-mediated inflammation. Activation of microglia and astrocytes by Aβ or following damage signaling leads to the secretion and release of inflammatory chemokines and cytokines, including IL-1, IL-6, and TNF-α



Source: (Fakhoury, 2018).

They act a part in both innate and adaptive immune responses, rapidly clearing away apoptotic cell debris and other harmful substances that ensure the survival of neurons (Hanisch & Kettenmann, 2007; Schafer et al., 2012).

Microglia are essential for maintaining brain health and function, particularly in cognitive processes like learning and memory in human. Morphologically, microglia; can be classified as branched (dormant/resting), active, and ameboid (phagocytotic) (Nimmerjahn, Kirchhoff, & Helmchen, 2005; Stence, Waite, & Dailey, 2001). When activated by pathological stimuli, resting ramified microglia can undergo morphological changes and transform into amoeboid and motile shapes (Eggen, Raj, Hanisch, & Boddeke, 2013). Resting microglia, with their ramified morphology, continuously survey the brain parenchyma, allowing them to detect subtle changes without disturbing neuronal activity. When activated by pathological stimuli, such as exogenous DAMPs released from damaged cells or endogenous PAMPs released from pathogens, resting

ramified microglia can undergo morphological changes, transforming into amoeba-like and motile forms. (Heneka et al., 2015; Nimmerjahn et al., 2005). They internalize these pathogens by pathways such as pinocytosis, phagocytosis or receptor-mediated endocytosis.

Microglia are critical players in the neuroinflammatory process as well as in the endocytic pathways and work to eliminate pathogens by activating the expression of relevant gene modules such as chemokine receptors and interferons (Owens, Khorooshi, Wlodarczyk, & Asgari, 2014; Solé-Domènech, Cruz, Capetillo-Zarate, & Maxfield, 2016). This inflammatory process usually resolves when the pathogenic stimulus that activates the immune system is removed. However, functional deterioration of microglia can be seen in the aged brain, leading to continued activation and contributing to the pathogenesis of neurodegenerative diseases (Norden & Godbout, 2013).

3.1.2. Microglial Cell Classification

Microglia have versatile functions in the progression of AD due to their distinct phenotypes and diverse activation pathways. The mechanisms of opposing states of microglial activation have been outlined by Gordon S. (Gordon, 2003). The M1 and M2 classification system indeed provides a framework for understanding the dual roles of microglia in inflammation and tissue repair M1 Microglia: these are classically activated microglia that produce pro-inflammatory cytokines like IL-1β, TNF-α, and nitric oxide (NO). They are typically induced by signals such as IFN-γ and LPS. This state is essential for initiating immune responses but can also contribute to neuroinflammation if dysregulated.

The other phenotype is alternatively activated M2. In contrast, M2 microglia are alternatively activated. The M2

phenotype is associated with anti-inflammatory responses and tissue repair, with different signals such as IL-10, TGF-β, CSF1, and IL-6 (Varin & Gordon, 2009). Due to the functional diversity of tissue macrophages, M2 microglia can be further subdivided into M2a, M2b, M2c (Darwish, Elbadry, Elbokhomy, Salama, & Salama, 2023). M2a, induced by IL-4 and IL-13, focusing on anti-inflammatory functions and promoting tissue repair. M2b, triggered by immune complexes and TLR signaling, these cells can produce a mix of pro- and anti-inflammatory cytokines. M2c, representing a more deactivated state, help suppress inflammation and support recovery (Cunningham, 2013; Lyman et al., 2014). While the M1-M2 model has been useful for research, it oversimplifies the diverse functional states of microglia. Emerging evidence shows that microglia exist on a spectrum, exhibiting various activation states that do not fit neatly into the M1 or M2 categories. This complexity reflects their roles in a variety of physiological and pathological contexts. Despite these nuances, the M1-M2 classification remains a useful tool for conveying the general idea that microglia can exert protective (M2) or detrimental (M1) effects depending on the context. Future research will likely continue to refine our understanding of microglial biology and their roles in health and disease, moving beyond this simplified model (Grabert et al., 2016; Wes, Holtman, Boddeke, Möller, & Eggen, 2016).

3.1.3. Microglia in Alzheimer’s Disease

Many autopsy studies have shown that microglial activation is significantly increased in the brains of patients with Alzheimer's Disease (AD), especially concentrated around Aβ plaques (Dal Bianco et al., 2008; B. Liu & Hong, 2003). The role of reactive microglia in AD is quite important. Studies have shown that activated microglia cluster near Aβ plaques by morphological observations and immunohistochemical staining

(Bouvier et al., 2016; Savage, Carrier, & Tremblay, 2019). In vivo imaging techniques have also shown that microglial activation is associated with both Aβ and tau pathology. Activated microglia accumulate in damaged areas. This accumulation is a hallmark of neuroinflammation in AD. Microglia show morphological changes when they transition from a resting state to an activated state (Perry & Gordon, 1988).

Microglial activation is driven by DAMPs or PAMPs, which increase inflammatory responses as they attempt to clear harmful protein deposits within the brain (Heneka et al., 2015). The process is triggered by the binding of cell surface receptors (such as CD36, CD47) to abnormal proteins such as Aβ. Once activated, microglia are directed to lesion sites and this process is associated with the secretion of inflammatory molecules (Bamberger, Harris, McDonald, Husemann, & Landreth, 2003). However, when overactivated, microglia can also trigger neuronal damage and cognitive decline. Some studies have shown that the ability of microglia to phagocytose Aβ can reduce amyloid plaque accumulation and neurodegeneration, while others have found that microglial activation promotes Aβ dissemination and plaque development (Heckmann et al., 2019; Wang et al., 2021). In this sense, the role of microglia in Alzheimer's disease is complex and bidirectional.

3.2.Astrocytes

3.2.1. Development and Functions

Astrocytes arise from radial glial cells during development, particularly during prenatal stages. These radial glial cells can undergo asymmetric division to produce neurons and astrocytes. After birth, most astrocytes are produced by symmetric division of preexisting astrocytes, a process that allows the astrocyte population to expand in response to various

physiological needs. This mechanism, which emphasizes the dynamic nature of astrocyte biology and their ability to proliferate and adapt after the initial developmental stage, was described by Ramon y Cajal (y Cajal, 1913). Astrocyte development is quite complex and involves multiple mechanisms. Astrocytes can arise from the direct transformation of radial glial cells, which act as scaffolds for migrating neurons during development, or from oligodendrocyte precursor cells (OPCs) and intermediate glial precursor cells found in the layers of the cortex (Jovanovic et al., 2023; Verkhratsky & Nedergaard, 2018).

In fetal brain development, it is known that the expressions of glial fibrillary acidic protein (GFAP) and calcium-binding protein (S100β) direct the differentiation mechanisms of astrocytes (Guillemot, 2007; He et al., 2005). Beyond the expression of these two proteins, the development of astrocytes in the embryonic period is directed by the BMP-SMAH, Notch and JAK-STAT signaling pathways. The JAK/STAT signaling pathway is activated by the IL-6 cytokine family and helps initiate gliogenesis by promoting the differentiation and proliferation of astrocytes (Preman, Alfonso-Triguero, Alberdi, Verkhratsky, & Arranz, 2021). The JAK/STAT and Notch pathways interact in a complex manner during astrogenesis. JAK activation enhances Notch signaling by increasing the release of Notch ligands. Notch activity activates the JAK/STAT cascade by increasing the phosphorylation of STAT proteins. This increases the transcription of astrocytic genes and promotes gliogenesis. The two pathways work together to increase the signal strength required for astrocyte differentiation and development (Kanski, van Strien, van Tijn, & Hol, 2014). TGF-β and BMP ligands trigger phosphorylation of SMAD proteins. Phosphorylated SMAD proteins form the SMAH-SMAH4 complex, increasing

the transcription of astrocytic markers such as GFAP (Glial Fibrillary Acidic Protein) and S100β. These genes are critical for astrocyte differentiation and maturation (Krencik, van Asperen, & Ullian, 2017; Takizawa, Ochiai, Nakashima, & Taga, 2003).

Stereology studies on postmortem human brain samples have revealed that 20% of cells in the neocortex are astrocytes, 75% are oligodendrocytes, and 5% are microglia (Pelvig, Pakkenberg, Stark, & Pakkenberg, 2008). Their star-shaped morphology is characterized by cellular processes extending from the soma (Placone et al., 2015). A large number of receptors present on astrocytes enable sensing of neuronal activity, and activation of these receptors triggers astrocytic ionic signaling mediated by changes in cytosolic concentration of Ca^{2+} and Na^{+} (Rose & Verkhratsky, 2016). Clearance of neurotransmitters such as glutamate, GABA, adenosine, and endocannabinoids is critical for maintaining synaptic transmission, preventing excitotoxicity, and providing neuroprotection.

Astrocytes form the perisynaptic membranous sheath, which is essential for synaptogenesis and synaptic maintenance. They support synaptogenesis by producing factors such as thrombospondins, glypicans and cholesterol. Astrocyes also coordinate synapse elimination by cooperating with microglia (Allen & Eroglu, 2017; Baldwin & Eroglu, 2017). The toe tips come into contact with blood vessels, forming the blood-brain barrier (BBB) and regulating local blood flow through the neurogliovascular unit (Sweeney, Zhao, Montagne, Nelson, & Zlokovic, 2018). Astrocytes provide energy by storing glycogen, which they metabolize into pyruvate and lactate. Finally, they play a critical role in maintaining the homeostatic balance of the central nervous system by controlling the volume of the

extracellular space and transporting ions, protons, and metabolites (Verkhratsky & Nedergaard, 2018).

Astrocyte development is vital in cortical layer formation, metabolic support for neurons, regulation of synaptic activity, blood-brain barrier formation, response to injury, and regulation of inflammation. Overall, the diverse origins and developmental pathways of astrocytes underscore their essential roles in both brain development and homeostasis throughout life.

3.2.2. The Impact of Astrocytes on Alzheimer's Disease

Studies on the role of astrocytes in AD have been notable for their interaction with senile plaques and reactive astrocytosis. Early evidence suggests that astrocytes are associated with Aβ deposits in the brains of AD patients. Recent studies suggest that reactive astrocytes accumulate in the vicinity of Aβ and play a role in phagocytosis of dendrites and synapses (Matsuoka et al., 2001; Nagele, D'Andrea, Lee, Venkataraman, & Wang, 2003). This process creates a structure similar to glial scarring and reports of profound astrocytosis around Aβ. Aβ causes to the secretion of inflammatory cytokines (such as IL-1, IL-6, TNF-α) that activate astrocytes, and this promotes neurodegenerative processes in AD (Sajja, Hlavac, & VandeVord, 2016). The interaction of astrocytes with Aβ occurs through a variety of receptors, which enable Aβ to bind and recruit astrocytes. Aβ aggregates stimulate the production of chemotactic molecules, causing astrocytes to recruit to the lesion site (Ries & Sastre, 2016). These interactions contribute to inflammatory processes, with Aβ promoting the accumulation of immune cells.

The effects of astrocytes on Aβ are still controversial. Some studies suggest that reactive astrocytes contribute to the

clearance of Aβ in vitro (R.-X. Liu, Huang, Bennett, Li, & Wang, 2016; Wyss-Coray et al., 2003). Extracellular clearance of Aβ is a complex process in which astrocytes play a key role. Matrix metalloproteinases (MMP-2 and MMP-9) are critical in helping astrocytes disassemble amyloid plaques (Wojtowicz, Sitarz-Glownia, Wnuk, Kajta, & Szychowski, 2023). However, under inflammatory conditions, astrocytes can promote Aβ production. In particular, TGF-β1 alone or in combination with IFN-γ, TNF-α or IL-1β can trigger Aβ accumulation by increasing Aβ production in astrocytes (Luo, 2022; Zhao, O'Connor, & Vassar, 2011). This situation leads to negative consequences such as astrocytic damage and neuronal apoptosis in the long term (Söllvander et al., 2016). Astrocytes and other glial cells are thought to play an important role in the evolution of NFTs in AD (Sheng, Mrak, & Griffin, 1997). In the parahippocampal cortex, the number of activated astrocytes is associated with the formation of NFTs, and the expression of serine proteases such as thrombin, which contribute to the degradation of tau proteins, by astrocytes and microglia supports this idea (Arai, Miklossy, Klegeris, Guo, & McGeer, 2006; Olesen, 1994).

These findings recommend that astrocytes play an critical role in the pathogenesis of AD and may undertake both detrimental and protective functions. However, the mechanisms underlying these processes are not yet clear.

4. CONCLUSION

The cumulative effects of amyloid plaque accumulation, tau pathology, neuroinflammation, and other pathological changes significantly contribute to cognitive decline and impair daily life activities in patients with AD (Mrdjen et al., 2019). These processes result in severe brain atrophy, impaired innate

immune responses, increased reactive astrocytes, and damage to the blood-brain barrier, all of which exacerbate the clinical manifestations of the disease.

The pathophysiology of AD is complex, involving intricate interactions between amyloid plaques, tau hyperphosphorylation, and neuroinflammation. Ongoing research is crucial for elucidating these relationships and developing effective therapeutic strategies. In neurodegenerative conditions, neuroinflammation can become chronic, leading to sustained activation of microglia and astrocytes. This persistent inflammation is believed to further exacerbate disease pathology, making it a critical target for therapeutic intervention.

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EPIGENETIC BIOMARKERS IN PSORIASIS[1]

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1. INTRODUCTION

Psoriasis, an inflammatory skin condition that significantly reduces the quality of life of patients and is associated with many comorbidities, affects approximately 125 million people worldwide (Armstrong & Read, 2020; Korman, 2020). Characterized by erythematous plaques with well-defined borders and covered with white scales, this disease has a symmetrical distribution involving the scalp, trunk, elbows and knees (Griffiths & Barker, 2007). It is typically treated with phototherapy or topical agents and is considered a disease limited to the skin. These types of therapies are not sufficient to elucidate the underlying disease pathogenesis (Boehncke & Boehncke, 2014). Therefore, new targeted therapies are being developed to elucidate the disease pathogenesis.

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2. PATHOGENESIS

The pathogenesis of the disease is complex and has not been fully elucidated. Excessive activation of immune system elements plays a fundamental role in the pathogenesis of the disease (Lin, Ambikairajah, & Holmes, 2002). It is thought that the pathogenesis is caused by hyperproliferation and differentiation of keratinocytes at the beginning. Plasmacytoid dendritic cells, neutrophils, keratinocytes, monocytes, endothelial cells and various cytokines play an important role in the disease stage (Chong, Kopecki, & Cowin, 2013). When the characteristic features of the disease are examined, inflammatory cell infiltration in the dermis and epidermis, expansion of dermal vessels and keratinocyte hyperproliferation occur. According to the pathogenesis studies, many cells, cytokines and pathways have been identified (Georgescu vd., 2019).

The first changes in the pathogenesis of the disease include Langerhans cells, which are responsible for capturing antigens. These antigens are processed and then presented to Class I and Class II MHC molecules. After antigen presentation, T cell proliferation occurs and these cells migrate to the area where the antigen is concentrated. Thus, activated T cells initiate inflammation by secreting cytokines that activate keratinocytes, monocytes and neutrophils (Galadari, Sharif, & Galadari, 2005).

3. BIOMARKER

Biomarkers, which are indicators of normal physiological processes, pathogenic reactions, therapeutic interventions, and responses to interventions, are a reliable indicator of disease activity that is standardized. Several candidate biomarkers have been proposed to monitor psoriasis improvement during treatment (Robb, McInnes, & Califf, 2016).

Recently, omics-based technologies have been used in biomarker discovery, and some promising biomarkers have been discovered for psoriasis. Thus, new data have been obtained on the signaling pathways and molecular mechanisms underlying the disease pathogenesis (Jiang, Hinchliffe, & Wu, 2015). Most of the biomarkers in psoriasis are related to abnormal keratinocyte differentiation and proliferation (Villanova, Di Meglio, & Nestle, 2013).

4. EPIGENETIC MECHANISMS

The mechanism that does not cause changes in DNA sequence and structure but includes phenotypic changes is called epigenetics. It is the mechanism that determines where, when and for how long genes will work, and that occurs in the emergence of genetic information without any change in DNA sequence. Recent studies have revealed that not only genetic factors but also epigenetic mechanisms such as DNA methylation, long non-coding RNA (lncRNA), histone modifications and microRNA (miRNA) should be evaluated in disease pathogenesis (Can & Aslan, 2016). Epigenetic mechanisms such as DNA methylation, long non-coding RNA (lncRNA), histone modifications and microRNA (miRNA) can play a role in gene expression and chromatin remodeling (Cao, 2014; P. Zhang, Su, & Lu, 2012).

4.1.Non-Coding RNAs

Single-stranded, non-protein-translated RNAs with 18-26 nucleotides are miRNAs. They are transcribed from the transcription start point and their primary transcripts (pri-miRNA) are formed. These pri-miRNAs are capped and polyadenylation is added to them and they become pre-miRNAs. The pre-miRNA, which is cut by the Dicer enzyme, is formed into mature miRNAs by the RNase III enzyme. This miRNA

forms a complementary structure with the mRNA sequence (Can & Aslan, 2016).

IncRNAs are RNAs that are 200 or more nucleotides long and do not code for protein (Quinn vd., 2016). According to the results of the study, there are 15,000 different IncRNAs. It is transcribed by RNA polymerase II (Pol II) and contains exon-exon splicing junctions by adding caps and polyadenylation (Hülyam, 2018).

4.2.Histone Modifications

Histones, which are responsible for DNA packaging, bind to negatively charged DNA thanks to the high amount of positively charged amino acids they contain. Histones, which remain intact throughout the cell cycle, are separated from DNA only during replication and then recombine. There are many evolutionarily conserved histone modifications, some of which are specific, while others can be active or inactive in transcription regions. They are affected by stress and other environmental factors (Dolinoy, Weidman, & Jirtle, 2007).

4.3.DNA Methylation

DNA methylation, which is the mechanism of adding methyl groups to organic bases in the DNA structure, is mostly formed as a result of adding a methyl group to the cytosine base. Studies have shown that inactive DNA in mammalian X chromosomes, which is inactive, is generally much more methylated compared to active DNA (Can & Aslan, 2016). This mechanism, which is mostly formed by adding a methyl group to cytosine in the CpG area, mainly plays a role in X chromosome activation, imprinting and cell differentiation. Methylation can play a role in gene silencing processes and can change chromatin structure. CpG dinucleotides in the DNA structure are specifically methylated (Nestler, 2014). In a study conducted on two different organisms, abnormalities are

observed in embryonic development in the event of insufficiency in DNA methylation as a result of the deficiency of the enzyme that performs methylation. The gene that undergoes methylation shows its existence in the same way throughout the cell cycle (Dolinoy vd., 2007).

5. EPIGENETIC BIOMARKERS IN PSORIASIS DIAGNOSIS

When psoriatic areas are compared with control groups, a significant increase is seen in DNA methylation profile. The first study on methylation in psoriasis is the study showing demethylation of Shp-1 promoter 2. In addition, hypermethylation of Id4 promoter has been associated with parakeratosis and differentiation in psoriasis (Ruchusatsawat vd., 2011). When the promoter methylation status of p15 and p21 genes is examined, higher methylation was observed in the control group compared to psoriasis (K. Zhang, Zhang, Li, Yin, & Niu, 2009). For future clinical studies, Selenbp1, Ptpn22 and several methylated genes are suggested as potential targets for psoriasis treatment (Chandra, Ray, Senapati, & Chatterjee, 2015). In addition, the demethylated region of FoxP3, which is specific to Treg, was found to have higher methylation levels in psoriasis patients in a study conducted by Ngalamika et al. (Ngalamika vd., 2015). According to a study examining the effects of UV phototherapy on psoriasis and DNA methylation, it was observed that abnormal methylation status was improved after phototherapy in patients showing clinical improvement (Gu vd., 2016). DNA methylations in the Tımp2 and Pdcd5 loci using the methylated DNA immunoprecipitation sequencing (MeDIP-Seq) method may play a role in the pathogenesis of psoriasis (Peng Zhang vd., 2013). Some methylation-sensitive genes such as Lfa-1, Shp-1 and P16ınk4α are highly expressed

in psoriasis patients (P. Zhang vd., 2012). In a study on CpG methylation, it was determined that the methylation status was different between the psoriatic lesion region and the control group (Roberson vd., 2012). Overexpression in Kynu, Oas2, S100a12 and Serpınb3 genes are important indicators of psoriasis. After 1 month of TNF-α inhibitor treatment, methylation levels may return to normal levels (Roberson vd., 2012).

lncRNAs cause abnormal keratinocyte differentiation in psoriasis (Quinn vd., 2016; Tang, Liang, Xie, Yang, & Zheng, 2019). According to the results of some studies, some new IncRNAs are expressed differently in control and psoriatic skin lesions (Tsoi vd., 2015). This shows that some IncRNAs may play a role in the pathogenesis of psoriasis. The first IncRNA study reported that the RNA gene associated with psoriasis susceptibility (PRINS) may play a role in the pathogenesis of psoriasis (Sonkoly vd., 2005). The expressions of Cyp4z2p, Hınt1 and Trhde-As1 are different in psoriatic lesions and Card14, Il23r, Lce3b and Lce3c have been identified to be adjacent to psoriasis susceptibility loci (Gupta vd., 2016). In a study, it was determined that the decreased expression of Ccl27 regulated by lncRNA-Al162231.4 was related to the development of psoriasis (Li vd., 2020).

In a study on histone modifications, hypoacetylation of histone H4 observed in psoriasis vulgaris patients was found to be inversely correlated with the PASI score (Peng Zhang, Su, Zhao, Huang, & Lu, 2011). In a study against drug responses, decreased acetylated histone H3 and H4 and increased histone H3 lysine K4 (H3K4) methylation were reported (Ovejero-Benito vd., 2018).

Expressions of miRNAs in serum can be used as biomarkers in prognosis and diagnosis. The first miRNA

specific to skin is miR-203 (Sonkoly vd., 2005). Considering the role of this miRNA in reducing IL-17 and JAK2/STAT3, it is a potential therapeutic target (Hou vd., 2016; Xu vd., 2017). In a study, it was determined that the expressions of miR-143 and miR-223 were parallel to the PASI score (Løvendorf, Zibert, Gyldenløve, Røpke, & Skov, 2014). The expressions of angiogenic miRNAs miR-21, miR-31, miR-100 and miR-378, epithelial differentiation miRNAs miR-135b, miR-203-AS and miR-205, miR-99a and miR-146b involved in keratinocyte differentiation and miR-142-3p associated with inflammation are increased in psoriatic skin lesions (Joyce vd., 2011; Lerman vd., 2011). Another miRNA that has higher expression in psoriasis patients compared to the control group is miR-1266 (Ichihara vd., 2012).

6. RESULT

Although various epigenetic changes have been detected in psoriasis, the relationship between them has not yet been determined. However, when the results are examined, it is thought that epigenetic changes have important roles. According to the current study results, it is thought that epigenetic changes may have very important functions in psoriasis. Therefore, it can contribute to the diagnosis and treatment of patients.

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TIBBİ BİYOLOJİ

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