Insulin Resistance Related Paradoxical Cell Cycle Activities in Brain as A Unifying Mechanism for Alzheimer's Disease

Alzheimer Hastalığında İnsulin Direncine Bağlı Olarak Beyinde Gelişen Paradoksik Hücre Siklusu Aktiviteleri

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ABSTRACT Mitotically active glial cells provide metabolic support to active neurons, contribute to coupling between synaptic activity and local blood flow, protecting against oxidative stress. Disturbances of the complex neuron –glia interrelation are recognized increasingly as potentially important pathophysiological mechanism in a wide of neurological disorders including neurodegeneration. Peripheral insulin resistance related increased oxidative stress in glial cells reason in DNA damage response-induced senescence in glial cells. Senescent glial cells cannot provide the expected metabolic and immune support to neurons. The neurons are the prototypical post-mitotic cells, however, some subsets of neurons are known to reactivate cell-cycle activity in response to certain triggers of neuronal apoptosis including genotoxic stress generated by redox changes due to pathological alterations in supporting astroglial cells. Thus, paradoxical cell cycle block in glial cells and re-entry in neurons due to cellular redox alterations created by peripheral insulin resistance may cause Alzheimer's disease.

Key Words: Senescence, cell cycle, Alzheimers disease, oxidative stress

ÖZET Mitotik olarak aktif olan glial hücreler nöronlara metabolik destek, lokal kan akımı ve sinaptik aktivite düzenlemeleri sağlayarş oksidatif stres gelişimine karşı önemli fonksiyon görürler. Nöron ve glial hücreler arasında yürüyen karmaşık ilişkilerin bozulması nörodejeneratif hastalıkların patofizyolojisinde önemli roller oynamaktadır. Periferal insülin direncinin yol açtığı sistemik oksidatif stres, glial hücrelerde DNA hasarına, buda daimi hücre siklusu blokajı olan glial senesens'e neden olur. Senesent glial hücreler, nöronlara kendilerinden beklenen metabolik ve immün destekleri sağlayamazlar. Öte yandan, nöronlar prototipik postmitotik hücrelerdir. Ancak, astroglial hücrelerdeki bu patolojik değişiklikler sonucunda oluşacak redoks değişikliklere cevaben kendilerini apopitotik kayba götürecek hücre siklusunu yeniden başlatma girişiminde bulunabilirler. Neticede, glial hücrelerde aktif olması gereken hücre siklusunun kalıcı engellenmesi ile giden senesens hadisesi ve nöronlarda inaktif olan hücre siklusunun paradoksik olarak yeniden başlama teşebbüsü Alzheimer's hastalığına neden olabilir.

Anahtar Kelimeler: Yaşlanma, hücre siklusu, Alzheimer's hastalığı, oksidatif stres

95% of the patients with Alzheimer's disease (AD) suffer from the sporadic form of the disease, the biological basis of which is unknown.[1] Several hypotheses have been proposed in attempts to explain the pathogenesis of AD, including senile plaque and neurofibrillary tangle formation, increased oxidative stress, and cell cycle abnormalities.[2] Emerging evidences have shown that insulin resistance is associated with increased oxidative stress. Hyperinsulinemia, hyperglycemia, and hyperleptinemia are considered as important components of the insu-

lin resistance.[3] Thereby, it seems likely that pathological changes in insulin signaling pathways appear to play very important roles in this process.

INSULIN SIGNALING CHANGES RELATED TO AD

Biological actions of insulin are initiated by the binding of insulin to its cell surface receptor, which is a ligand-activated tyrosine kinase. Activated insulin receptors phosphorylate intracellular substrates, including insulin receptor substrate family members and Shc, which serve as docking proteins for downstream signaling molecules. Tyrosine phosphorylated motifs on IRSs specifically bind to adaptor proteins, such as the p85 regulatory subunit of phosphatidylinositol 3-kinase (PI3K) or Grb-2.When p85 binds to tyrosine-phosphorylated IRS, this results in activation of catalytic subunit of PI3K. Activation of PI3K initiates a cascade of serine kinases, which phosphorylate and activate Akt. Akt, in turn, phosphorylates and activates or inactivates its very important substrates. This cascade, in a general sense is responsible from the metabolic actions of insulin.[3,4] A similar signaling pathway proceeds from Grb-2 via a cytoplasmic guanine nucleotide exchange factor (GEF=Sos), and activates a small GTP binding protein Ras, which then initiates a phosphorylation cascades ultimately activating MAP kinase pathway.[5]. This signaling cascade, in turn, is responsible for the mitogenic effects of the insulin. Insulin signal transduction pathways constitute a highly complex network that includes multiple feedback loops, cross-talk between major signaling branches, and cross-talk from signaling pathways of heterologous receptors.

A key feature of insulin resistance is that it is characterized by specific impairment in PI3K-dependent signaling pathways, whereas Ras/MAPK- dependent pathway is unaffected.[6] This has very important pathophysiological implications because metabolic insulin resistance is accompanied by compensatory hyperinsulinemia to maintain euglycemia. Thus, hyperinsulinemia will overdrive unaffected MAP kinase-dependent pathways, leading to an imbalance between PI3K and MAPK-dependent functions of insulin. Importantly, increased Ras activation results in an increase intracellular ROS level.[6,7]

INSULIN RESISTANCE LINKED TO CELLULAR SENESCENCE

Cells sense changes in their environment by activating signal transduction pathways that direct biochemical programs to mediate proliferation, differentiation, and survival. MAPK family represents an important group of signaling proteins that can regulate these fundamental cellular processes.[8] Activated ERK (extracellular regulated kinase) and JNK (c-jun NH2 terminal kinase) can lead to increased proliferation and survival. In the contrast, the p38 MAPK pathway, which has very important opposing function by suppressing the uncontrolled proliferation mediated by these two proteins, is implicated in suppression of tumorigenesis because it can inhibit cell growth. In addition, p38 behaves as a sensor of oxidative stress. Activation of the p38 MAPK by reactive oxygen species (ROS) is mediated by ASK which is the MAPK kinase kinase.[8,9]

Besides its well-known roles in inflammation and stress responses, recent studies have demonstrated an additional function of p38 pathway in tumor suppression as indicated above. There are good evidences supporting the role for p38 in the regulation of the tumor suppressor protein p53, mainly through the phosphorylation of p53 induced by several stress.[8,9] The most important one is ROS. Upon activation, p53 coordinates a complex cellular response, which can lead to either reversible cell-cycle arrest, an irreversible senescence-like state or apoptosis. In addition, p38 has crucial role in maintaining contact inhibition in nontransformed cells by activating p27 CDK inhibitor. In response to DNA damage, eukaryotic cells undergo proliferative arrest to enable DNA repair, which is important for maintaining genome stability and preventing tumorigenesis.[10] The p38 pathway has a prominent role in DNA damage response. In normal non-transformed cells, oncogene activation sometimes triggers senescence. Like apoptosis, senescence is a tumor-suppressing defense mechanism that must be compromised for tumorigenesis to occur. Recent studies have revealed a major role of the p38 pathway in senescence caused by oncogenic ras or its downstream effector raf, which stimulates p38 activity. Increased Ras activation results in an increase intracellular ROS level. This rise in ROS appears to be important for the activation of p38-induced senescence.[11]

Reactive oxygen species (ROS) together with the reactive nitrogen species are oxygen free radicals that are highly reactive toward cellular constituents including proteins, lipids and DNA. The most important source of ROS formation is endogenous aerobic metabolism.[12] Cells have developed numerous antioxidant systems to prevent excess generation of ROS. In healthy states, generated ROS in physiological level have been shown to
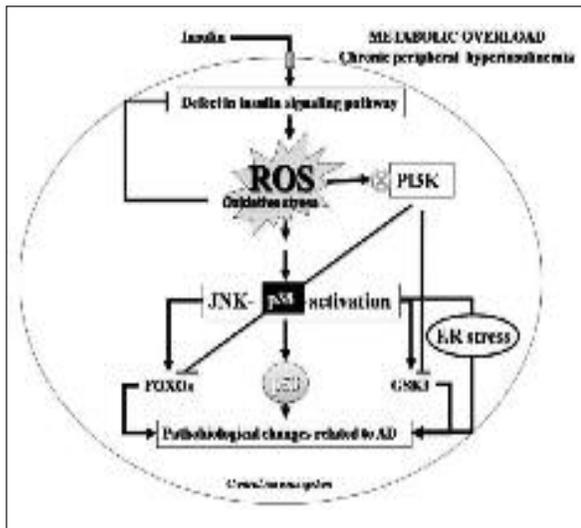
FIGURE 1

trigger most of the signaling pathways downstream of insulin (growth factor) receptors, including PI3K signaling, JNK and p38 MAPK family. Metabolic overload and chronic peripheral hyperinsulinemia in insulin resistance results in adverse cycles, such as protein misfolding cycles, thus ER stress and oxidative damage cycles, sustaining excessive ROS production and oxidative stress (Figure 1).[13]

Cellular generation of ROS is central to redox regulation. A redox sensitive protein, p53 is also under control of redox regulation. As stated previously, there is close interaction between ROS and p53. Tumor suppressor protein p53, which is activated by various stress factors, particularly by ROS, occupies a pivotal position in maintaining genomic integrity. In response to cellular stresses that lead to DNA damage, wild-type p53 orchestrates the transcription of numerous genes and directs cells to cell cycle arrest, senescence, or apoptosis via differential activation of target genes, preventing the propagation of damaged DNA.[13,14]

Multiple members of the DNA damage response (DDR) pathway appear to be generally anti-proliferative and are likely to be beneficial in the short term by preventing the emergence of clones of cells that could be cancerous. In the long term, however, sufficient number of stem cells with DNA damage may be killed through apoptosis or rendered dysfunctional through senescence. This, in turn, may lead to loss of tissue homeostasis and the associated tissue atrophy that may ultimately result in organ failure and death.[15]

DNA DAMAGE RESPONSE IN BRAIN

In most cell types, activation of p53 is crucial for initiating the senescence response following DNA damage. It is applicable to define senescence as a metabolically viable cell cycle arrest with persistent DNA damaging signaling. Cellular senescence has a complex genetic program and final cell fate decision is permanent cell growth arrest. Senescent cells are known to be metabolically active and are able to secrete a variety of inflammatory mediators. Because they have lost the ability to proliferate, senescent cells can no longer participate in tissue renewal and repair.[16]

Terminally differentiated, post mitotic neurons and mitotically active astroglial cells with their proliferating capacity are two major types of cells present in the central nervous system. There is no other tissue in the body that mixes up two different types of cells so completely, comprising extensive signaling network.[17]

A "two-hit hypothesis, which is one of the landmark hypotheses to explain the mechanisms for the process of AD, is developed by a team including and in the leadership of Dr Smith.[18] This hypothesis suggests that activation of mitotic processes is the first important factor of AD progression at the early stages. This would be a bit confounding when we remember the definition for postmitotic neurons, which are thought in terminal cell cycle arrest. However, more than a decade ago, Vincent and Davies first showed that cell cycle activation occurs in the brains of AD patients.[19] Induction of oxidative stress is the second, but equally important factor of AD pathogenesis. After the first hit, neurons recruit adaptive changes and enter a new "steady state" for many years functioning normally or at worse in a compromised fashion.[1] Compensatory changes induced by adaptation to the first hit make neuronal cell vulnerable to following insults ("the second hit") requiring additional compensatory alterations in other signaling pathways.[1,18]

In mature neurons, the cell cycle is normally arrested at the G0 phase. Hence, neurons must be subjected to potent stimuli to trigger the re-expression of cell cycle proteins and progression into G1 phase.[20] Amyloid beta acts as a proliferative signal for differentiated neurons, driving them into the cell cycle.[21] The cycle follows the typical sequence of events observed in proliferating cell, but does not progress beyond the S phase. In attempts to proceed to S phase of cell cycle, p53 intervenes and enforcing them to apoptotic process.[22] In another words,

any events that force a mature neuron back into the cell cycle are lethal rather than mitogenic for the neuron.

CONCLUSION

Insulin resistance related metabolic changes increase the oxidative stress in brain, which may result in DNA damage. This initiates DNA damage response in the diverse cells of the brain, which display close interrelations. In mitotically active glial cells, DDR initiates cell cycle arrest leading to senescence of cells. This, in turn, in the time period, renders the cell functional disability. In stead of supporting the neurons, they become the sources of events impairing neuronal function through their harmful and inflammatory secretions. On the other hand cell cycle re-entry due to DDR in the neurons renders them ready for the cell death processing.

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