Journal of Experimental and Basic Medical Sciences 2021;2(1):76-79

Review

Stress and Cancer

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ABSTRACT

Cancer, whose incidence is increasing day by day, is the uncontrolled division and proliferation of a cell. One of the factors that cause cancer is stress. Stress factors trigger the secretion of cortisol. Cortisol readily crosses the blood-brain barrier and binds to high affinity glucocorticoid (GR) and low affinity mineralocorticoid (MR) receptors. Cortisol activates the Wnt/β-catenin or PI3K/AKT signaling pathways by increasing the expression of growth factors and causes the proliferation of cells. These signaling pathways are associated with oncogenes such as Myc, cSRC. Oncogenes are the transformed form of protooncogenes and they transform normal cells into cancerous cells. Tumor suppressor genes are genes that fight with oncogenes and play a negative role in the cell proliferation process. In this review, all these signaling pathways triggered by stress and how they may cause cancer was mentioned and discussed.

Keywords: Cancer, cSRC, Myc, oncogene, stress, tumor suppressor gene, Wnt/β-catenin.

CANCER-STRESS RELATIONSHIP

All tissues and organs in our body consist of cells. Each cell has a certain division ability. When a cell begins to divide and multiply uncontrollably, it causes cancer. This uncontrolled cell division can be caused by genes, viruses that cause cancer, exposure to radiation, chemicals, impairments in the immune system, environmental factors or faulty DNA replication. In addition, excessive stress can lead to cancer.[1]

Factors such as environmental, physiological and chemical factors that disrupt the homeostasis of the body create stress. Some stress response is of course necessary for life. Short-term stress may increase motivation. However, the body naturally has a self-regulating mechanism. Because no organism can function properly under stress for a long time. Prolonged stress suppresses the immune system, keeps the rhythm of the sympathetic nervous system high and affects the endocrine system. The hypothalamus-pituitary-adrenal axis (HPA axis), the limbic system and the sympathetic part of the autonomic nervous system provide the neuroendocrine stress response in the body.[2]

Stress signals from the environment control the secretion of corticotropin-releasing hormone (CRH) from the paraventricular nucleus (PVN) of the hypothalamus to the pituitary. CRH releases adrenocorticotropic hormone (ACTH) from the pituitary. Glucocorticoid (CORT) is released from the adrenal glands in response to ACTH. This glucocorticoid is cortisol in humans and corticosterone in rats. Glucocorticoids can easily cross the blood brain barrier. Subsequently, glucocorticoids bind to high affinity glucocorticoid (GR) and low affinity mineralocorticoid (MR) receptors.[3]

Mineralocorticoid is most commonly found in the hippocampus.[4] The hippocampus is the place that connects various sensory, emotional and cognitive components of the brain as a result of any experience and creates the memory for all these experiences. This frame stores it in such a way that it can be taken as a conscious memory when the same experience is encountered later on.[5] Mineralocorticoid balances the basal activity of the HPA axis. Glucocorticoids

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Cite this article as: Çelik S, Çini N, Atasoy Ö, Erbaş O. Stress and Cancer. JEB Med Sci 2021;2(1):76-79.

doi: 10.5606/jebms.2021.75640

Received : March 03, 2021
Accepted : March 29, 2021
Published online : May 31, 2021

are found in many regions of the brain, including the frontal and cingulate cortex, hippocampus, basolateral and medial nuclei of the amygdala, nucleus accumbens, and thalamus. These receptors are involved in the formation of negative feedback mechanisms against the increased glucocorticoid response following stress.[4] When stress signals also activate neurons in the amygdala that synthesize CRH, the central limbic system is stimulated.[6] The limbic system processes sensory data input from the internal and external environment to decide the emotional, autonomic, motor and cognitive responses necessary for self-preservation and survival through memory and motivation.[7]

Catecholamine and norepinephrine secretion increases with the activation that occurs in the sympathetic nervous system in response to stress. Norepinephrine has a stimulating role in the CRH-secreting neurons of PVN. Catecholamines also play a role in negative feedback mechanisms by causing changes in hippocampal corticosteroid receptors.[8,9]

Cortisol secreted during stress actually helps the body to get rid of stress and regain homeostasis.[10] It is also known that excess cortisol secreted under extreme stress is associated with cancer survival.[11]

Women who are exposed to stress have a higher risk of developing breast cancer than women who are not exposed stres.[12] Investigating the effects of various hormones on cultured mouse breast cells. This cells constantly exposed to hydrocortisone (cortisol that used as medicine) had a decrease in the expression of the BRCA1 gene related to breast cancer. BRCA1 is a tumor suppressor gene involved in a number of cellular processes, including regulation of DNA repair and cell death.[13] Cancer metastases reduce by blocking stress hormones in animal models.[14]

Stressing the mice with physical restraint and excessive activation of their sympathetic nervous systems also caused more cancer lesions to occur in the bone. Treating these mice with propranolol, a beta-blocker (which blocks certain effects of the sympathetic nervous system), reduced the number of lesions in the bone.[15]

Cortisol has a proliferative effect in bovine endometrial epithelial cells. This effect occurs by increasing the expression of growth factors (VEGF and CTGF), activating the Wnt/β-catenin and PI3K/AKT signaling pathways. Growth factors (VEGF, CTGF and tgf-β1) play a role in proliferation, differentiation, and matrix repair. The PI3K/AKT pathway is a regulator of cell cycle, proliferation and apoptosis. And the Wnt/β-catenin signaling pathway plays a role in the proliferative phase of wound healing.[16]

It is known that there is an increase in cortisol level in postpartum depression cattle due to various stress causes. Komiyama et al.[17] reported that cortisol suppresses apoptosis of luteal cells to protect cattle. Junsheng Dong et al.[16] gave different doses of cortisol to study the expression of growth factors and the effect of cortisol levels on proliferation in bovine endometrial epithelial cells. After treatment with 5 ng/mL, 15 ng/mL and 30 ng/mL cortisol, VEGF mRNA levels increased at the treatment group compared to the control group.

These data show that 15 ng/mL cortisol promotes the growth of bovine endometrial epithelial cells by accelerating the G0-G1-S phase transition in the cell cycle. It has been shown that cyclin D1 and C-Myc are required for the transition of the G1/S and G2/M phases, respectively (16). And under 15 ng / mL cortisol treatment these C-Myc, cyclin D1, and β-catenin protein expression levels were also significantly increased. Thus, the increase of β-catenin activates the Wnt/β-catenin signaling pathway. Facilitation of the G1/S phase transition is a common phenotype in cancer cells.[18]

ONCOGENES

Oncogenes are genes that can turn normal cells into cancerous cells and are normally kept inactive in our body. Oncogenes are the form that proto oncogenes transform after differentiation due to different reasons such as DNA damage or virus effect. On the other hand protooncogenes are responsible for the expression of many proteins that function in the mechanisms that go on from the cell membrane to the nucleus by the signals they receive for growth, proliferation and apoptosis (cell death).[19]

MYC GENE AND WNT SIGNAL

Myc gene; is a transcription factor. It is effective on the expression of some genes involved in cell proliferation. Translocations affecting the Myc gene deregulate the gene but leave the protein coding region intact.[20] The gene reconstructs the resulting messenger RNA (mRNA). This genetic change prevents the Myc gene from functioning and causes it to turn into an oncogene. Amplification of Myc, n-Myc, and MYB genes is found in various tumor types, leading to an increase in encoded protein levels.[21]

Wnt signal activates Myc expression in cancer cells. A pathologically active Myc gene can cause an abnormally rapid cell turnover,[22] and disrupting cell proliferation in a wide range of cancer cells.[23] This process can be facilitated by the selection of enhancer regions, called super enhancer (OSE, oncogenic super enhancer), consisting of several hundred kilobases and to which proteins can be attached.[24] These types of OSEs increase the expression of target genes such as Myc by activating different signaling pathways. The affinity of OSE to active Myc alleles has been shown to be associated with increased nuclear expression of Myc mRNAs in colon cancer cells.

In computer modeling, the removal of Myc transcripts from the nuclear decay system of the cell confirmed that it explained the difference in Myc mRNA levels between colon cancer cells and normal colon epithelial cells. Since this feature is antagonized by the removal of the-catenin–TCF4 complex30, Wnt signaling appears to be an important way of establishing OSE-mediated gene transition function in colon cancer cells.[25]

C-SRC GENE AND WNT SIGNAL

c-Src is one of the protooncogene and non-receptor protein tyrosine kinases.[26] It can be activated by key receptor tyrosine kinases (epidermal growth factor receptor (EGFR)) and platelet-derived growth factor receptor (PDGFR) and protein tyrosine phosphatases (e.g., PTP1B and PTPPEST).[27,28] Once activated, c-Src can interact with various substrates and key effectors of oncogenic signal cascades that affect cellular functions such as cell cycle, cell proliferation, cell differentiation, and cell migration,[26,29] It is known that c-Src is overexpressed or over-activated in many human cancers, including prostate and breast.[30,31]

Overexpression of human epidermal growth factor 2 (HER2) leads to growth of breast tumor cells. HER2-mediated breast cancer progression requires Wnt/β-catenin signaling. There is a correlation between HER 2/3 overexpression and phosphatase and tensin homolog (PTEN) deletion with the Wnt signalling. Wnt activity is known to be insensitive to PI3K inhibitors, but sensitive to SRC-I1 (SRC inhibitor). Inhibition of cSRC resulted in a strong inhibition of Wnt activity, cell migration and metastasis. Upregulation of c-Src stabilizes HER2 and vice versa.[32]

DNA REPAIR GENES AND TUMOR SUPPRESSOR GENES

DNA repair and tumor suppressor genes are genes that play a negative role in cell proliferation. Tumor suppressor genes that directly suppress proliferation are called "gatekeeper" genes. Gatekeeper genes control the cell cycle. It can also direct the cell to apoptosis. APC, p53, Rb genes are examples of gatekeeper genes.[33] Apart from the gatekeeper genes, there are "caretaker" genes. Caretaker genes are the genes that repair DNA and prevent mutation formation. BRCA1, BRCA2, MLH1 and MSH2 genes are caretaker genes. And TP53 is an important tumor suppressor gene with both properties.[34]

In addition to these, there are tumor suppressor microRNAs (miRNAs). miRNA is a class of small RNAs that do not encode protein but regulate gene expression. Also some miRNAs regulate cell proliferation and apoptosis processes. Therefore, miRNAs can function as oncogenes or tumor suppressors. It has been observed that overexpression of miRNA let-7 (miRNA precursor) inhibits cancer cell growth. miRNAs fight together with p53 against RAS and Myc oncogenes that cause lung cancer.[35]

RESULT

In the light of experimental studies, it can be said that long-term stress directly causes cortisol release. Cortisol binds to MR receptors located in the hippocampus in the brain. Later on, when faced with the same stress factor, it creates a stress response by establishing a link with old memories stored in the hippocampus. High cortisol levels cause the release of growth factors. These growth factors also cause a faster phase transition in the cell cycle. The rapid phase transition of cells is a common condition in cancer cells. At the same time, high cortisol levels increase β-catenin protein expression levels. This activates the Wnt/β-catenin signaling pathway and causes cell proliferation. Wnt signaling activates Myc expression in cancer cells. Hence Myc oncogene can cause an abnormally fast cell cycle. At the end of all these processes, DNA repair genes and tumor suppressor genes take part in cell cycle phases or in direct suppression of oncogene expression in order to prevent cancer formation.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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