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LINKING STRESS WITH TELOMERASE DYNAMICS: A REVIEW

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ABSTRACT

Telomerase (the cellular enzyme primarily responsible for telomere length and maintenance) is a predictor of long term cellular viability. Telomerase activity is considered as a useful biomarker to understand the process of ageing. Evidence shows that chronic stress accelerates ageing by reducing telomerase activity resulting in the shortening of the length of telomeres. A correlation between telomerase activity and ageing has been established which proved that reducing psychological stress by intensive meditation training resulted in increased telomerase activity and telomere length which was correlated to increase in life span. In addition to telomere maintenance, telomerase has several non-telomeric functions that are still being explored. Recent studies have shown the neuroprotective effects of telomerase reverse transcriptase (the catalytic sub-unit of telomerase) in the brain tissue. Further research on the regulation of telomerase dynamics under stressful situations would offer the possibility of treating stress related and age related neurodegenerative diseases. This review focuses on the telomeric and non-telomeric functions of telomerase with special emphasis on linking stress with telomerase dynamics and telomerase in the brain tissue.

KEYWORDS: stress, telomerase, TERT, depression, anxiety, brain tissue.

INTRODUCTION

The relationship between psychological functioning and physical health has long been documented and today numerous studies have demonstrated links between chronic stress and indices of poor health including risk factors for the development of depression/anxiety, cardiovascular disease and poorer immune function.[1] At the physiological level, though the mechanism of the stress response involving the glucocorticoids and the Hypothalamo-Pituitary-Adrenal (HPA) axis has been well established, the mechanism by which stress influences depression or anxiety is largely unknown.

At the cellular level, the correlations between psychological functioning and physical health are only beginning to be understood.[1] Today, modern science proves that chronic stress accelerates cellular ageing by reducing telomerase activity resulting in the shortening of the length of telomeres.[1] Ageing works at different levels, with signs first appearing at the elementary level of a cell. On a very basic level, the human body is a combination of cells. In the year 1960, a research by Dr. Leonard Hayflick, concluded that differentiated cells could undergo only a limited number of divisions before dying. After each cell division (mitosis) the telomeres at the ends of chromosomes shorten till they reach a critical point after which further division becomes increasingly difficult (eventually impossible) for each subsequent copy of the cell. Some cells do not encounter Hayflick limit due to telomere lengthening. Human germ line cells (sperm and ova) and cancer cells show no Hayflick limit.[2] Subsequent research by Elizabeth H. Blackburn *et al.* made a major scientific breakthrough which has revealed that the enzyme telomerase is responsible for the maintenance of telomere length at the ends of chromosomes. There is a correlation between telomerase activity and ageing with decrease in telomerase activity resulting in premature ageing.[1]

Telomere length has recently been proposed as a useful 'psychobiomarker' linking stress and disease.[3] Shortened telomere length and reduced telomerase (the cellular enzyme primarily responsible for telomere length and maintenance) predict a host of health risks and diseases[4,5], and new findings suggest they may be regulated in part by psychological stress, and well-being.[6,7] A study performed by the nobel laureate, Elizabeth H. Blackburn, revealed that an intensive meditation training for a period of 3 months reduced psychological stress and increased telomerase activity in leucocytes with implications for telomere length and immune cell longevity.[1] In view of all these studies, it is understood that chronic stress influences telomerase activity and drugs that reduce chronic stress, depression

or anxiety, could increase telomerase activity. With this idea, this review brings together various studies linking stress and telomerase dynamics along with an overview on the nature of depression and anxiety, drugs used for the treatment of these disorders and the effects of antidepressant drugs on telomeres and telomerase in the peripheral blood mononuclear cells with special emphasis on telomerase dynamics under stress in the brain tissue.

Structure and function of telomeres

Telomeres are protective DNA sequences at the ends of eukaryotic chromosomes that maintain genomic stability during the process of cellular replication, but they shorten with each cell division and additionally shorten under conditions of oxidative stress unless counteracted by telomerase action. Below a critical telomere length, cell division can no longer occur and a cell is at a higher risk for entering a state of senescence.[1] In humans they consist of several kilobases of the 6 base pair repeats (TTAGGG). These nucleoprotein structures harbor binding sites for a group of telomeric proteins, which collectively constitute the shelterin complex that executes protective mechanisms against chromosomal degradation, end-to-end fusions and DNA-damage responses. The shelterin complex is composed of six members—telomeric repeat binding factor 1 (TRF1), TRF2, TRF1-interacting nuclear factor (TIN2), protection of telomeres 1, TIN2 organizing protein, and repressor-activator protein 1 (RAP1). Besides their role in capping chromosome ends, shelterin components have been demonstrated to regulate telomerase recruitment and activity at the telomere.[8] Telomeres and telomeric proteins play a nonredundant role in maintenance of chromosomal stability and genomic integrity. However, extra-telomeric roles of shelterin components have been uncovered by a number of recent studies, revealing a new perspective on telomeres as biologic signalling hubs in mammals.[8] Telomeres protect the ends of chromosomes from degradation by exonucleases and ligases and from end-to-end fusion, rearrangements, and the loss of terminal DNA segments that occur during the process of replication.[9] The DNA of telomeres-the terminal DNA - protein complexes of chromosomes - differs notably from other DNA sequences in both structure and function. The outstanding work of Elizabeth H Blackburn has highlighted its remarkable mode of synthesis by the ribonucleoprotein reverse transcriptase, telomerase, as well as its ability to form unusual structures in vitro. Moreover, telomere synthesis by telomerase has been shown to be essential for telomere maintenance and long-term viability.[10]

Telomeres in human somatic cells gradually shorten with each successive cell division through replication-dependent sequence loss at DNA termini resulting in chromosome instability, leading to cellular senescence. A possible cause of human telomere shortening is repression of telomerase, a specialized ribonucleoprotein complex that consists of multiple protein subunits and a structural RNA component that contains a template sequence for the telomeric repeat.[1] Due to its own RNA moiety, telomerase is able to extend the 3' overhang of telomeres, generated during DNA replication and thus counteract telomere shortening. Without sufficient telomerase activity present, telomeres shorten due to the inability of conventional DNA polymerases to replicate the lagging strand at the end of chromosomes, called the '*end replication problem*'.[11] Research has shown that telomerase activity is inactivated or repressed in the majority of normal somatic tissues but is activated in germ cells and in most malignant tumors . Telomerase reactivation could thus be a major step in human carcinogenesis.[9]

Structure and function of telomerase

Structure of telomerase:

The telomerase enzyme consists of two major components that work together. The component produced from the TERT gene is known as TERT (Telomerase Reverse Transcriptase), the catalytic sub-unit of telomerase. The other component is produced from a gene called TERC and is known as TR (Telomeric RNA). The TR component provides a template for creating the repeated sequence of DNA that telomerase adds to the ends of chromosomes. The TERT component then adds the new DNA segment to chromosome ends.[12]

Function of telomerase.

Telomerase maintains structures called telomeres, which are composed of repeated segments of DNA found at the ends of chromosomes. Telomeres protect chromosomes from abnormally sticking together. In most of the cells, telomeres become progressively shorter as the cell divides. After a certain number of cell divisions, the telomeres reach a critical length and they trigger the cell to stop dividing or to self destruct (undergo apoptosis). Telomerase counteracts this shortening of telomeres by adding small repeated segments of DNA to the ends of chromosomes each time the cell divides.[12]

Additionally, telomerase can contribute to cell survival and stress resistance in a largely telomere-independent manner. Telomerase has been shown to shuttle dynamically between different cellular locations. Under conditions of increased oxidative stress telomerase is excluded from the nucleus and can be found within mitochondria. This phenotype correlates with decreased oxidative stress within telomerase expressing cells and improved mitochondrial function. It has been, therefore, suggested that mitochondrial protection could be an important non-canonical function for telomerase in cell survival and ageing.[13]

There is growing evidence that telomerase has other (non-canonical) functions. These functions can be divided further into those that require telomerase activity but not telomere lengthening (non-canonical I or NC I) and those that require neither telomerase activity nor

telomere lengthening (non-canonical II or NC II). NC I functions are associated with the induction of neoplasia in both epidermis and mammary gland, the correct response to DNA damage, and insensitivity to transforming growth factor beta. In contrast, NC II functions are not sufficient for the induction of neoplasia and are associated with the activation of the WNT and MYC signalling pathways in keratinocytes and a more general resistance to the induction of apoptosis by a variety of stimuli. The over expression of either TERT or TERC appears to be capable of providing NC I functions but NC II functions require neither TERC nor the integrity of the TERT catalytic site. The molecular mechanisms underpinning both NC I and NC II are still unclear.[12]

In most types of cells, telomerase is either undetectable or active at very low levels. However, telomerase is highly active in cells that divide rapidly, such as those that line the lungs and gastro intestinal tract, cells in bone marrow, and cells of the developing fetus. Telomerase allows these cells to divide by maintaining telomere length thereby preventing cell damage or apoptosis. Telomerase is also abnormally active in most cancer cells, which grow and divide without control.[12]

Relation between TERT and telomerase activity

The TERT gene provides instructions for making one component of an enzyme called telomerase.[12] TERT is the catalytic subunit of telomerase.[14] The telomerase catalytic subunit (TERT) in association with the telomerase RNA component (TERC) forms an enzyme, the telomerase (TERT-TERC), with reverse transcriptase activity that recognises the 3'-OH at the end of the G-strand overhang and elongates the telomere using TERC as the template. TERT has a role as a transcriptional modulator of the WNT-Î²-catenin (Î²-cat) signalling pathway. On stimulation of WNT receptors at the plasma membrane, TERT forms a complex with the WNT transcription factor BRG1 (also known as SMARCA4) and binds to the promoters of WNT-target genes, regulating their expression. In the mitochondria, TERT associates with the RNA component of mitochondrial RNA processing endoribonuclease RMRP, and this complex shows an RNA-dependent RNA polymerase (RDRP) activity. TERT-RMRP RDRP produces RMRP-derived double-stranded RNAs (dsRNAs) that are further processed into small interfering RNAs (siRNAs) in a Dicer-dependent manner that controls the endogenous levels of RMRP.[8] It has been speculated that TERT association with, as yet unidentified, RNAs may regulate gene expression by generating specific siRNAs. In the mitochondria, TERT has also been processed to have a role in regulating oxidative damage-induced apoptosis. Oxidative stress triggers nuclear export of TERT to the mitochondria.[8]

The 'Stress' Physiology

The word 'stress' pertains to a set of physiological response mechanisms regulated by the endocrine system. It is a protective mechanism that facilitates an organism to cope with various stressful situations and this process brings about psychological and biological changes that work within the organisms' homeostasis mechanism. Chronic stress when left untreated leads to serious disorders like weakened immune system, high blood pressure, anxiety, insomnia, depression, heart disease and obesity.[15] The relation between stress and mental illness can be better understood with a thorough comprehension of the physiology of stress. Two interrelated systems are involved in stress physiology - the *Sympathetic-Adreno-Medullary* (SAM) system and the *Hypothalamic-Pituitary-Adrenal* (HPA) axis. In SAM activation, a stimulus that disturbs an organism's homeostasis is labelled as a stressor by the cerebral cortex. This information is transmitted to the hypothalamus which initiates an immediate fight or flight response. This is mediated by the sympathetic part of the autonomic nervous system resulting in the stimulation of sympathetic nerves and the adrenal medulla to secrete the catecholamines, epinephrine and norepinephrine.[16] The secreted catecholamines results in increased heart rate, blood pressure, blood glucose, and dilation of bronchioles. Activation of SAM axis is a short term and immediate response to stress. In the long term, the HPA axis is activated. The stressor stimulates the hypothalamus to release corticotrophin releasing hormone (CRH) which stimulates the anterior pituitary to secrete adrenocorticotrophic hormone (ACTH) which in turn stimulates the release of glucocorticoids and mineralocorticoids from the adrenal cortex resulting in increased catabolism of fat and protein, increased gluconeogenesis, decreased inflammatory and immune response, increased blood pressure. All these changes together result in a prolonged response to stress.[16]

'Stress' becomes detrimental only when it crosses the limits of the bodily regulatory systems. The regulatory mechanisms fail to operate beyond a threshold limit thereby resulting in the manifestation of a psychological disorder associated with physical symptoms, depending on the duration and intensity of the stressor. Although genetic and congenital factors could result in these disorders, their percentage is relatively very low compared to the disorders that occur due to inefficient stress management.[15] The common manifestations of chronic stress are depression and anxiety. The nature of these disorders has been described briefly.

Depression

Depression is a potentially life-threatening disorder that affects millions of people all over the world. This disorder can occur at any age from childhood to late life and causes severe distress and disruption of life and, if left untreated, can be fatal. Depression is not a homogeneous disorder, but a complex phenomenon, which has many subtypes and probably more than one etiology. It includes a predisposition to episodic and often progressive mood disturbances, differences in symptomatology ranging from mild to severe symptoms

with or without psychotic features, and interactions with other psychiatric and somatic disorders. The psychopathological state involves a triad of symptoms with low or depressed mood, anhedonia, and low energy or fatigue.[17] Other symptoms such as sleep and psychomotor disturbances, low self esteem, feelings of guilt, suicidal tendencies, and autonomic and gastrointestinal disturbances, are also often present. Another important aspect of depression is the high rate of comorbidity with other psychiatric disturbances. Anxiety, especially panic disorder, is often associated with affective disorders.[17]

Anxiety

Everyone experiences symptoms of anxiety, but they are generally occasional and short-lived, and do not cause problems. But when the cognitive, physical and behavioural symptoms of anxiety are persistent and severe, and anxiety causes distress in a person's life to the point that it negatively affects his or her ability to work or study, socialize and manage daily tasks, it may be beyond normal range.[18] These symptoms may indicate an anxiety disorder: Cognitive symptoms: anxious thoughts, anxious predictions and anxious beliefs; Physical symptoms: excessive physical reactions relative to the context. The physical symptoms of anxiety may be mistaken for symptoms of a physical illness, such as a heart attack; Behavioural symptoms: avoidance of feared situations, avoidance of activities that elicit sensations similar to those experienced when anxious, subtle avoidances and safety behaviours.[18] Three major neurotransmitters are involved in anxiety: serotonin, norepinephrine, and gamma-aminobutyric acid (GABA).[19]

The glucocorticoid stress response and telomere dynamics

The vertebrate 'stress response' is a suite of integrated physiological response mechanisms regulated primarily by the endocrine system, which allows organisms to cope with stressors. The cascade of hormones released during a stress response trigger a reallocation of resources to physiological processes and behaviours that maximize chances of survival. Two of the major hormone classes involved are catecholamines, including adrenaline and noradrenaline, and steroid glucocorticoid hormones (GCs), such as cortisol and corticosterone. While the major glucocorticoid in humans is cortisol, in rodents it is corticosterone. Secretion of these hormones is regulated in part by a negative feedback system. Both physical and psychological conditions at the time of activation of the stress response impact an organism's response; thus the physiological state of the organism must be taken into account when evaluating the levels of stress.[20,8] The Hypothalamic-Pituitary-Adrenal (HPA) axis is responsible for the secretion of glucocorticoids. Glucocorticoids act to mobilize energy stores and also to inhibit other physiological systems (e.g reproduction, immune function, growth) in order to conserve energy during the stress response. Glucocorticoids also act on the brain to increase appetite and to increase locomotor activity and food-seeking behaviour, thus regulating behaviours that control energy intake and expenditure.[21] To maintain normal physiological function, glucocorticoids are secreted at a baseline level, although currently there is controversy whether baseline levels of glucocorticoids are a reliable indicator of an organism's fitness.[22] During stress, glucocorticoid secretion increases in part to mobilize more metabolic fuel to cope with the stressor, and once the stress is overcome glucocorticoids return to a baseline level. While the immediate stress response provides significant benefits in the short term, the stress response may be detrimental and even fatal if activated for the long term.[23] One idea that has permeated gerontology for a century is that physiological stress accelerates the aging process. The risk of disease can be increased and exacerbated by prolonged exposure to psychological or physical challenges.[24] To better elucidate the link between physiological stress and oxidative stress, Epel *et al*.[25] connected data on chronically stressed individuals with measures of oxidative stress and telomere shortening. They found that women with higher levels of stress, by both an objective and subjective measure, had shorter telomeres, lower telomerase activity, and higher oxidative stress compared with women with lower levels of stress. This suggested physiological stress may directly influence premature cellular senescence as the lymphocytes of the stressed women had aged an equivalent of 9-17 more years based on telomeres loss in comparison to the low stress woman.[6] The pioneering work of Epel and colleagues established that chronic stress resulted in an increased rate of telomere shortening and decreased telomerase activity. Further work showed that elevated glucocorticoids were related to the negative effects on telomeres, suggesting that stress hormones mediate the destructive effect of stress on telomere maintenance.[26] This work has been correlative and studies exploring the mechanistic links between glucocorticoids and telomere regulation have been limited. Recently, a mechanism linking glucocorticoids and telomere loss was proposed. Chronic exposure to cortisol in vitro down- regulates telomerase activity in activated human T lymphocytes. Specifically, this effect is caused by a reduction in the transcription of TERT, the catalytic component of telomerase,[27] and it may be that elevated glucocorticoids hasten telomere loss through this mechanism.

Linking depression with telomerase activity

Chronic stress is generally manifested with varying degrees of severity ranging from mild symptoms of anxiety to severe forms of depression. The severity, type, and duration of the stressor coupled with the ability of the organism to cope with the stressor will determine the disorder. Major depressive disorder (MDD) is among the leading causes of disability worldwide, but its underlying pathology is poorly understood. Research is now aimed at characterising its pathophysiology on a cellular and molecular level.[28,29] A novel locus of cellular pathology,

leukocyte telomere shortening, has recently been proposed. Premature telomere shortening could suggest an accelerated rate of cell aging in MDD, which could have important health consequences.[30,31,32,33,34] Recent studies have suggested prematurely shortened leukocyte telomeres in individuals with MDD, chronic stress,[25,35,36,37] histories of childhood adversity or maltreatment,[38] and several diseases associated with aging.[39,40,41,42,43] A study carried out by Wolkowitz et al, proposed that - it is possible that either high or low telomerase activity could be associated with shortened telomeres. Low telomerase activity could cause shortened telomeres by limiting the replenishment of shortened telomeres.[44] Conversely, unusually high telomerase activity could represent a compensatory attempt to maintain telomere length in the face of cellular stress.[35,45] Further, as telomerase has a number of poorly understood non-telomeric functions,[14,46,47,48,49,50] and abnormal telomerase activity in depression could result in unanticipated consequences.

Evidence of TERT gene expression & telomerase activity in the brain tissue

Telomerase has been thought that it is not expressed in post-mitotic cells. Research performed by Haiyan *et al*,[14] reveal that telomerase activity and its essential catalytic subunit, telomerase reverse transcriptase (TERT), are expressed in neurons in the brains of rodents during embryonic and early postnatal development, and are subsequently down regulated. TERT exerts its anti-apoptotic action at an early stage of the cell death process prior to mitochondrial dysfunction and caspase activation. TERT may serve to promote neuron survival in the developing brain, and down regulation of TERT in the adult brain may contribute to the increased neuronal vulnerability in various age related neurodegenerative disorders.[14]

A few experiments have proved the existence of TERT in neurons of the adult brain *in vitro*. A study carried out by Li *et al*, has demonstrated the neuroprotective role and mechanisms of TERT in neurons with oxygen-glucose deprivation *in-vitro*.[51] Research carried out by Haiyan *et al*, has demonstrated a protective role for the telomerase protein TERT in cultivated mouse neurons during brain development, against excitotoxic stresses from N-methyl-D-aspartate (NMDA) & glutamate, and agents known to be involved in neurodegenerative diseases such as beta amyloid peptides and hyperphosphorylated tau.[14] In contrast, lack of telomerase and TERT protein increase oxidative stress and decrease neuronal survival. There is emerging evidence of a beneficial role of telomerase in human brains and animal models of neurodegenerative diseases suggesting to explore the possibility of using telomerase activators as neuroprotective agents to combat brain ageing and to ameliorate neurodegenerative diseases.[14]

An *in vivo* study by Barry E. Flanary,[52] has shown that telomerase activity was found to slowly increase from day 21 to approximately 6 months of age with the cerebellum exhibiting higher activity than cortex in all instances which corresponds to the shortening of telomeres from day 21 to approximately 5 months of age. The results of the study indicate that telomere shortening occurs in rat brain *in vivo* with increasing age, and that the low levels of telomerase activity present may be preferentially recruited to maintain the shortest telomeres while allowing the longer ones to shorten more rapidly.[52] Glia, particularly microglia, are the only adult cell type in the central nervous system (CNS) that exhibit a significant mitotic potential, and are thus susceptible to telomere shortening and telomerase activity.[52]

CONCLUSION

Though there are studies on the effect of stress on leukocyte telomerase activity, studies on the effect of long-term stress on telomerase activity in the adult brain tissue *in vivo* are inadequate. Determination of telomerase activity or TERT regulation in adult brain tissue *in vivo* and establishing a relation between leukocyte telomerase activity and telomerase activity in the brain tissue is therefore necessary to deepen the understanding of the relation between stress, psychological disorders and telomerase activity.

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