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## Clinical implications of cellular stress responses

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### Abstract

Cellular stress response is a reaction to changes or fluctuations of extracellular conditions that damage the structure and function of macromolecules. Different stressors trigger different cellular responses, namely induce cell repair mechanisms, induce cell responses that result in temporary adaptation to some stressors, induce autophagy or trigger cell death. Inability to repair the damage or exposure to prolonged stress may contribute to aging. Persistent cellular stress often enhances susceptibility to cancer and aging associated diseases. Cells and tissues are increasingly being used for transplants and other novel therapeutic methods in which the quality

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well being of cells is of paramount importance for the treatment to succeed. Therefore, discovering the mechanisms of cellular stress responses and the ability to detect and ameliorate them is important in prevention of development of disorders developed by persistent stress and for the success of transplantation and other cell related methods of regenerative medicine.

**KEY WORDS:** Cell stress, adaptive response, aging, transplantation, cancer, cardiovascular disease

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## Types of cellular stress responses

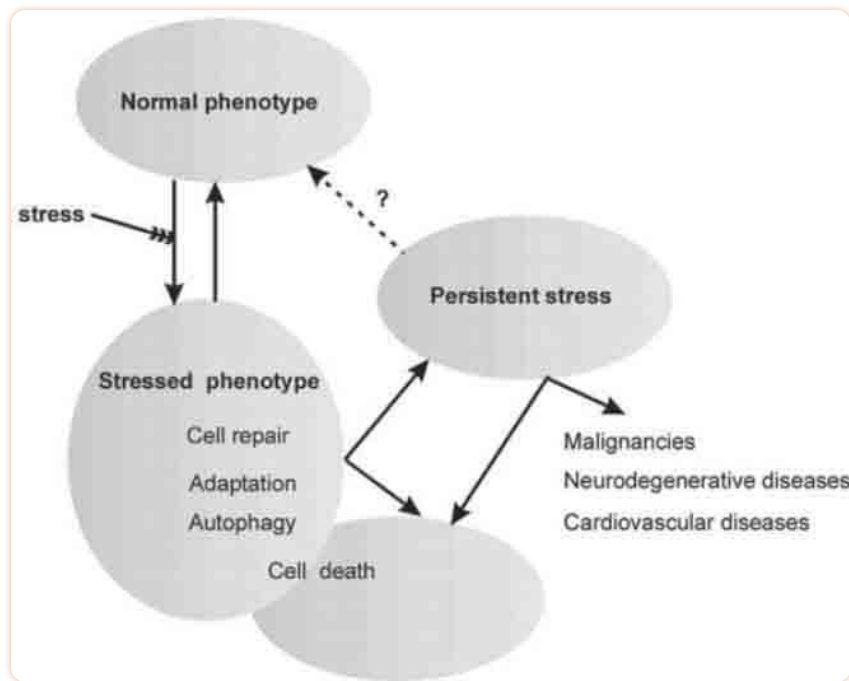
Cells are exposed to many internal and external stimuli when they are a part of a normal tissue or when they grow in culture, some of which induce stress. Stressors can trigger a variety of stress responses. Depending on the severity and duration of stress encountered, the cells either re-establish cellular homeostasis to the former state or adopt an altered state in the new environment. For example, stressors can damage intracellular macromolecules, including proteins, DNA, RNAs and lipids. This results either in cell reparation or cell death. Less severe stress may change cellular responses to subsequent environmental signals [1]. There are four basic types of responses (Figure 1). The stressors can (1) induce cell repair mechanisms, (2) induce cell responses that result in temporary adaptation, (3) induce autophagy or (4) trigger cell death [2]. Most of the responses are intended to restore the normal physiology of cells; in the process, they can use considerable amounts of resources. The responses that result in temporary adaptation to stress are reported the least systematically. Nevertheless, many biological and biomedical disciplines independently documented adaptive responses of organisms after the exposure of low doses of stressors [3]. For example, a

low dose of mutagen would protect against damage from a subsequent exposure to the same, and sometimes different, mutagen [4, 5]. Adaptive response was also observed in the field of epidemiology; initially on alcohol consumption and various parameters of cardiovascular diseases [6]. Other examples of adaptation to low doses of stressors include the reports on the effects of low doses of radiation [7], ischaemia [8] and other chemicals [9]. Also, anti-aging and life-prolonging effects of many stressors, such as e.g. calorie restriction, point in the same direction [10]. The above papers only reported observations of the connection of low dose of stressor to adaptation. The report by Nipic et al. [1] demonstrated the first mechanism behind the cellular adaptation to stress; the adaptation to stress results in inhibition of apoptosis triggering by caspase-9 in stress phenotype.

Therefore there is no triggering of apoptosis through one of the two main apoptotic triggering pathways (i.e. intrinsic pathway) in the stress phenotype. Nevertheless, the suitable triggers can still trigger apoptosis through different pathways [1]. The question remains whether different types of stressors result in the same phenotype, or better whether the adaptation to one type of stress would protect the cells and organisms to moderate amounts of other stressors as well? Various types of low dose of external stressors induce the adaptation to stress from yeast to higher organisms [11, 12] (Figure 2). Whether the adaptation to various stressors results in the same or in different types of cellular and organismal responses remains to be determined in future. The connection between the intracellular (intrinsic) stressor and potential adaptation is even more difficult to establish.

Stressors can trigger cellular responses, from within cells and by the immune system. The stress responses of non-immune cells are described sometimes as an intrinsic stress response, while the stress responses of the immune system are called extrinsic stress response [13]. The latter functions by signaling with cytokines and clonal selection of cells. The transcription of many of the genes that participate in immune response is regulated by NF- $\kappa$ B, which is a growth and divi-

sion-promoting factor and can thus turn into an oncogene. The intrinsic stresses can be DNA damage, hypoxia, low levels of glucose and amino acids, interference with mitochondrial and ribosomal biogenesis, the action of some toxins, etc. The transcription factor transformation-related protein 53 (p53) responds to such stressors. p53 also regulates many genes that prevent DNA damage or help in the DNA repair. Hypoxia, glucose levels and mitochondrial and ribosomal biogenesis are regulated by the interactions of the p53 pathway genes with the insulin-like growth factor 1 (IGF-1)/mTOR pathways and the regulation of the endosomal compartment by p53-induced genes [14]. In addition to its functions as a transcription factor in the nuclei, cytoplasmic p53 has transcription independent activities [15]. p53 is inactive in unstressed cells. Stress signal results in higher levels of p53, through post-translational modifications, which are selectively activated by different stress signals. This leads to transcription of different sets of genes resulting in cell cycle arrest, apoptosis or the cells lose the ability to divide (are senescent). The activation of p53 or NF- $\kappa$ B including pathways are mutually exclusive within the cells. The activation of p53 results in slowing glycolysis and restoring oxidative phosphorylation, while the activation of NF- $\kappa$ B pathway activates cell division and utilizes large amounts of glucose and predominant use of glycolysis [13]. Studying the adaptation to stresses is extremely important for the field of medicine, both for basic medical science and clinical practice. The contribution of stress responses to aging and disease development will be described in this paper. Testing for the possible adaptation to stress can improve the design and models of studies in different fields: in pharmacology how safe and effective doses of drugs are determined (and tested), how environmental, occupational and consumer exposure standards are derived and how risks and benefits are assessed.



**FIGURE 1**

Cellular responses to stress and their consequences Stress can induce the changes from normal to stressed cell phenotype. Characteristic are one or more of the following pathways: the induction of cell repair mechanisms, cell responses that result in temporary adaptation, autophagy or cell death. Most of these responses can restore the normal physiology of cells; failure to do so result in prolonged stress or cell death. Prolonged stress enhances the susceptibility to cancer and to aging associated diseases.

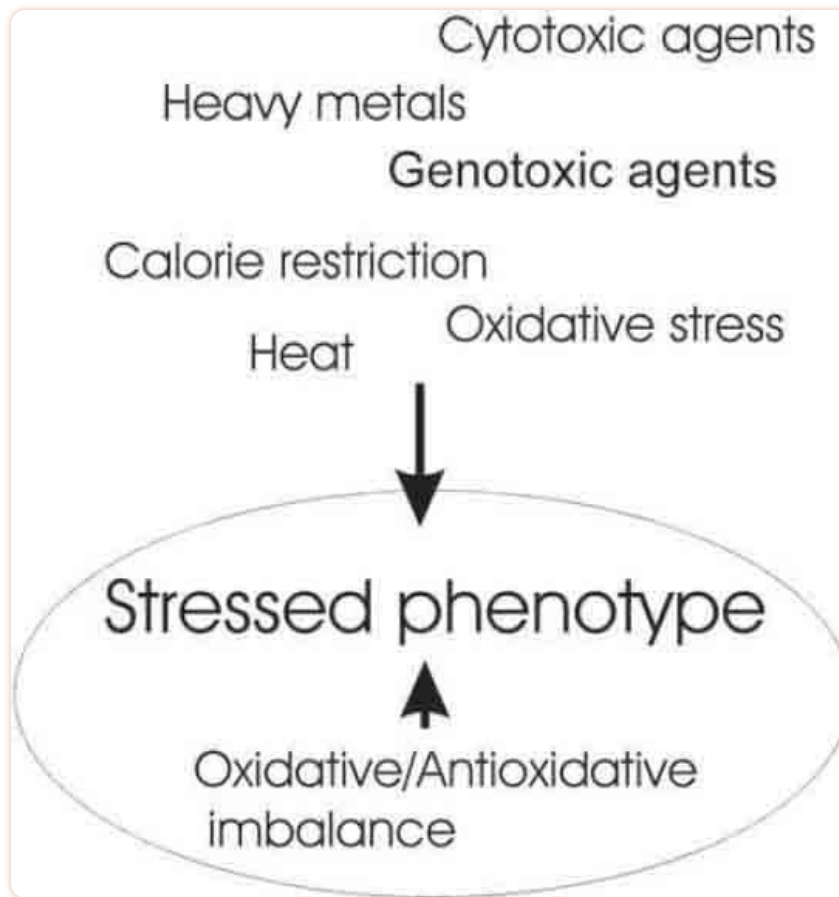


FIGURE 2

External and internal stressors can induce cellular adaptation to stress. Potent inducers of cellular stress from within and outside the cells are excessive amounts of oxidants. As some oxidants (reactive oxygen species) are needed for proper functioning of the organism, it is the oxidative/antioxidative imbalance that results in cellular stress [19].

## Stress and aging

Accumulation of damaged macromolecular structures over time was long recognized to lead to aging. There are many studies, which link the decline in the effectiveness and integration of stress responses to ageing and the development of age-related diseases [16]. Modulation of mitochondrial and metabolic functions and mobilization of macro-

molecular maintenance and repair leads to life extension in modeling organisms. The mitochondrial free radical theory of aging implies that aging is caused by damage of macromolecules by mitochondrial reactive oxygen species (ROS) [17]. Whether ROS damage is an initial trigger or the main effector of the aging process is a topic of current debates [18]. Certainly, the aging process results from a loss of homeostasis due to accumulation of molecular damage to DNA, proteins and lipids. However, the transient generation of ROS, within boundaries, seems to be essential to maintain the cellular homeostasis during physiological and stress conditions. This is supported by the observations of the importance of proper oxidative/antioxidative balance for health and longevity [19]. The administration of antioxidants to various species of invertebrates and humans did not result in anticipated beneficial effects. On the other hand, low amounts of ROS may act as secondary messengers in cells; the studies in *C. elegans* and rodents have even reported that the increased production of ROS in young animals resulted in life extension [20, 21, 22]. This may be an evidence of the beneficial role of stress responses. Needless to say that higher amounts of ROS exposure may be involved in aging and disease progression and in such cases the toxicity of ROS participates in creating a damage, which is well documented in aging and neurodegenerative diseases [23].

### Stress and chronic diseases

Excessive amounts of ROS, overloading of the peroxidized polyunsaturated fatty acids (hydroxynonenals), products of cholesterol oxidation, mutations favoring protein misfolding, altered glycosylation, etc. may cause a severe stress and lead to accumulation of unfolded or misfolded proteins in brain cells [24]. The so called 'aggregated proteins' accumulation is a hallmark of many neurodegenerative diseases, like Alzheimer's, Parkinson's, Huntingdon's, amyotrophic lat-

eral sclerosis and Friedreich's ataxia [24, 25]. Cell stress and stress proteins have a profound effect in triggering/developing the cardiovascular diseases, too. It was first observed in 1970's that the patients infected with *Mycobacterium tuberculosis* or *M. leprae* have antibodies to an antigen, which was identified subsequently as heat shock protein (Hsp60). It is now confirmed that Hsp60 and other chaperones, like Hsp10, Hsp70 and Hsp90 family members are strong immunogens and immunomodulators in experimental models of arthritis, diabetes and atherosclerosis [26]. Apart from the potent intracellular role of Hsp proteins as facilitators of correct protein folding and re-folding of misfolded proteins, many of them are potent activators of immune cells and may act as adjuvants and as immunogens, possibly as in the case of Mycobacterial infection. Atherogenesis may be driven by cross reactive immunity to bacterial Hsp60 proteins. Namely, the host Hsp60 proteins are expressed on the stressed endothelial cells. The exposure to long term severe non-lethal stress may therefore result in pathology.

### Cellular adaptation to stress in tumor and normal cells

The accumulation of damage over long-term enhances the susceptibility to aging-associated illnesses, described above, and also to cancer (Figure 1). Rudolf Virchow observed the connection between chronic inflammation and cancer in 1863 [27]. It still stands that the increased risk of malignancy is connected to chronic inflammation caused either by chemical and physical agents or autoimmune and inflammatory reactions of uncertain aetiology. Prolonged stress therefore may result in malignancy. The well known examples include the connection of prolonged exposure to silica, asbestos and cigarette smoke to the increased risk of developing bronchial cancer; chronic infections with *H. pylori* and *Papillomavirus* and the risk of developing gastric and cervical cancers, respectively, etc [27]. When normally



growing cells are in contact with carcinogens, they may respond by undergoing growth arrest, apoptosis or necrosis. Also, a population of genetically modified cells may emerge with intrinsic or induced resistance to apoptosis [28]. Control of intracellular concentration of ROS seems critical for the survival of cancer cells. For example, the acute increases in intracellular concentrations of ROS may cause the inhibition of glycolysis and divert the glucose flux into the pentose phosphate pathway in human lung cancer cells [29]. This generates sufficient antioxidant response for detoxification of ROS, therefore enables the cancer cells to withstand the initial oxidative stress and subsequently enables their proliferation. The epithelial cells detached from the extracellular matrix would normally not survive, as such cells lose the ability to take up glucose, which result in ATP deficiency. The detached epithelial cells can be rescued through two different pathways [30]. The expression of cancer promoting oncogene ErbB2 restores the cell's ability to take up glucose and reduces the levels of ROS through the antioxidant-generating pentose phosphate pathway. Alternatively, the ATP deficiency could be rescued by antioxidant treatment, which stimulates fatty acid oxidation otherwise inhibited by detachment-induced ROS. The latter cell rescue occurs without the rescue of glucose uptake. Therefore, the perturbation of oxidant/antioxidant balance (the lowering of oxidative stress) promotes the survival of pre-initiated tumor cells even detached from the extracellular matrix environment by altering metabolic regulation, which results in enhanced malignancy [30]. To summarize, pre-cancer cells may lead to neoplasia as a result of their altered growth/death ratio, due to disrupted cell cycle control, genomic instability or altered metabolism. Even tumor cells can become more invasive if they are preexposed to stress, i.e. preconditioned. Acutely hypoxic tumor cells were found to be more metastatic than normoxic [31]. Patients with hypoxic primary tumors have an increased frequency of locoregional treatment failure, increased incidence of distant metastases and poor disease-free and survival rates [32]. Mice exposed to acute cyclic hy-

poxia showed increased incidence of pulmonary metastases, their primary tumors have increased blood perfusion, microvascular density and expression of vascular endothelial growth factor-A.

Preconditioning against the proteins induced as the consequence of stress responses may improve the outcome of cancer therapy in experimental models. Neutralization of vascular endothelial growth factor (VEGF) in endothelial cells by specific antibody could enhance the anti-tumor activity of carboplatin in an *in vivo* ovarian cancer model [33]. On the other hand, decreasing the stress response in tumor cells by preconditioning them with various agents is often explored in experimental models with the aim of developing the method to increase the susceptibility of tumor cells to treatment. For example, the abolition of stress-induced protein synthesis by cycloheximide sensitizes leukemia cells to anthracyclins, the currently successful anticancer drugs [34]. In conclusion, the connection between chronic inflammation and cancerogenesis is known for over hundred years; one of the recently established hallmarks of cancer is the presence of stress phenotypes [35].

## Stress and transplantation

As discussed above, the adaptation of normal cells to stress is beneficial in the short term and can be detrimental in the long term. There are medical procedures during which the cellular resistance to stress is beneficial, for example, when handling the cells and tissues for transplants. Also, the transplanted cells must thrive *in vivo* at the site of transplantation, in spite of the fact that the stress factors, which caused the deterioration of original cells, may be still present at the site of transplantation. The increased survival of cells in experimental models is attempted often through preconditioning of transplanted cells with chemical agents and by gene transfer [36-39]. The preconditioning of retinal pigment epithelial cells by limited exposure to

non-lethal oxidative stress results in protection against subsequent H<sub>2</sub>O<sub>2</sub>-induced cell death [40]. Such preconditioning of retinal cells may improve the survival of these cells after the transplantation into the environment with increased oxidative stress. Therefore, such preconditioning is potentially important as a basis for the development of new treatment procedures. Preconditioning has a physiological role, too. Some of the cells in the organism need appropriate stress in order to function properly. For example, vascular endothelial cells need appropriate physical stimuli to maintain their structure and function [41]. The vascular endothelial cells of liver, the sinusoidal vascular endothelial cells, have small pores, through which shear stress is applied to hepatocytes as well. There is an almost constant shear stress in undamaged liver. Remodeling of sinusoidal structures was observed in the liver culture exposed to either no shear stress or to high shear stress, compared to the tissue exposed to moderate shear stress [41]. This find seems to have important implications for medical procedures on liver. Rapidly increased portal flow producing high shear stress may occur after massive liver resection or during ischemia/reperfusion in liver transplantation [41]. The increased portal flow may result in postoperative hepatic insufficiency in serious cases. Also, when a small-for-size graft is implanted in adult living donor liver transplantation, the increased portal flow after reperfusion (in the small graft) contributes to the poor prognosis following the transplantation. Therefore, perioperative flow management during the surgical procedures on liver is important and may improve the postoperative result.

## CONCLUSIONS

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Encountering the stressors is the normal consequence of living in a fluctuating environment; therefore, the cells have developed mechanisms to ameliorate the stress or to adapt to it. This is achieved

through the repair of damage, adaptation, reuse of resources and a limited cell death. Living with stressors is unavoidable in the life of organisms and cells, thus the cells have to divert at least some of their resources from other pathways, to deal with the consequences of stressors. Our cells are well adapted to exposure to a mild stress for a short time. In contrast there are potentially serious consequences of exposure to the prolonged stress. Cellular stress can at least contribute to, or even trigger, many diseases and malignant transformations and has an important role in aging. To ameliorate or repair these processes the cells are being used in cell therapies and regenerative medicine. For maximal therapeutic success it is important to use the cells in the best condition possible or those adapted to stress.

Discovering the detailed mechanisms of stress responses, some of which are described here, will improve the assessment of the condition of transplanted cells and to better their handling and transplant survival rates. Even more important, the knowledge of cell stress responses is important for the well being of normal cells and may form a basis for development of preventional measures and treatments of diseases significantly influenced by persistent stress, like cancer and neurodegenerative diseases.

## DECLARATION OF INTEREST

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We have no conflict of interest to declare.

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