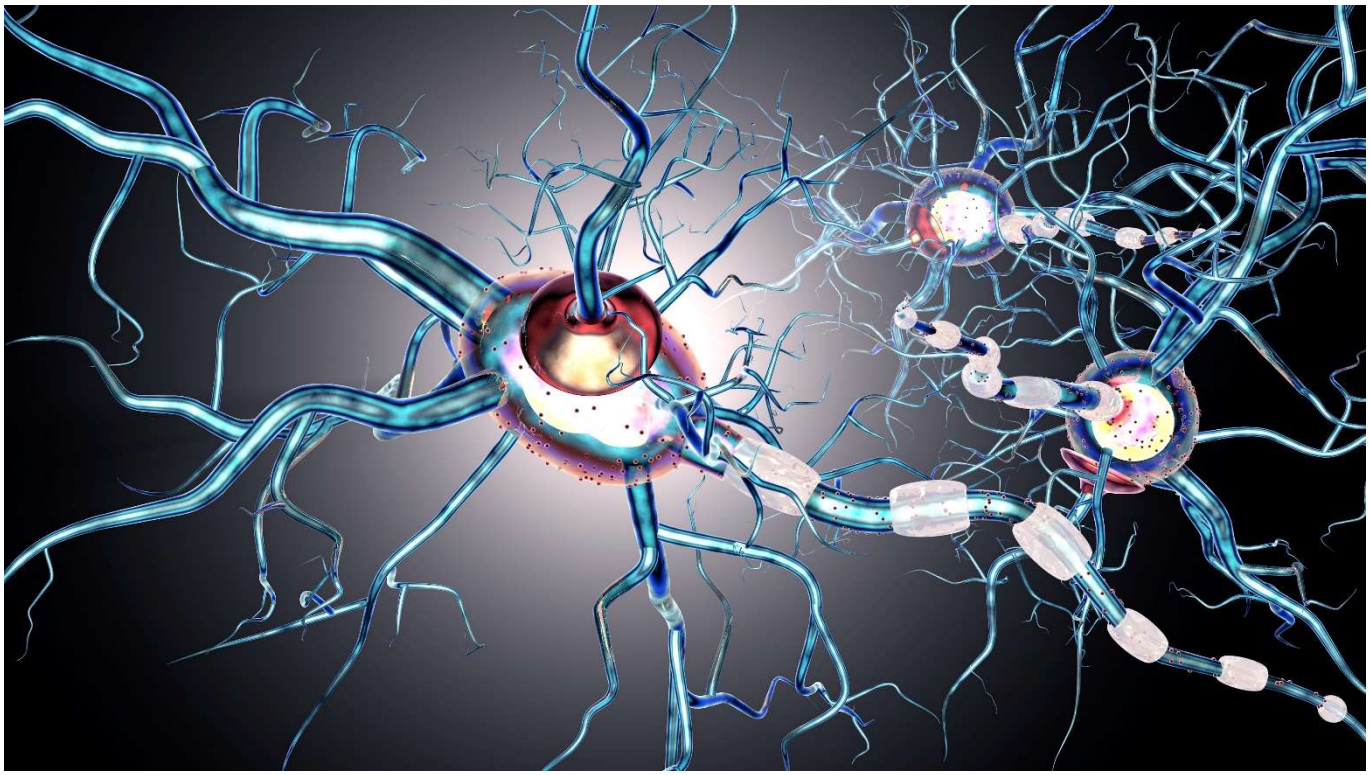

INHIBITORS OF PERK-DEPENDENT SIGNALING PATHWAY AS A PROMISING THERAPY FOR CANCER TREATMENT

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ABSTRACT

Currently, cancer constitutes a primary health problem worldwide, since elimination of cancer cells is still inadequate due to insufficient treatment strategy. The newest data has reported that PERK-dependent signaling branches have a significant impact on development and progression of many human diseases including cancer. Hypoxia is the major hallmark of tumour microenvironment, that is strictly associated with rapid cancer progression and induction of metastasis. Low oxygen tension within cancer cells may trigger aggregation of unfolded and misfolded protein within the Endoplasmic Reticulum (ER) lumen and subsequently evoke ER stress condition. As a response to Protein kinase RNA-like endoplasmic reticulum kinase (PERK) oligomerization and trans-autophosphorylation the Unfolded Protein Response (UPR) signaling pathways is activated and regulates their downstream effector such as Eukaryotic Initiation Factor 2 alpha (eIF2α). The eIF2α plays a key role in maintenance of cellular homeostasis via attenuation of global protein synthesis and expression of only selected pro-adaptive genes. Interestingly, UPR has a dual role, since under excessive, long-termed pathological conditions activated PERK contributes to increased translation of CCAAT-enhancer-binding protein homologous protein (CHOP), which may switch on the death signal within cells, that results in apoptotic death of cancer cells. The molecular mechanisms that switch the signal from pro-adaptive into pro-apoptotic is still unknown, but there is an ample of evidence, that utilization of small-molecule PERK inhibitors may lead to the activation of apoptotic cell death and provide an effective elimination of tumour cells. Thereby, potent, highly-selective inhibitors toward PERK may provide a ground-breaking, anti-cancer treatment strategy.

BACKGROUND

Every year more than a million patients are diagnosed with cancer and more than 500,000 patients die of cancer in the United States. Due to above-mentioned statistical data cancer constitutes a major health problem worldwide [1]. In highly developed countries it has become the second cause of human mortality after cardiovascular diseases and it will affect half of men and one third of women during their lifetime [2]. The newest data has reported that, cancer may soon become the main cause of death worldwide due to significant improvement of treatment and prevention of cardiovascular diseases [1, 3].

Tumour is composed of cells, which the characteristic hallmark is uncontrolled proliferation due to their genomic instability and deregulation of cell cycle checkpoint [4, 5]. Moreover, these abnormal cells may rapidly spread in any part of the whole body. We can specify two main types of tumours. The first one is benign tumour, that most commonly grows in a certain location and remains separated from healthy tissues. The latter is known as a malignant tumour. It has an ability to invade surrounding healthy tissues and also to spread from its primary location to other parts of the body, either though lymphatic or vascular system [1]. This process is termed metastasis and it is a major clinical problem due to the fact, that location and time of presenting tumours in other parts of the body is uncertain [6]. There are hundred distinct kinds of human cancer with various behaviour, which vary not only in their areas of body localization, but also on the molecular level including presented mutations and abrogation of numerous signaling pathways, that are directly responsible for maintenance of cellular homeostasis. Due to numerous types of cancer and their unique combinations of genetic alterations elimination of cancer cells by currently used anti-tumour drugs is still inadequate [1, 2].

Cancer development is strongly connected with uncontrolled growth of cells as well as inactivation of apoptosis. The abnormal proliferation of tumour mass contribute to structural disturbances and impaired angiogenesis resulting in hypoxic state. That leads to the occurrence of the ER (Endoplasmic Reticulum) stress conditions, which may directly activate the UPR (Unfolded Protein Response) signaling branches. The subsequent phosphorylation of eIF2α (Eukaryotic Initiation Factor 2 alpha), by activated PERK (Protein kinase R (PKR)-like Endoplasmic Reticulum kinase) triggers rapid downregulation of global protein synthesis and translation of only preferential genes encoding proteins, that play a vital role during adaptation of tumour cells to hypoxic conditions. On the contrary, the long-termed activation of the UPR may lead to the initiation of the apoptotic cell death. There is an ample of evidence, that this dichotomic pathway plays a key role in pathogenesis of many human disease entities such as: atherosclerosis, renal disease, type 2 diabetes, neurodegenerative disease and cancer. Nowadays, development of treatment strategies, which may evoke a pharmacological switch of the UPR signaling pathways from the pro-adaptive into pro-apoptotic has become the main target of numerous studies. Detailed knowledge in this area may contribute to the development of a new, innovative treatment methods, that may overcome current problems of ineffective therapies against various human diseases including cancer [7-9].

ER STRESS AND THE UNFOLDED PROTEIN RESPONSE

The ER is a dynamic membrane system of tubules and sacs. It is made up of different domains such as nuclear envelope (NE), smooth and rough ER as well as the parts contacting with other organelles. The ER plays a key role in synthesis of phospholipids as well as a secretory and membrane proteins [10]. Proteins folding and their subsequent modifications are strictly controlled inside the ER lumen. Misfolded or unfolded proteins are targeted for degradation by the ubiquitin-proteasome pathway [11]. Balance between synthesis and degradation of abrogated proteins results in cellular homeostasis, that may be disturbed by a range of environmental and genetic factors. Hence, redox and calcium homeostasis as well as molecular signaling transduction depend on the proper functioning of the ER [12]. Not only redox, but also intracellular calcium concentration and proper release of calcium ions from the ER lumen are vital in ER-mitochondrion interactions and play the pivotal role during controlling of the cell death by apoptosis [13].

It has been reported, that a range of pathological conditions such as viral infections, toxins, inflammatory cytokines, hypoxia, nutrient deficiency and increased cell proliferation directly evoke perturbation in the ER homeostasis that results in the aggregation of unfolded and misfolded proteins within the ER lumen, and subsequently triggers activation of the UPR branches, which play an important role in restoration of the cellular homeostasis [14]. The UPR is associated with the activation of three ER transmembrane receptors: Activating transcription factor 6 (ATF6), Inositol requiring enzyme 1 (IRE1) and Protein kinase RNA PKR)-like ER kinase (PERK) [15, 16]. ATF6 is classified as a II transmembrane protein kinase, that upon ER stress conditions is translocated from the ER towards the Golgi Apparatus (AG), where undergoes a proteolytic processing to release ATF6 cytosolic fragment that moves towards the nucleus, where plays a key role, as a transcription factor, for various pro-adaptive UPR genes [17]. Adversely to ATF6, IRE1 and PERK belong to the I transmembrane serine/threonine protein kinases and they are activated via oligomerization and trans-autophosphorylation, that lead to the activation of PERK-an IRE1-dependent signaling pathways [18]. As the first response to the ER stress conditions the pro-adaptive branches of the UPR are activated. That inhibits the global protein synthesis within cells, which allows for the reduction of the new protein load in the lumen of the ER. On the other hand, excessive, long-termed ER stress conditions may change the UPR signal towards the pro-apoptotic pathway. The molecular mechanism, that is solely responsible for switch of the UPR signaling

pathways from the pro-adaptive into pro-apoptotic pathway is still unknown [19-21].

PRO-ADAPTATIVE RESPONSE OF THE UPR SIGNALING PATHWAYS IN TUMOR PROGRESSION

Hypoxia, a major hallmark of tumour microenvironment, is strictly associated with rapid cancer progression as well as induction of metastasis. Low oxygen tension within cancer cells may trigger aggregation of unfolded and misfolded protein within the Endoplasmic Reticulum (ER) lumen and subsequently evoke ER stress condition [22]. PERK, under physiological conditions, is associated with the heavy chain binding protein (BiP) also known as glucose regulated protein 78 (GRP78) chaperones. When the unfolded and misfolded proteins accumulate in the ER lumen the BiP/GRP78 are released from the domains of the ER stress receptors. That subsequently leads to oligomerization and trans-autophosphorylation of PERK [23]. Activated PERK phosphorylate its direct substrate such as *α* subunit of the eIF2 in Ser51. As a result, under pathological, hypoxic conditions, the global protein synthesis is significantly arrested [24]. Moreover, translation of only selected proteins like ATF4 (Activating transcription factor 4) is markedly enhanced, that upregulates a board range of cytoprotective genes [25]. Moreover, due to inhibition of global protein synthesis, phosphorylated eIF2α suppresses translation of *cyclin D1*, which causes cell cycle arrest in a G1 phase, thus inhibition of cell proliferation. Thereby, the eIF2α is often referred as a master regulator of cell adaptation to ER stress conditions [26].

PERK-DEPENDENT PRO-APOPTOTIC SIGNALING PATHWYS

During long-termed ER stress conditions, the ATF4, as a transcription factor, promotes expression of *DDIT3* genes encoding protein CCAAT-enhancer-binding protein homologous protein (CHOP), which is commonly known as a major initiator of the pro-apoptotic cascade [27]. Increased expression of CHOP downregulates expression of the anti-apoptotic *Bcl-2* genes and inversely, upregulates expression of genes encoding the pro-apoptotic BH3 domain-only proteins [28]. Additionally, CHOP disrupts the redox homeostasis within the cell, which rapidly evokes cell death via apoptosis [29]. CHOP also acts as a transcription factor of the genes encoding the Growth arrest and DNA damage-inducible protein (GADD34), which promotes dephosphorylation of the eIF2α. Above-mentioned event resumes the global protein translation in stressed cells leading to increased ER proteins load and further promotes ER stress and pro-apoptotic signaling axis of the UPR [30, 31]. The ER oxidoreductin 1α (ERO1α) is the ER membrane enzyme, which requires a molecular oxygen to promote formation of disulphide bonds in newly translated proteins. Expression of the *ERO1α* is enhanced by CHOP under prolonged ER stress conditions, that may lead to excessive production of H_2O_2, resulting in hyperoxidizing environment and apoptotic cell death [32, 33]. High concentration of Reactive oxygen species (ROS) in the ER lumen activates the ER calcium release channel inositol-1, 4, 5-thriphosphate receptor 1 (IP3R1) resulting in calcium leakage into the cell cytoplasm from the ER lumen. Then, calcium/calmodulin-dependent protein kinase II (CaMKII) is activated, which triggers activation of pro-apoptotic signaling branches of the UPR. Activation of the CHOP-ERO1α-IP3R1-CaMKII-dependent signaling pathway leads to induction of nicotinamide adenine dinucleotide phosphate-oxidase (NADPH oxidase) subunit 2 (NOX2), that subsequently promotes generation of ROS and expression of *DDIT3* genes. Hence, that positive feedback loop is created by ROS, which enhances CaMKII activation and, as a result, translation of pro-apoptotic CHOP protein [20, 34]. The newest data has suggested, that CHOP-mediated cell apoptosis may also be triggered by suppression of cell cycle regulator protein 21 (p21/WAF1). It has a pivotal role in inhibition of the cell cycle in a G1 phase after the interaction with the cyclin-dependant kinase (Cdk) [15, 35]. Expression of WAF1 is closely correlated with tumour suppressor protein p53 (p53). Under stress conditions p53 upregulates WAF1, which results in cell cycle arrest in a G1 phase as a pro-adaptive cellular response [36]. It has been reported that possible crosstalk between CHOP and p21 may be the explanation of transition from pro-adaptive into pro-apoptotic pathway of the UPR under stress conditions. The p21 is controlled by CHOP and while the stress conditions are low to moderate the regulation is stimulated. On the other hand, during chronic or acute stress conditions, the regulation between CHOP and p21 may be suppressed, which leads to apoptotic cell death. Hence, above-mentioned data indicate that the shift of UPR from pro-adaptive into pro-apoptotic pathway in tumour disease may result from the p21 and PERK/eIF2α/ATF4/CHOP pathway interaction [37, 38].

SMALL-MOLECULE PERK INHIBITORS AS A NOVEL TREATMENT STRATEGY

Recent data has confirmed that inhibition of the UPR signaling pathways, activated upon ER stress conditions, may constitute a novel, ground-breaking treatment strategy against various human diseases. There is an ample of evidence, that pathogenesis of several neurodegenerative diseases including Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), prion disease and ischaemia lies on the molecular level. Thus, excessive accumulation of misfolded and unfolded proteins in ER lumen triggers disruption of the PERK-dependent signaling pathways [39]. It has been confirmed that deposition of senile plaques and neurofibrillary tangles among the neurons within tissue brain is closely connected not only with genetic factors, but also with overactivation of the ER-stress dependant signaling pathways [40]. Aggregation of amyloid beta (Aβ) plaques in tissue brain activates the PERK-dependant signaling pathways, which is solely implicated in AD development and progression. Interestingly, it has been reported, that phosphorylated eIF2α is present in high levels in brain cells of AD patients leading to the attenuation of global protein synthesis and

promotion of ATF4 synthesis. During excessive, prolonged ER stress conditions ATF4 triggers upregulation of the expression of genes encoding pro-apoptotic CHOP. That results in apoptotic cell death of neuronal cells, thus decreased mass of tissue brain in AD patients. There is an ample of evidence, that inhibition of PERK may decrease the level of phosphorylated eIF2α, which may significantly slow down or completely stop progression of β-amyloidogenesis. Due to the fact, that nowadays only symptomatic treatment against neurodegenerative diseases is available, use of highly-specific, small-molecule inhibitors of PERK may provide a novel, promising therapy against neurodegenerative diseases [41-43].

Moreover, PERK-dependent signaling pathways play a key role in cancer development and progression [20]. The characteristic hallmark of cells in neoplastic disease, due to disturbed angiogenesis and structural malformation, is low oxygen and glucose environment. That evokes activation of the pro-adaptive UPR signaling networks, which enable rapid proliferation of tumour cells [44, 45]. It has been reported that pro-adaptive branches of the UPR has been activated in human glioblastomas, cervical carcinomas, breast and lung cancer [46]. The dichotomic role of PERK-dependent signaling pathway is still poorly understood, but the newest data has reported, that use of small-molecule PERK inhibitors may provide a new, promising anti-cancer strategy, which may evoke the molecular switch of the UPR from the pro-adaptive into pro-apoptotic signaling pathways [47].

GSK2606414 was the first PERK inhibitor synthetized by GlaxoSmithKline. Available data reported that it attenuates subcutaneous pancreatic human tumour xenograft growth in mice [48]. It also attenuated the protein synthesis in prion-infected mice preventing further neurodegeneration [49]. Thereby, it can be concluded, that highly-selective, small-molecule inhibitors of PERK are worthy of further analysis in *in vitro* and *in vivo* models before the clinical trials to gather a detailed knowledge about their impact on whole human organism and potential side effects [50].

CONCLUSIONS

Low oxygen tension within tumour cells is strictly associated with their structurally and functionally abnormal vessels, that directly evokes rapid cancer progression and metastasis. There is an ample of evidence, that hypoxic tumours, compared to better-oxygenated tumours, are characterized by higher resistance to currently used anti-cancer treatment strategies and thereby with poorer overall prognosis. The newest data has reported that tumorigenesis is closely associated with significant perturbation on the molecular level within cells, since hypoxic conditions activate ER stress, and subsequently the UPR signaling pathways, that has a dual pro-adaptive or pro-apoptotic role, which depends on the severity and time of duration of pathological conditions. Currently used anti-cancer therapy evokes numerous side effects in patients, since it target not only cancer, but also normal, healthy cells. Thus, advancing molecular insight into the mechanisms, that are solely responsible for switch of the UPR signaling pathways into its pro-apoptotic branch as well as additional investigations of highly-selective PERK inhibitors are necessary for development an effective, promising anti-cancer therapeutic agents.

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ABBREVIATIONS

Aβ – amyloid beta
AD – Alzheimer's disease
ATF4 – activating transcription factor 4
ATF6 – activating transcription factor 6
BiP – binding protein
CaMKII – calcium/calmodulin-dependent protein kinase II
Cdk – cyclin-dependant kinase
CHOP – CCAAT- enhancer-binding protein homologous protein
ER – endoplasmic reticulum
ERO1α – ER oxidoreductin 1alpha
eIF2α – eukaryotic initiation factor 2 alpha
GRP78 – glucose regulated protein 78
GADD34 – growth arrest and DNA damage-inducible protein
HD – Huntington's disease
IP3R1 – inositol-1, 4, 5-thriphosphate receptor 1
IRE1 – inositol requiring enzyme 1
NE – nuclear envelope
NOX2 – nicotinamide adenine dinucleotide phosphate-oxidase (NADPH oxidase) subunit 2
PD – Parkinson's disease
PERK – protein kinase RNA-like endoplasmic reticulum kinase
ROS – reactive oxygen species
UPR – unfolded protein response

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