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The integrated stress response system in cardiovascular disease

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The integrated stress response system represents an ancillary, extremely conserved signalling pathway present in virtually all eukaryotic cells, which plays an important part in the pathophysiology of several disorders such as cancer and neurodegeneration. However, its role in the cardiovascular system remains largely elusive. Hence, this review aims to acknowledge recent findings regarding the action of the eIF2α kinases in the cardiovascular system and their role in the pathophysiology of related disorders.

Introduction

Q2 The integrated stress response (ISR) system is one of the most important signalling pathways involved in the cellular adaptation to stress, and it is presumed to exist in all eukaryotic cells [1]. It consists of four serine/threonine kinases, namely general control nonderepressible (GCN)2, heme-regulated inhibitor (HRI), PKR-like endoplasmic reticulum kinase (PERK) and protein kinase double-stranded RNA-dependent (PKR), that, when activated, owing to either extrinsic or intrinsic stressors, phosphorylate the α subunit of eukaryotic translation initiation factor 2 (eIF2α) at Ser51, leading to an immediate cellular gene expression reprogramming to overcome the imposed stress and restore normal cell function [2].

Each eIF2α kinase senses and responds to distinct cellular stresses, and some overlap of their activities does exist [3]. These kinases share great homology, albeit some differences in their regulatory domains, and, upon a stressful stimulus, they need to dimerize and undergo autophosphorylation to become fully functional and to phosphorylate eIF2α [4]. The phosphorylation of eIF2α results in the inhibition of eIF2α-GTP recycling, which is necessary for the initiation of mRNA translation, reducing overall translation, while selectively favouring the translation of proteins implicated in stress recovery, such as activating transcriptional factor (ATF)4 [5]. This key factor can induce the expression of several genes involved in the regulation of apoptosis, metabolism, redox balance, amino acid (AA) biosynthesis and transport, by forming homo- and/or hetero-dimers that bind to specific DNA regions designated as the C/EBP-ATF response element (CARE) [4]. According to the nature of the stimulus that triggered eIF2α phosphorylation, as well as its intensity and duration, the gene reprogramming can help to promote cell survival or induce cell death [1].

Proper termination of the ISR signalling is essential, because it enables cells to reactivate protein synthesis and return to normal function. eIF2α dephosphorylation is mediated by the association of protein phosphatase (PP)1 and its catalytic subunit PP1c to either growth arrest and DNA-damage-inducible protein (GADD34), which is induced downstream of ISR signalling, or to constitutive repressor of eIF2α phosphorylation (CReP), which exists at basal levels even under unstressed conditions and helps to maintain low levels of phosphorylated eIF2α [4] (Fig. 1).

Since the discovery of these kinases and their implication in cellular stress adaptation and fate-decision, they have been increasingly studied in the context of several disorders, such as respiratory [6], metabolic [7], tumoral [8] and neurodegenerative

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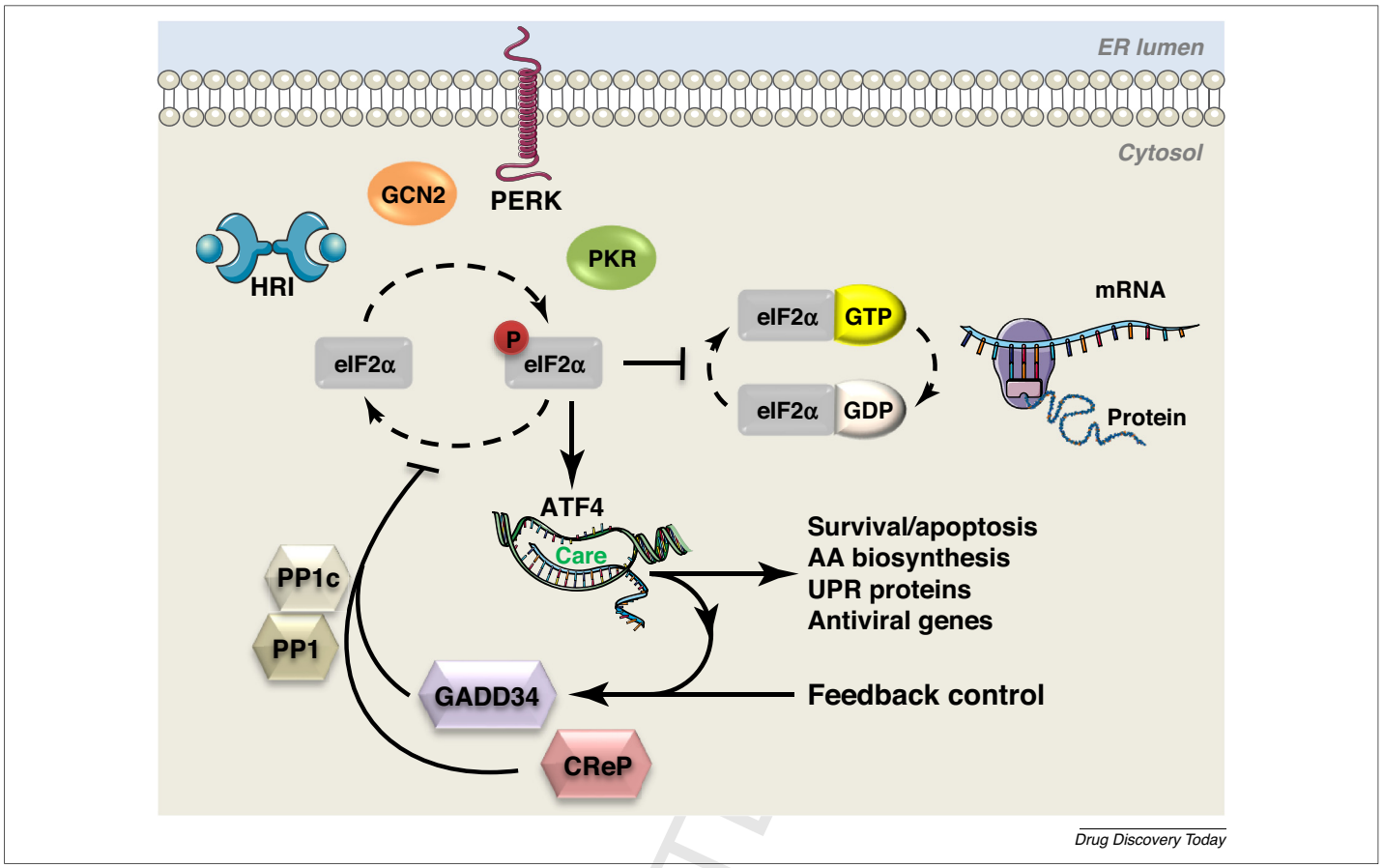

FIGURE 1

Overview of the ISR system. Upon a stressful stimulus, eIF2α is phosphorylated by either HRI, GCN2, PERK or PKR. eIF2α phosphorylation results in an immediate arrest of global protein synthesis, throughout the inhibition of eIF2α-GTP recycling. Upon its selective transcription, ATF4 binds to specific DNA regions called CARE. Depending on the nature of the stimulus that triggered eIF2α activation, the consequent gene reprogramming could either promote cell adaptation and survival or apoptosis. eIF2α dephosphorylation is mediated by the association of PP1 and its catalytic subunit PP1c to either GADD34 or CReP. *Abbreviations*: ATF4, activating transcriptional factor 4; CARE, C/EBP-ATF response element; CReP, constitutive repressor of eIF2α phosphorylation; eIF2α, α subunit of eukaryotic translation initiation factor 2; GADD34, growth arrest and DNA-damage-inducible protein; HRI, heme-regulator inhibitor; GCN2, general control nonderepressible 2; GDP, guanosine diphosphate; GTP, guanosine triphosphate; PERK, PKR-like endoplasmic reticulum kinase; PKR, protein kinase double-stranded RNA-dependent; PP1, protein phosphatase 1; PP1c, catalytic subunit of protein phosphatase 1.

diseases [9]. However, their role in the cardiovascular system remains largely unexplored. The scope of this review is therefore not to detail the structure and mechanics of the eIF2α kinases, extensively reviewed elsewhere [2], but rather to overview and explore the current knowledge on eIF2α kinases in the cardiovascular function and pathophysiology.

The eIF2α kinases

GCN2

GCN2, also called eukaryotic translation initiation factor 2 alpha kinase 4 (EIF2AK4), is a protein kinase that was initially discovered as being responsible for the detection and resolution of AA starvation in yeast [10]. However, it is currently acknowledged that GCN2 is also capable of detecting and answering to several other types of stimuli, such as hypoxia [11], DNA damage [12], ultraviolet radiation [13], among others [1], although the mechanisms by which they are able to activate GCN2 remain unknown. It has been speculated that other stresses, aside from AA unavailability, might end up disturbing the AA pool of the cell, eventually leading to GCN2 activation through its canonical pathway [4].

During periods of AA deprivation, the cellular levels of uncharged transfer RNAs (tRNAs) increase, and GCN2 can sense and bind to these tRNAs through its histidyl-tRNA synthetase (HisRS)-like and C-terminal domains, undergoing autophosphorylation at Thr^{898}/Thr^{903} leading to the activation of its protein kinase catalytic domain and subsequent phosphorylation of eIF2α [10]. Recently, GCN2 was also found to be present in the cell nucleus where it interacts with small RNA transcripts. GCN2 was able to modulate polymerase-III-mediated RNA transcription in the nucleolus to repress the excessive production of small RNA during AA shortage situations, inhibiting excessive protein translation [14].

HRI

HRI, also termed eIF2α kinase 1 (EIF2AK1), is a protein mainly expressed in erythrocytes, unlike the other eIF2α kinases that are widely expressed, that can detect low heme (an iron-coupled cofactor present in haemoglobin) levels and can promote the survival of erythroid precursors. HRI is also able to coordinate erythropoiesis and the production of globin chains according to heme

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