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Parkinson's disease proteins: Novel mitochondrial targets for cardioprotection

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ABSTRACT

Ischemic heart disease (IHD) is the leading cause of death and disability worldwide. Therefore, novel therapeutic targets for protecting the heart against acute ischemia/reperfusion injury (IRI) are required to attenuate cardiomyocyte death, preserve myocardial function, and prevent the onset of heart failure. In this regard, a specific group of mitochondrial proteins, which have been linked to familial forms of Parkinson's disease (PD), may provide novel therapeutic targets for cardioprotection. In dopaminergic neurons of the substantia nigra, these PD proteins, which include Parkin, PINK1, DJ-1, LRRK2, and α-synuclein, play essential roles in preventing cell death—through maintaining normal mitochondrial function, protecting against oxidative stress, mediating mitophagy, and preventing apoptosis. These rare familial forms of PD may therefore provide important insights into the pathophysiology underlying mitochondrial dysfunction and the development of PD. Interestingly, these PD proteins are also present in the heart, but their role in myocardial health and disease is not clear. In this article, we review the role of these PD proteins in the heart and explore their potential as novel mitochondrial targets for cardioprotection.

Contents

Abbreviations: CHD, Coronary heart disease; Cyp D, Cyclophilin D; Erk 1/2, Extracellular signal-regulated kinases 1/2; ETC, Electron transport chain; GPCRs, G-protein coupled receptors; IMM, Inner mitochondrial membrane; IPC, Ischemic preconditioning; IPSCs, Induced pluripotent stem cells; IPost, Ischemic postconditioning; ISCM, Ischemic cardiomyopathy; IRI, Ischemia/reperfusion injury; Mfn2, Mitofusin-2; MIBG, ^{123}I-metaiodobenzylguanidine; MPP, 1-methyl-4-pyridinium; mPTP, Mitochondrial permeability transition pore; PD, Parkinson's disease; PINK1, PTEN-induced putative kinase 1; PKC, Protein kinase C; PTEN, Phosphatase and tensin homologue; RISK, Reperfusion injury salvage kinase pathway; ROS, Reactive oxygen species; VCAM-1, Vascular cell adhesion molecule 1; MEFs, mouse embryonic fibroblasts.

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1. Introduction

Ischemic heart disease (IHD) is the leading cause of death and disability worldwide. The major clinical manifestations of IHD arise from the detrimental effects of acute ischemia/reperfusion injury (IRI) on the myocardium. Therefore, novel therapeutic targets for protecting the heart against IRI are required to limit cardiomyocyte death, preserve myocardial function and prevent the onset of heart failure.

In this regard, a specific group of mitochondrial proteins that have been linked to familial forms of Parkinson's disease (PD) may provide

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novel therapeutic targets for cardioprotection. In dopaminergic neurons of the substantia nigra, these PD proteins, which include Parkin, PINK1, DJ-1, LRRK2, and α-synuclein, have been reported to play essential roles in preventing cell death. This is achieved by maintaining normal mitochondrial function, protecting against oxidative stress, mediating mitophagy and preventing apoptosis. These rare familial PD proteins may provide important insights into the pathophysiological mechanisms underlying mitochondrial dysfunction and the development of PD. Crucially, these PD proteins are also present in the heart, but their role in myocardial health and disease is not clear. In this article, we review the role of these PD proteins in the heart and as potential therapeutic targets for cardioprotection.

2. Parkinson's disease

After Alzheimer's disease, PD is the second most common neurodegenerative disorder (de Lau & Breteler, 2006). The prevalence of PD in industrialized countries is estimated at 0.3% of the entire population (Nussbaum & Ellis, 2003) and approximately 1.0% of the population over the age of 60 is affected (Abou-Sleiman et al., 2006). The disease is expected to impose an increasing health, social and economic burden on societies with aging populations. Clinically, PD is characterized by rigidity, bradykinesia, resting tremor and postural instability. At the subcellular level, there is a loss of dopaminergic neurons particularly in the substantia nigra pars compacta region of the brain. Most PD cases are sporadic with only a small proportion (about 5–10%) being attributable to genetic mutations—these result in rare familial forms of PD (Mounsey & Teismann, 2011).

Interestingly, several clinical studies have reported an increased risk of cardiovascular disease in PD patients, with a lower life expectancy than the general population (Morgante et al., 2000), with heart failure (Fernandez & Lapane, 2002) and IHD (Ben-Shlomo & Marmot, 1995) being common causes of death in elderly PD patients. The prevalence of heart failure in elderly PD patients was shown in one cross-sectional study to be over twice that of age-matched non-PD patients (Zesiewicz et al., 2004). The reasons for this are unclear but may relate to several factors including the disease process itself, cardiac sympathetic denervation (Goldstein et al., 2000), PD medications (associated with heart valve disease) (Pritchett et al., 2002), and concurrent co-morbidities (such as age hypertension, diabetes, IHD and so on). Several of the mitochondrial proteins which have been linked to PD are present in the heart and are reviewed in the subsequent sections.

3. Parkin

3.1. Introduction

Parkin (PARK2) was the first gene to be associated with autosomal recessive PD (Kitada et al., 1998). It encodes a 52 kDa protein, which is found in the liver, kidney, testis, brain, skeletal muscle and heart (Kitada et al., 1998). Parkin is an E3 ubiquitin ligase which catalyzes the transfer of ubiquitin from an E2 ubiquitin-conjugating enzyme to a protein substrate in a process called ubiquitination (reviewed in Winklhofer, 2014). Under basal conditions, Parkin is located mainly in the cytosol, where its ubiquitin ligase activity is inhibited. Following cellular stress, Parkin translocates to damaged mitochondria in a PINK1-dependent manner to ubiquitinate a number of mitochondrial substrates mediating mitochondrial fragmentation, degradation and mitophagy (Matsuda et al., 2010).

3.1.1. Parkin-mediated mitophagy

PINK1 and Parkin have been shown to mediate the selective removal of damaged mitochondria by inducing mitophagy (reviewed in Winklhofer, 2014) (Fig. 1). In healthy mitochondria with normal membrane potential, PINK1 is imported into the mitochondria and becomes degraded by proteolysis. However, in damaged mitochondria, the depolarization of the membrane potential allows the stabilization of PINK1 in the outer mitochondrial membrane (OMM), where it phosphorylates ubiquitin resulting in the activation of Parkin (Iguchi et al., 2013; Koyano et al., 2014). The latter then ubiquitinates mitochondrial proteins (such as Mfn1 and Mfn2 and other proteins) (Gegg et al.,

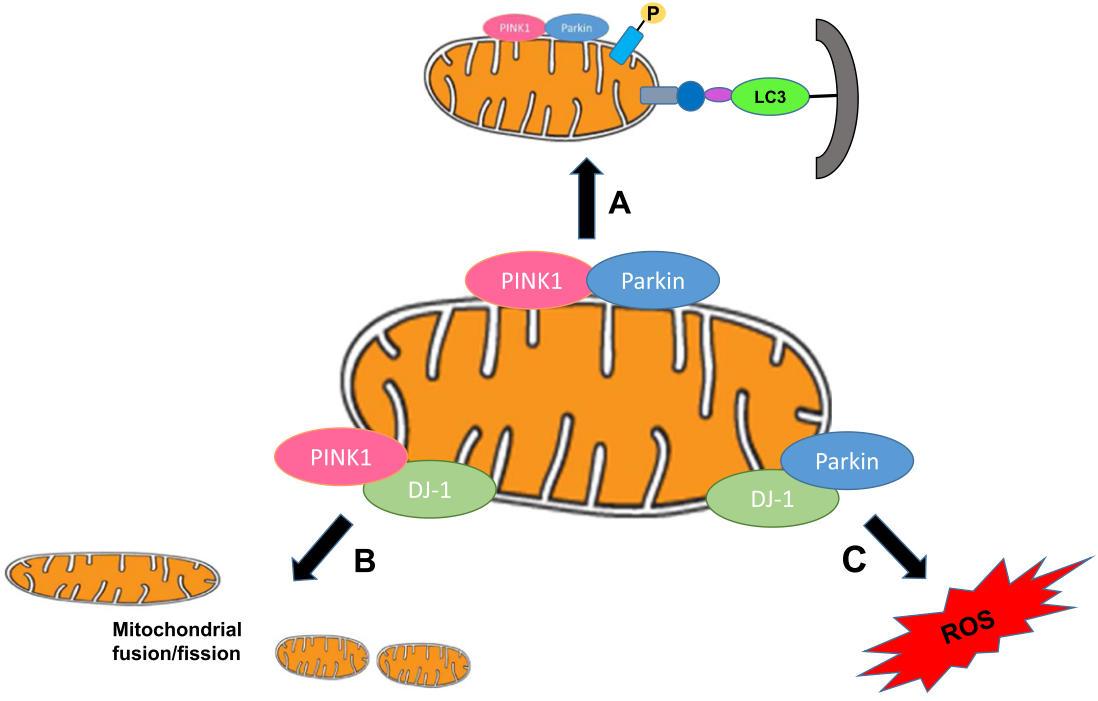

Fig. 1. Schematic diagram showing the interplay between PINK1, Parkin, and DJ-1. (**A**) PINK1 accumulation leads to phosphorylation of mitochondrial proteins leading to recruitment of Parkin. Parkin then ubiquinates its substrates leading to the localization of P62 and LC3 for subsequent mitophagy. (**B**) PINK1 and DJ-1 are recruited to the mitochondrial outer membrane and coordinate mitochondrial dynamics in a parallel fashion. (**C**) Parkin and DJ-1 interact with each other in an oxidative stress-dependent manner.