subsequent cell death response (Tann et al., 2011; Guicciardi et al., 2013; Virag et al., 2013; Dorn, 2013). In the current experimental model, early oxidant-mediated mitochondrial PARP1 activation, as well as other mitochondrial events, such as a progressive mitochondrial oxidant production (Fig. 2A) and mitochondrial electron transport defects (Fig. 11), probably contribute to the cell death. The results of the current research demonstrate that these processes are attenuated by blocking the early-onset PKA activation and the subsequent PARP1 activation. The working model outlined in Fig. 12 shows one possible interpretation of the findings of the current report: the cAMP/PKA axis is stimulated by β-adrenoceptor agonists (such as isoproterenol), cAMP analogs (such as 8-bromo-cAMP), and by adenylyl cyclase activators (such as forskolin), leading to mitochondrial PARP1 phosphorylation and increased PARP activity. Moreover, the cAMP/PKA axis is inhibited by β-adrenoceptor antagonists (such as propranolol), by adenylyl cyclase inhibitor (such as DDA) and by inhibition/downregulation of PKA (by the pharmacological inhibitor Rp-cAMP or by genetic silencing of PKA) leading to the inhibition of mitochondrial PARP1 phosphorylation and decreased PARP activity. In the Fig. 12, mitochondrial PKA is shown to be stimulated by cytosolic cAMP. It must be pointed out that multiple lines of data indicate that the cytosolic and mitochondrial cAMP pools do not communicate in most cases. At the same time, several sets of data also indicate that cell membrane and cytosolic signals can elevate intramitochondrial PKA activity, followed by phosphorylation of intramitochondrial proteins (reviewed in Lefkimmiatis and Zaccolo, 2014). Yet another possibility may be the extramitochondrial phosphorylation of PARP1, followed by its transport into the mitochondria, even though the early time course of extranuclear PARP1 phosphorylation (see Fig. 9) tends to speak against this possibility.

Although many additional details of the underlying mechanisms remain to be explored, the current findings may have implications for a number of cellular processes that are known to be regulated by PARP1, including cellular metabolism and DNA repair, given the fact that both of these processes can be regulated by the β-adrenoceptor/cAMP system (Carlucci et al., 2008; Cho and Juhnn, 2012; Valsecchi et al., 2013; Lefkimmiatis and Zaccolo, 2014). However, these aspects remain to be directly investigated in further studies. The current findings may also provide a mechanistic explanation for our previously observed clinical/translational findings (Olah et al., 2011) showing that treatment of patients with severe burn injury with propranolol suppresses PARP1 activation in endothelial cells and tissue-resident mononuclear cells. Further studies are needed to determine whether modulation of PARP1 phosphorylation and its consequent catalytic activity by various drugs targeting the β-adrenoceptor/cAMP/PKA system may be used for therapeutic modulation of PARP1 in various pathophysiologic conditions associated with oxidative stress.

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Authorship Contributions

Participated in research design: Szabo, Brunyanszki and Szczesny.
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