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Review Article

Molecular identity of the mitochondrial permeability transition pore and its role in ischemia-reperfusion injury

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ABSTRACT

The mitochondrial permeability transition is a key event in cell death. Intense research efforts have been focused on elucidating the molecular components of the mitochondrial permeability transition pore (mPTP) to improve the understanding and treatment of various pathologies, including neurodegenerative disorders, cancer and cardiac diseases. Several molecular factors have been proposed as core components of the mPTP; however, further investigation has indicated that these factors are among a wide range of regulators. Thus, the scientific community lacks a clear model of the mPTP. Here, we review the molecular factors involved in the regulation and formation of the mPTP. Furthermore, we propose that the mitochondrial ATP synthase, specifically its c subunit, is the central core component of the mPTP complex. Moreover, we discuss the involvement of the mPTP in ischemia and reperfusion as well as the results of clinical studies targeting the mPTP to ameliorate ischemia-reperfusion injury. This article is part of a Special Issue entitled "Mitochondria".

Contents

Abbreviations: ADP, adenosine diphosphate; ANT, adenine nucleotide transporter; ATP, adenine triphosphate; C1QBP, complement component 1Q subcomponent-binding protein; Ca^{2+}, calcium; CK, creatine kinase; CsA, cyclosporine A; CYCLE, CYCLosporinE A in reperfused acute myocardial infarction; ER, endoplasmic reticulum; ETC, electron transport chain; FADD, Fas-activated with death domain; FLIP, FLICE-inhibitory protein; GIK, glucose-insulin-potassium; GLP-1, glucagon-like peptide 1; GSK3-β, glycogen synthase kinase 3 beta; HF, heart failure; HK, hexokinase; Hot-DOG, ^{3}H 2-deoxyglucose; IHD, ischemic heart disease; IF-1, inhibitor protein F1; IMM, inner mitochondrial membrane; IMS, intermembrane space; IRI, ischemia-reperfusion injury; K^{+}, potassium; LV, left ventricular; Mg^{2+}, magnesium; MI, myocardial infarction; MITOCARE, prospective, multicenter, randomized, double-blind, placebo-controlled, phase IIa study; MPT, mitochondrial permeability transition; mPTP, mitochondrial permeability transition pore; mtCypD, mitochondrial cyclophilin D; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; MVO, microvascular obstruction; Na^{+}, sodium; NO, nitric oxide; OMM, outer mitochondrial membrane; OSCP, oligomycin sensitivity conferring protein; OXPHOS, oxidative phosphorylation; PCI, percutaneous coronary intervention; PEG, polyethylene glycol; P_i, inorganic phosphate; PiC, inorganic phosphate carrier; PM, plasma membrane; PPIF, peptidylprolyl isomerase f; PK11195, *N*-butan-2-yl-1-(2-chlorophenyl)-*N*-methylisoquinoline-3-carboxamide; PK, protein kinase; RISK, reperfusion injury survival kinase; RO5-4864, 4′-chlorodiazepam; ROS, reactive oxygen species; SAFE, survivor activating factor enhancement; SR, sarcoplasmic reticulum; STEMI, ST elevation myocardial infarction; TIMI, thrombolysis in MI; TNFα, tumor necrosis factor alpha; TNFR1, TNF receptor 1; TRAIL, TNF-related apoptosis-inducing ligand; TRO40303, 3,5-seco-4-norcholestan-5-one oxime-3-ol; TSPO, translocator protein; VDAC, voltage-dependent anion channel.

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1. Ischemia-reperfusion injury (IRI): introduction and clinical background

Ischemic heart disease (IHD) is the leading cause of death in Western countries. Each year, approximately 17 million people worldwide suffer from myocardial infarction (MI), and in 40% of cases, an ST segment elevation MI (STEMI) is presented [1]. Recent developments in myocardial reperfusion technique (e.g., primary percutaneous coronary intervention (PCI)) and in antithrombotic therapies permitted a significant improvement in the long-term outcome of STEMI patients [1]. Nevertheless, the mortality and disability associated with STEMI remain high [2] for several reasons, including a lack of therapy compliance and the under-use of specific cardiovascular drugs. Contemporaneously, the effectiveness of myocardial reperfusion remains a principal issue. It is estimated that approximately 50% of the final infarcted area is related to IRI [3], which consists of cardiomyocyte death following the restoration of blood flow in the related infarcted artery. IRI is strongly related to infarct size and to left ventricular (LV) remodeling. Both of these processes are known in daily clinical practice as strong and independent predictors of prognosis, heart failure (HF) and mortality [4].

Several clinical, cellular and molecular events occur during IRI (Fig. 1). The most relevant clinical events are as follows: reperfusion-induced arrhythmia, myocardial stunning, microvascular obstruction (MVO) and myocardial necrosis secondary to reperfusion (Fig. 1). The latter two entities are particularly well understood and are associated with increased infarct size and LV dysfunction severity. MVO is a phenomenon that occurs due to the following changes: capillary damage induced by vasodilatation, external compression caused by endothelial cell and cardiomyocyte swelling, micro-embolization of friable material released from the atherosclerotic plaque and infiltration of inflammatory cells [5]. The myocardial necrosis that occurs secondary to reperfusion includes apoptosis and necrosis of cardiomyocytes and endothelial cells at a higher percentage than expected, resulting in a complete loss of the benefits of myocardial reperfusion via PCI [3]. In recent years, the complex mechanism that promotes the onset of IRI has been extensively studied but is currently only partially understood. This field

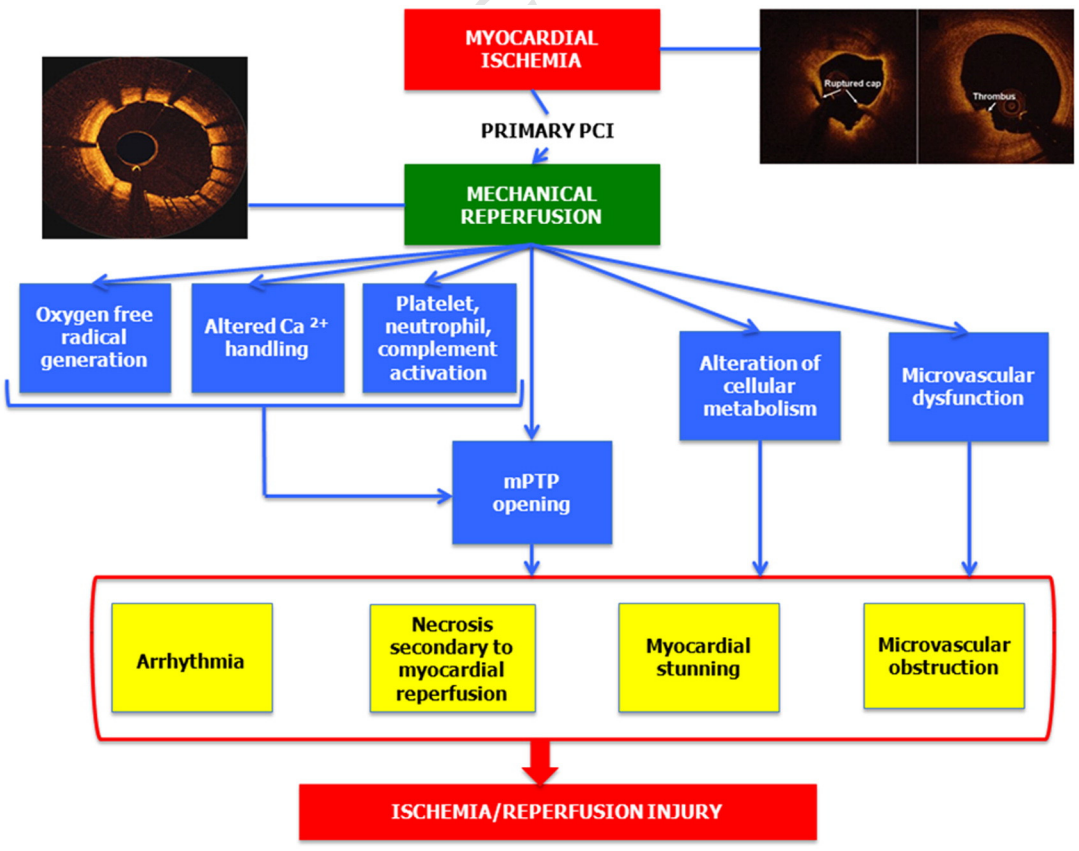

Fig. 1. Ischemia-reperfusion injury during acute myocardial infarction.

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