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Review article

The mitochondrial permeability transition pore and its role in myocardial ischemia reperfusion injury

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ABSTRACT

Ischemic heart disease (IHD) remains the leading cause of death and disability worldwide. For patients presenting with an acute myocardial infarction, the most effective treatment for limiting myocardial infarct (MI) size is timely reperfusion. However, in addition to the injury incurred during acute myocardial ischemia, the process of reperfusion can itself induce myocardial injury and cardiomyocyte death, termed 'myocardial reperfusion injury', the combination of which can be referred to as acute ischemia–reperfusion injury (IRI). Crucially, there is currently no effective therapy for preventing this form of injury, and novel cardioprotective therapies are therefore required to protect the heart against acute IRI in order to limit MI size and preserve cardiac function. The opening of the mitochondrial permeability transition pore (MPTP) in the first few minutes of reperfusion is known to be a critical determinant of IRI, contributing up to 50% of the final MI size. Importantly, preventing its opening at this time using MPTP inhibitors, such as cyclosporin-A, has been reported in experimental and clinical studies to reduce MI size and preserve cardiac function. However, more specific and novel MPTP inhibitors are required to translate MPTP inhibition as a cardioprotective strategy into clinical practice. In this article, we review the role of the MPTP as a mediator of acute myocardial IRI and as a therapeutic target for cardioprotection. This article is part of a Special Issue entitled "Mitochondria: From Basic Mitochondrial Biology to Cardiovascular Disease".

Contents

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Abbreviations

ADP	Adenosine diphosphate
ANT	Adenine nucleotide translocase
ATP	Adenosine triphosphate
Ca^{2+}	Calcium ion
CABG	Coronary artery bypass graft
cGMP	Cyclic guanosine 3′,5′-monophosphate
CK-MB	Creatine kinase
Cl^-	Chloride ion
CsA	Cyclosporin-A
CypD	Cyclophilin D
Drp1	Dynamin-related protein 1
ER	Endoplasmic reticulum
Erk	Extracellular signal-regulated kinase
GSH	Reduced glutathione
GSK	Glycogen synthase kinase
GSSG	Oxidized glutathione
GST	Glutathione S-transferase
H^+	Hydrogen ion
HCO_3^-	Hydrogen carbonate ion
hFis1	Human Fission protein 1
HK	Hexokinase
IHD	Ischemic heart disease
IMM	Inner mitochondrial membrane
IPC	Ischemic preconditioning
IPost	Ischemic postconditioning
IR	Ischemia reperfusion
IRI	Ischemia–reperfusion injury
LV	Left ventricular
MCU	Mitochondrial calcium uniporter
MI	Myocardial infarct
MitoKATP	Mitochondrial ATP-sensitive potassium channel
MPTP	Mitochondrial permeability transition pore
MRI	Magnetic resonance imaging
Na^+	Sodium ion
NO	Nitric oxide
NOS	Nitric oxide synthase
NHE	Sodium hydrogen exchanger
OMM	Outer mitochondrial membrane
Opa1	Optic atrophy 1
P_i	Inorganic phosphates
PiC	Mitochondrial phosphate carrier
PKA	Protein kinase A
PKB	Protein kinase B
PKC-ε	Protein kinase C-epsilon
PKG	Protein kinase G
PPCI	Primary percutaneous coronary intervention
PPIF	peptidylprolylisomerase F
RIC	Remote ischemic conditioning
RISK	Reperfusion injury signaling kinase
RNA	Ribonucleic acids
ROS	Reactive oxygen species
SAFE	Survivor Activating Factor Enhancement
siRNA	Small interfering RNA
STAT-3	Signal transducer and activator of transcription 3
STEMI	ST segment elevation myocardial infarction
TIMI	Thrombolysis in Myocardial Infarction
VDAC	Voltage-dependent anion channel
$\Delta\Psi_m$	Mitochondrial membrane potential

Clinical Studies

CYCLE	CYCLosporine A in Reperfused Acute Myocardial Infarction
CIRCUS	Cyclosporine and Prognosis in Acute Myocardial Infarction Patients
CLOTILDE	Cyclosporine in Acute Myocardial Infarction Complicated by Cardiogenic Shock

1. Introduction

Ischemic heart disease (IHD) is the leading cause of death and disability in the world, with over 1.9 million and 600,000 deaths per year, in Europe (http://www.escardio.org/about/what/advocacy/EuroHeart/Pages/2012-CVD-statistics.aspx) and the United States (http://www.cdc.gov/heartdisease/facts.htm), respectively. Although mortality rates from IHD appear to be falling in the developed world, survival after heart failure has decreased over the last few years [1]. The major clinical manifestations of IHD result in the heart being subjected to acute ischemia–reperfusion injury (IRI), the detrimental effects of which are myocardial injury, cardiomyocyte death and cardiac dysfunction, resulting in cardiac arrhythmias, heart failure and death. Apart from limiting acute myocardial ischemic injury by timely reperfusion, there is currently no effective therapeutic intervention for protecting the heart against acute IRI, and therefore, novel cardioprotective therapies are still required to improve clinical outcomes in patients with IHD [2,3].

In this regard, the mitochondrial permeability transition pore (MPTP) has emerged as a critical mediator of acute IRI, thereby making it an