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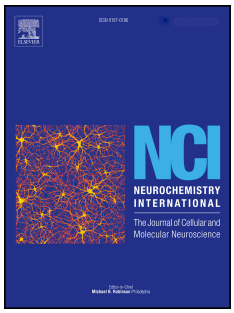


Mitochondrial permeability transition pore: Back to the drawing board

Christos Chinopoulos

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# Mitochondrial permeability transition pore: back to the drawing board

Christos Chinopoulos

Department of Medical Biochemistry, Semmelweis University, Budapest, 1094, Hungary
MTA-SE Lendület Neurobiochemistry Research Group

To whom correspondence should be addressed: Christos Chinopoulos, MD, PhD, Department of Medical Biochemistry, Semmelweis University, Budapest, Tuzolto st. 37-47, 1094, Hungary, Tel: +361 4591500 ext. 60024; Fax: +361 2670031; E-mail: chinopoulos.christos@eok.sote.hu

## Abstract

Current models theorizing on what the mitochondrial permeability transition (mPT) pore is made of, implicate the c-subunit rings of ATP synthase complex. However, two very recent studies, one on atomistic simulations and in the other disrupting all genes coding for the c subunit disproved those models. As a consequence of this, the structural elements of the pore remain unknown. The purpose of the present short-review is to i) briefly review the latest findings, ii) serve as an index for more comprehensive reviews regarding mPT specifics, iii) reiterate on the potential pitfalls while investigating mPT in conjunction to bioenergetics, and most importantly iv) suggest to those in search of mPT pore identity, to also look elsewhere.

Keywords: c-subunit ring; ATP synthase; dimers; bioenergetics

## INTRODUCTION

The mitochondrial permeability transition (mPT) pore is a megachannel of the inner mitochondrial membrane with a diameter of 2-3 nm (Zoratti and Szabo, 1995) exhibiting a non-selective conductance of 1-1.3 nS (Kinnally et al., 1989), (Petronilli et al., 1989), allowing flux of metabolites with a molecular weight of up to 1.5 kDa (Haworth and Hunter, 1979), (Bernardi et al., 2015b). Mechanisms of induction, inhibition, regulation, implication in physiological and pathological states as well as historical perspectives of this phenomenon are outlined under "Index of reviews on mPT specifics". Mindful that mPT is not an *in vitro* artifact (Bernardi et al., 2006), its prolonged opening leads to mitochondrial demise causing cell death (Petronilli et al., 2001) and that this seems to be a final common pathway in major maladies of our times such as in heart disease (Halestrap and Pasdois, 2009), it is not surprising that the race for identifying its components –which could serve as targets amenable to pharmacological manipulation- is going strong. Indeed, the mPT modulator cyclophilin D, has been implicated in a number of pathologies involving mitochondrial dysfunction (Giorgio et al., 2010), such as in collagen VI diseases (Lampe and Bushby, 2005). The immense interest in establishing mPT as a pharmacological target can be better appreciated by the number and extent of commentaries on a recent study (Cung et al., 2015) recruiting 970 patients with myocardial infarction (MI) and assessing the effect of cyclosporine A administration, a cyclophilin D inhibitor and a universally-accepted negative effector of mPT (Waldmeier et al., 2003), (Giorgio et al., 2010). Cung and colleagues reported that "cyclosporine did not result in better clinical outcomes than those with placebo and did not prevent adverse left ventricular remodeling at 1 year", thus arguing against using cyclosporine A as pharmacological treatment for MI; notably, this study has been scrutinized in seven commentaries (Bernardi and Di Lisa, 2016), (Zografos and Katritsis, 2016), (Hausenloy and Yellon, 2015), (Linkermann et al., 2016), (Lim, 2015), (Santos-Gallego and Badimon, 2016), (Pottecher et al., 2016).

So far, the only two proteins verified as modulatory but not structural elements of the pore are cyclophilin D (Baines et al., 2005), (Nakagawa et al., 2005), (Basso et al., 2005), (Schinzel et al., 2005), and the adenine nucleotide translocase (ANT), isoform 1 (Doczi et al., 2016). Remarkably, there is