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Review

Mitochondrial fusion/fission dynamics in neurodegeneration and neuronal plasticity

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ABSTRACT

Mitochondria are dynamic organelles that continually move, fuse and divide. The dynamic balance of fusion and fission of mitochondria determines their morphology and allows their immediate adaptation to energetic needs, keeps mitochondria in good health by restoring or removing damaged organelles or precipitates cells in apoptosis in cases of severe defects. Mitochondrial fusion and fission are essential in mammals and their disturbances are associated with several diseases. However, while mitochondrial fusion/fission dynamics, and the proteins that control these processes, are ubiquitous, associated diseases are primarily neurological disorders. Accordingly, inactivation of the main actors of mitochondrial fusion/fission dynamics is associated with defects in neuronal development, plasticity and functioning, both *ex vivo* and *in vivo*. Here, we present the central actors of mitochondrial fusion and fission and review the role of mitochondrial dynamics in neuronal physiology and pathophysiology. Particular emphasis is placed on the three main actors of these processes *i.e.* DRP1, MFN1-2, and OPA1 as well as on GDAP1, a protein of the mitochondrial outer membrane preferentially expressed in neurons. This article is part of a Special Issue entitled: Mitochondria & Brain.

Contents

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1. Introduction

Mitochondria are dynamic organelles that continuously move, fuse and divide. These dynamic events have been mainly studied in cultured cells, but emerging approaches allow the observation of mitochondrial morphology and dynamics in tissues and/or organisms (Bolea et al., 2014; Mils et al., 2015; Pham and Chan, 2014). Mitochondrial dynamics are essential for maintenance, function, distribution and transmission of mitochondria and have been further involved in apoptosis. Before developing the specific roles of mitochondrial dynamics in neuronal degeneration and plasticity, we will introduce these dynamic processes, their general physiological relevance and the main players in the field.

Mitochondrial positioning and mobility modulate intracellular mitochondrial distribution and notably ensure the presence of mitochondria at sites of high ATP consumption. Numerous works concerning mitochondrial mobility and distribution were performed in the budding yeast *Saccharomyces cerevisiae* or in neurons in which asymmetric division or complex architecture, respectively, represent a real challenge for mitochondria. This subject has been extensively revised and we refer interested readers to these reviews (Saxton and Hollenbeck, 2012; Schwarz, 2013; Sheng, 2014; Vevea et al., 2014; Westermann, 2014). Briefly, position and mobility of neuronal mitochondria rely on interactions with the microtubule and actin cytoskeletons, which ensure their distribution between soma and neurites, their transport along axons and dendrites and their presence, in sufficient amounts, at nerve terminals and synaptic sites. For long-range transport mitochondria bind, *via* mitochondrial Miro1/2 GTPases and Milton/TRAK, to kinesin and dynein motors ensuring transport along the microtubule network. In contrast, short-range mitochondrial movements at presynaptic terminals are mediated by myosin motors and the actin cytoskeleton. Mobile neuronal mitochondria can be recruited in stationary pools, in axons and at synapses, where constant energy and Ca^{2+} homeostasis are crucial, *via* dynamic anchoring interactions between syntaphilin and microtubules and *via* actin-based anchoring receptors. Given their physiological relevance, defects in mitochondrial mobility and distribution appear directly linked to neuronal dysfunction and diseases (Nguyen et al., 2014 and see for review Pareyson et al., 2015).

In this review we will focus on the fusion/fission equilibrium, which primarily governs mitochondrial morphology and which requires specific ubiquitously expressed proteins (see below) and phospholipids (see for review Zhang et al., 2014). When fusion takes over fission, mitochondria appear as an interconnected network of filaments, while they turn into isolated particles when fission prevails. In contrast to numerous cells and to the soma of neurons, where mitochondria appear as a network of branched and interconnected filaments, the mitochondria in neurites appear mainly as short filaments or dots (Fig. 1).

It is important to note that fusion/fission dynamics are linked to mobility and positioning. Defects in mitochondrial fusion/fission and the consequent alterations of mitochondrial morphology affect mitochondrial mobility and distribution (see for review Chen and

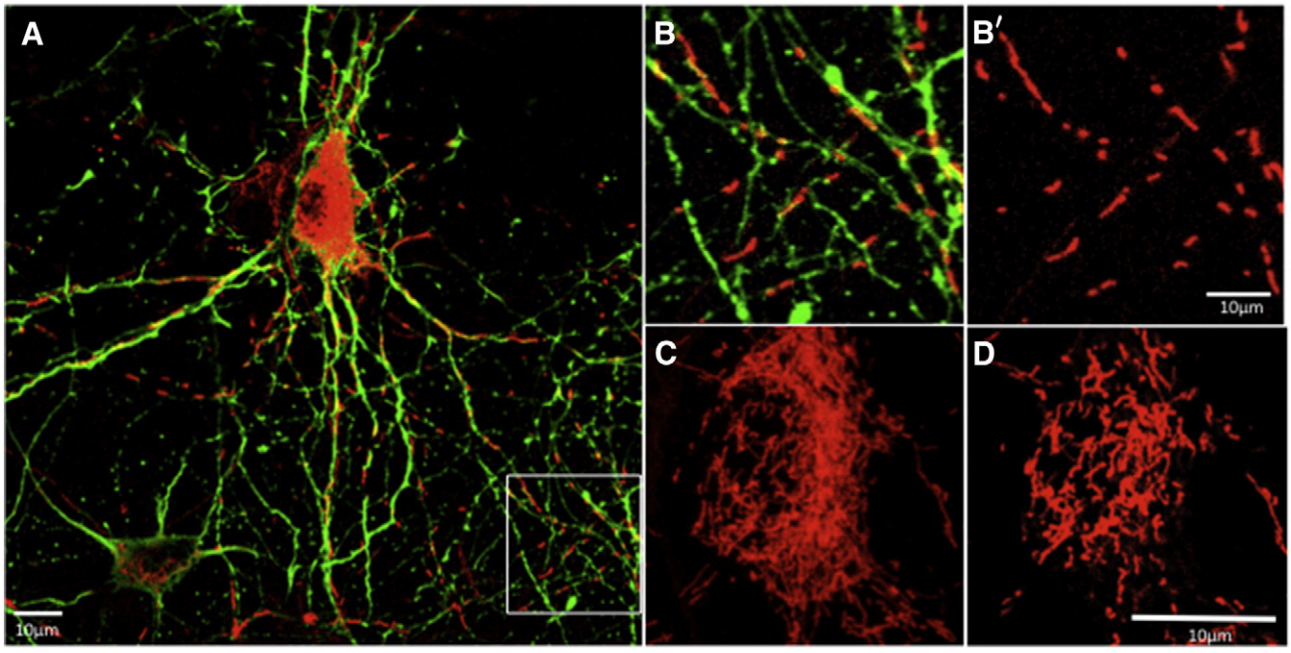

Fig. 1. Mitochondrial morphology in rat hippocampal neurons in primary culture. (A) Stack projection of confocal micrographs of rat hippocampal neurons in primary culture with mitochondria (red, MitoDsRed transfection) and neuronal β3 tubulin (green, immunodetection) (×63). Right panels in (B and B′) represent a zoom of the framed region of interest showing small distal mitochondria. Somatic mitochondria are shown in (C) as a 3D reconstruction of confocal z-sections (×63, zoom 6) including the section shown in (D). (Unpublished data from M.-C. Miquel.)