Neurochemistry International 109 (2017) 141–161

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/nci

Connecting mitochondrial dynamics and life-or-death events via Bcl-2 family proteins

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ARTICLE INFO

Article history:
Received 3 April 2017
Accepted 17 April 2017
Available online 28 April 2017

Keywords:
Mitochondria
Apoptosis
Mitochondrial dynamics
Neurons
Bcl-xL
Drp1

ABSTRACT

The morphology of a population of mitochondria is the result of several interacting dynamical phenomena, including fission, fusion, movement, elimination and biogenesis. Each of these phenomena is controlled by underlying molecular machinery, and when defective can cause disease. New understanding of the relationships between form and function of mitochondria in health and disease is beginning to be unraveled on several fronts. Studies in mammals and model organisms have revealed that mitochondrial morphology, dynamics and function appear to be subject to regulation by the same proteins that regulate apoptotic cell death. One protein family that influences mitochondrial dynamics in both healthy and dying cells is the Bcl-2 protein family. Connecting mitochondrial dynamics with life-death pathway forks may arise from the intersection of Bcl-2 family proteins with the proteins and lipids that determine mitochondrial shape and function. Bcl-2 family proteins also have multifaceted influences on cells and mitochondria, including calcium handling, autophagy and energetics, as well as the subcellular localization of mitochondrial organelles to neuronal synapses. The remarkable range of physical or functional interactions by Bcl-2 family proteins is challenging to assimilate into a cohesive understanding. Most of their effects may be distinct from their direct roles in apoptotic cell death and are particularly apparent in the nervous system. Dual roles in mitochondrial dynamics and cell death extend beyond BCL-2 family proteins. In this review, we discuss many processes that govern mitochondrial structure and function in health and disease, and how Bcl-2 family proteins integrate into some of these processes.

Contents

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http://dx.doi.org/10.1016/j.neuint.2017.04.009
0197-0186/

1. Introduction

Mitochondria are considered to have originated from the endosymbiosis of an α-proteobacterium. Vestiges of their bacterial ancestry are apparent by their micrometric size (similar to bacteria), double membrane, circular DNA, unique genetic code and ribosomes, and their semblance to bacterial cell division and movement. However, these microbial resemblances have been dramatically altered by 1–2 billion years of evolution resulting in the progressive loss of independence and further conversion from mitochondrial ancestor to *bona fide* eukaryotic organelle. This intracellular domestication was accompanied by transfer of most proto-mitochondrial genes to the nuclear genome and many other changes related to the intracellular environment of eukaryotic cells. The small number of mitochondria-encoded proteins (13 in humans) is counterbalanced by a rich mitochondrial proteome of nuclear-encoded proteins targeted to mitochondria by a diverse complement of signal sequences (Cotter et al., 2004).

Conversely, important eukaryotic traits apparently emerged from microbial acquisition, including a more advanced energy metabolism. Mitochondrial structure appears to have been exploited to take over not only energy production, but additional tasks to meet the needs of cells and organisms. Mitochondria of modern-day eukaryotic cells fulfill multiple cellular functions such as maintenance of ion homeostasis (e.g. calcium), steroid production, biosynthesis of specialized iron-containing complexes, heat production, cellular redox state regulation, generation of reactive oxygen species (ROS) (e.g. as second messengers) and initiation of apoptotic cell death by liberating key components into the cytosol, a process regulated by Bcl-2 family proteins (McBride et al., 2006; Nunnari and Suomalainen, 2012).

Like “soft robots” (Kim et al., 2013), mitochondria are highly dynamic organelles that emulate diverse outputs by adapting their number, shape, position, connectivity and motion in response to intracellular inputs and extracellular environment. Thus, mitochondrial morphology is intertwined with mitochondrial function, but most of the details are not yet known (Benard and Rossignol, 2008; Bindoff et al., 1991; Guillery et al., 2008; Wai and Langer, 2016). However, interest in this direction is spawned by the alterations in mitochondrial structure and function associated with aging, cancer, heart disease and a growing number of neurological disorders including epilepsy, stroke, Wolfram syndrome, Alzheimer's disease, Parkinson's disease, and Huntington's disease (Archer, 2013; Cagalinec et al., 2016; Corrado et al., 2012; Knott et al., 2008; Lee et al., 2016b; Rugarli and Langer, 2012; Schon and Przedborski, 2011; Vafai and Mootha, 2012). Much less is known about ultrastructural morphology and dynamics of mitochondrial inner membrane cristae despite being disrupted in neurodegenerative and other disease states. Research over the last two decades has begun to reveal the nature and complexity of cellular signaling pathways that sculpt the mitochondrial network (Burte et al., 2015; Nasrallah and Horvath, 2014).

One key protein family that influences both mitochondrial structure and function in both healthy and dying cells is the extended Bcl-2 family that apparently arose with metazoans (Aouacheria et al., 2013; Bhola and Letai, 2016). Members of this extended Bcl-2 protein conglomerate are thought to exert many of their functions on the cytosolic side of the mitochondrial membrane, where most research has focused on the events leading to apoptosis. A key event during apoptosis is pore-formation in the