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MCL-1 and its Role in Cancer Research

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MCL-1 plays critical roles in the eukaryotic cell and right down to the mitochondria. MCL-1 also has a significant role in the research of cancer and mitochondrial metabolism. As cancer being very prevalent throughout the world, there are new ways to go about how to research to vast complexity involving cell death of cancerous cells. MCL-1 is one of the primary topics in the field of cancer research and cell death. Completely understanding how MCL-1 functions and the jobs it takes on within the cell will open the door great advances in medicine and cell and molecular biology.

Introduction

Cell death regulates and maintains tissue homeostasis in eukaryotic cells, but more in more related terms, animal cells. This process is usually part of the embryonic development. This regulation of cell death is known as apoptosis. Apoptosis is an evolutionary conserved cell death pathway essential for tissue homeostasis [3]. The knowledge of its genetic encoding is essential for advances in biotechnology and medical advances. When the genetic encoding is deregulated, it is not only for understanding human pathologies like cancer, but also neuro-degeneration and autoimmunity diseases. A wide range of apoptotic stimuli trigger the release of apoptogenic factors, for example, cytochrome c which is from the mitochondria, results in the activation of caspases [3] (refer to figure 1). Caspases are vital enzymes in apoptosis and prompt morphological and biochemical components of BCL-2 proteins. MCL-1 is conveyed in multiple cell groups and is a significant member of this group of apoptosis regulator molecules.

Recent Progress

Structure

The cell death is regulated by the BCL-2 family. MCL-1 is a unique anti-apoptotic protein of the BCL-2 family, it has a short half-life and its amino terminus is longer than other antiapoptotic BCL-2 proteins and is essentially unstructured, which makes it excluded from structural analyses [1]. The human MCL-1 gene is found on chromosome 1q21 [2]. MCL-1 has a C-terminal (TM) domain that serves to limit MCL-1 to different intracellular membranes, mainly the outer mitochondrial membrane [2]. This innately gives MCL-1 control over activities within the mitochondria during apoptosis. The specific molecular mechanism through which MCL-1 induces cell survival is not entirely known**,** it is believed to include suppression of the cytochrome c in its release from the mitochondria. This is possibly in the process of heterodimerization, a combination of two identical molecules to form a compound, by means of deactivation of pro-apoptotic BCL-2 family proteins [2].

Mitochondria: Inner membrane

Groups have independently proven that full-length MCL-1 starts the proteolytic process**,** which means it breaks down into smaller polypeptides or amino acids. The proteolytic process occurs by hydrolysis of the peptide bond. MCL-1 is located on the outer mitochondrial membrane (OMM), MCL-1's amino-terminal domain gains temporary access to the inner mitochondrial membrane (IMM). The shortened or cut MCL-1 involved in mitochondrial metabolism and dynamics was shown [1]. This function is not part of the full-length MCL-1's ability to initiate apoptosis; which MCL-1 has to be taken into the mitochondrial matrix [1]. The matrix-localized MCL-1 supports normal mitochondrial ultra-structure by maintaining cristae morphology as well as the dynamics

of mitochondrial fission [1]. MCL-1 opposes apoptosis and stimulates mitochondrial function.

Mitochondria: Outer membrane

A recent study based on siRNA 'knockdown' proposed that the N terminus of the MCL-1 is apt to mitochondrial processing by the matrix-localized able peptidase and concluded that this is correlated to the import of MCL-1 into the interior of the organelle, which located MCL-1ΔN inside an internal compartment [3]. This suggests MCL-1ΔN is attached in the outer mitochondrial membrane (OMM) and exposed to the cytoplasm, this is certain that the MCL-1 C-terminal trans-membrane (TM) section is needed and arranged to mark and attach MCL-1 into the outer membrane lipid bilayer. In isolated intact mitochondria, endogenous MCL-1 and MCL-1ΔN were both found resistant to alkaline extraction, pH 11.5, which designated membrane combination [3].

Discussion

With a growing interest to develop BCL-2 family inhibitors, this has shown to be a stable cancer treatment method, which focuses on pushing for antipoptotic activity to accompany cell death. The deletion of the MCL-1 gene has shown to encourage cell death in cancerous cells regardless of reliable expression of other endogenous antiapoptotic family proteins [1]. Further study on the role of MCL-1 on antiapoptotic and metabolic functions in cancerous cells and in normal cells could help the understanding and development to produce more efficient MCL-1 inhibitors.

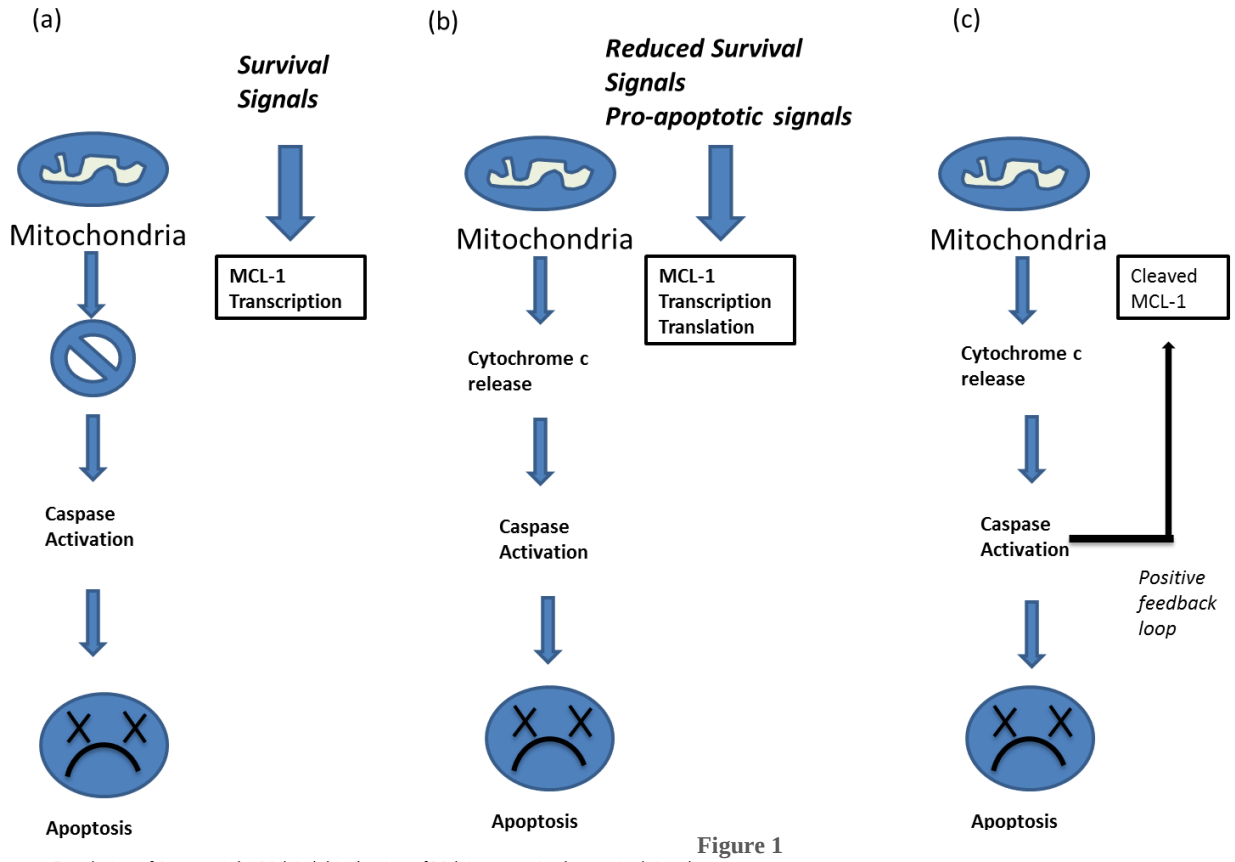

Figure 1

Regulation of Apoptosis by Mcl-1. (a) Induction of Mcl-1 expression by survival signals downregulation of Mcl-1 expression following removal of survival factors or exposure to other pro-apoptotic signals may contribute to apoptosis by promoting cytochrome c release. (c) Caspases activated during apoptosis can cleave remaining Mcl-1, generating a potent cell death promoting protein.

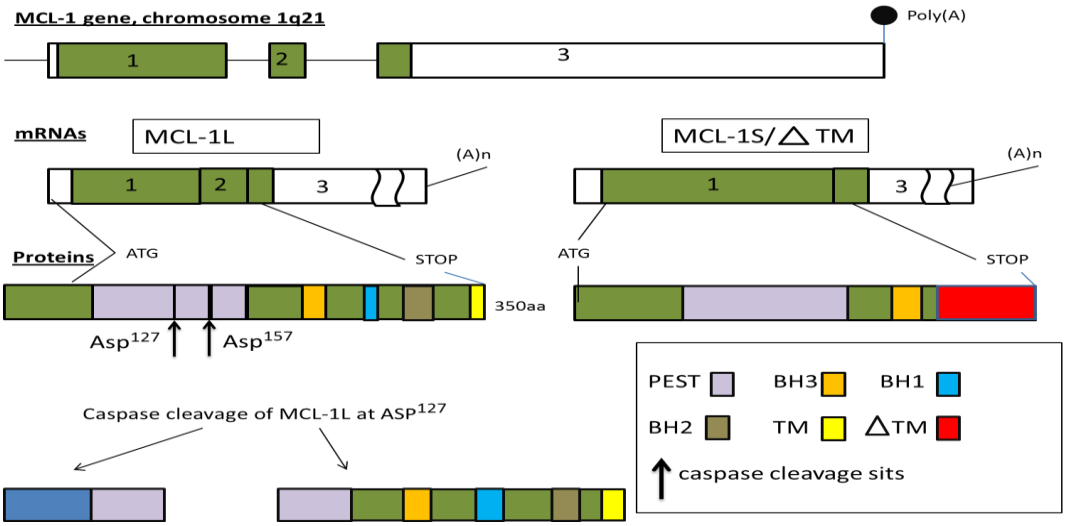

Figure 2 This is an organization of the human MCL-1 gene, which is located on chromosome 1q21. It has three exons that encode protein information (Figure from [2]).

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Figure 3

