در صد تخیف نوروزی ویژه کارگاه‌ها و فیلم‌های آموزشی

- اصول تنظیم قراردادها
- پروپوزال نویسی
- آموزش مهارت های کاربردی در ندوین و چاپ مقاله
Mitoptosis, a Novel Mitochondrial Death Mechanism Leading Predominantly to Activation of Autophagy

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Sometimes some members of multicellular organisms need to sacrifice for the good of the whole. Perhaps with the exception of immunomodulatory processes (1, 2), it is the intrinsic death pathway, often triggered by p53 (3-5), modulated by Bcl2-family members, and executed primarily by caspases that is most commonly employed to trigger cell death (6-8). Apoptotic or autophagic cell death is triggered by physical insults such as cold (9), natural compounds and their derivatives (10-12), viruses (13), or even disturbances within the cell cycle (14, 15). Apoptotic cell death is preceded by mitochondrial release of cytochrome c, which leads to increases in cytochrome c in serum (16). Mitochondria have been a cellular guest for millions of years and seamlessly transformed into a major functional cellular organelle. Until the last couple of decades, mitochondria were mainly viewed as powerhouses of the cell but more recent reports have indicated their crucial role in apoptosis, necrosis, and autophagy.

Opening of the permeability transition pore in the outer mitochondrial membrane, release of cytochrome c, and formation of apoptosomes is considered the turning point in apoptosis. Further studies showing the cellular localization and phenotypic and mechanistic modulations in mitochondria during cellular homeostasis, stress, and death, support the pivotal role of mitochondrial influenced cellular fate.

Thus, do mitochondria have the mechanisms to trigger host cell death or is the host directing the mitochondria depending on physiological needs? To what extent are mitochondria autonomous in their function and death? Recent reports about mitochondrial suicide (mitoptosis) and relocation of mitochondria to the nuclear periphery (thread-grain transition) may provide substantial answers to these basic questions. Two very interesting reviews (Skulachev, IUBMB Life 2000, and Skulachev, Apoptosis 2006) by Vladimir P. Skulachev elaborate the
Mitoptosis is a novel mitochondrial death mechanism that describes the process of mitochondrial cell death. It is characterized by the degradation of the mitochondrial matrix and cristae, followed by the release of vesicular remnants into the cytoplasm. Mitoptosis can be induced by various stimuli, such as apoptosis, and occurs primarily due to the loss of mitochondrial membrane potential. The fate of the degraded mitochondria can vary, with some becoming autophagosomes and others being extruded as mitoptotic bodies.

The process of mitoptosis involves two main forms: inner membrane mitoptosis and outer membrane mitoptosis. Inner membrane mitoptosis occurs when only the internal matrix and cristae are degraded while the external mitochondrial envelope remains intact. Outer membrane mitoptosis is characterized by the degradation of the outer mitochondrial membrane, followed by the release of vesicular remnants.

Mitoptosis is a fundamental understanding of mitochondrial suicide and the phenomenon of apoptosis. It is initiated by the loss of mitochondrial membrane potential, which can occur due to various stimuli, such as the apoptotic signal or disruption in the respiratory chain. The initial increase in mitochondrial membrane potential is thought to be due to the ATP dependency of apoptosis, leading to the release of apoptotic factors and the amplification of programmed cell death. Mitoptosis is further supported by studies using mitochondrial respiratory chain uncouplers and mitochondrial poisons, which can induce overproduction of reactive oxygen species (ROS) without reductions in cellular ATP levels leading to mitoptosis.

Mitoptosis is a complex process that involves the degradation of mitochondria and the release of vesicular remnants into the cytoplasm. It is a novel and important mechanism in the regulation of cell death and the maintenance of cellular homeostasis.
ic bodies that are subsequently released into the extracellular environment (19). The elimination of dysfunctional mitochondria is further supported by studies of cells treated with staurosporin, a common drug used to induce apoptosis, and by the use of pan-caspase inhibitors in which cells survive but lose their mitochondria (21). More recent studies on PINK1 and Drp1 in neural diseases suggest that dysfunctional mitochondria trigger autophagy and, thus, are eliminated (22). Thus, suggesting that mitochondrial dysfunction is a good enough reason for eliminating mitochondria and as Dr. Skulachev says, mitochondria follow the samurai’s law; “it’s better to die than to be wrong”.

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Author’s Contribution

JJ & JL jointly prepared the manuscript.

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References

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پروپوزال نویسی

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