Karolinska Research Lectures at NOBEL FORUM

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Programmed Cell Death in Diseases and Aging

Xiaodong Wang, Ph.D.

National Institute of Biological Sciences, #7 Science Park Road, Zhongguancun Life Science Park, Beijing 102206, China.

Specific loss of cell vitality during animal development and adult life is important part of normal animal physiology and defects in such a process cause many human diseases. These forms of cell death are executed by specific biochemical programs within the dying cell, thus termed programmed cell death. Our laboratory has been studing programmed cell death for the last twenty years aiming at three related goals. The first is to delineate the biochemical reactions of cell death programs; Secondly, to understand the physiological and pathological functions of programmed cell death; and finally, to derive therapeutic strategies based on the knowledge of programmed cell death to treat human diseases and in particular, cancer and age-associated organ deterioration.

The longest ongoing research program of our laboratory studies apoptosis, i.e. caspase-mediated cell death. One of our most surprising findings of these studies is the role of mitochondria, the classical viewed powerhouse and metabolic center of eukaryotic cells, in apoptosis in mammalian cells. Our laboratory discovered that cytochrome c, a component of mitochondrial electron transfer chain, is able to trigger the activation of apoptotic caspases once released from the mitochondria; and Smac that neutralizes caspase inhibition imposed by the inhibitor of apoptotic proteins, IAPs. The release of cytochrome c and Smac from mitochondria is regulated by the Bcl-2 family of proteins. How Bcl-2 family of proteins control the release of these apoptogenic proteins is now the focal point of our research and I will share our latest work on this subject in this upcoming lecture.

Based on the molecular mechanism how Smac functions, we designed a small molecule mimetic of Smac protein that is cell permeable and directly sensitizes treated cells for apoptosis. The Smac mimetic led us to an unexpected finding that in some cell types, a caspase-independent form of programmed cell death occurs in the presence of Smac mimetic in response to tumor necrosis factor family of cytokines or toll-like receptor ligands. We subsequently identified the receptor interacting kinase 3, RIP3, and its substrate, a peudokinase MLKL, as the core biochemical components of this form of cell death, also called necroptosis. We recently found that necroptosis in spermatogonial stem cells and Sertoli cells within the seminiferous tubules of mouse testis has a critical role in promoting male reproductive organs aging. The detailed molecular mechanism will also be discussed in my lecture.

Host: Boris Zhivotovsky, Karolinska Institutet
boris.zhivotovsky@ki.se