Study reveals the protein structure of the human apoptosome

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Programmed cell death, or apoptosis, plays a central role in the maintenance of human health by providing a line of defense against unrestricted cell growth that occurs in many cancers and AIDS as well as in neurodegenerative diseases and stroke.

Researchers from Boston University School of Medicine (BUSM) have for the first time mapped an active human apoptosome. This model, which appears online in the journal *eLife*, helps provide a better understanding of how cell death occurs and may lead to treatment options to either enhance or suppress this process.

Between 50-70 billion human cells commit suicide each day as a result of environmental stress or developmental cues. Damaged or unwanted cells undergo a process during which they are removed in a controlled manner and the resulting cellular components may be recycled.

Cellular signaling in the programmed death pathway culminates in a complex assembly of proteins termed the "apoptosome." This large wheel-like structure recruits and activates specific proteases (enzymes that split proteins) to dismantle proteins in the cytoplasm and the nucleus. Thus, the cell is broken down into pieces from the inside by this "wheel of death."

The research team, led by Christopher W. Akey, PhD, BUSM professor of physiology & biophysics, determined the near atomic structure of the apoptosome using cryo-electron microscopy and were able to build a

three-dimensional model.

According to the researchers the apoptosome is a wheel-like structure with seven spokes. On top of the wheel is a spiral-shaped disk formed by protease docking, while active domains of the proteases are flexibly-tethered to the disk. When active the apoptosome is a dynamic molecular machine with three to five protease molecules tethered to it at any given time. The number of proteolytic units parked on the wheel could vary, resulting in a changing level of dismantling activity. A soluble protease is in turn cleaved and activated by the active apoptosome and this soluble protease then targets cellular components.

"This study helps us to better understand the fundamentals of a critical system in the body that helps regulate tissue development and stability. Our hope is to find drugs to target this wheel of death to either enhances or suppress its function," said Akey.

More information: Tat Cheung Cheng et al, A near atomic structure of the active human apoptosome, *eLife* (2016). DOI: 10.7554/eLife.17755

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