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TEMASEK LIFESCIENCES LABORATORY

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Identification of caspase downstream pathways and their importance to cell death execution

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Dr. Akihisa Nakagawa graduated from Kanazawa University, Japan, with a Bachelor of Pharmacology, Master of Pharmaceutical Sciences, and Ph.D. of Medical and Pharmaceutical Sciences in 1999, 2001, and 2004, respectively. He did his postdoc training in Colorado University, USA, and has revealed several downstream pathways of caspase CED-3 in C. elegans cell death. He is now interested in oxidation and reduction in the context of cell death regulation and diseases.

Caspases, a family of cysteine proteases, play critical roles in apoptosis execution. However, the downstream pathways of caspases and their importance and contributions to cell death execution are poorly understood. Through sensitized genetic screens, several downstream pathways of the CED-3 caspase in C. elegans have been identified. Each pathway promotes different aspects of cell death execution events, including chromosome fragmentation, inactivation of the AKT survival pathway, phosphatidylserine externalization, and mitochondria elimination. The Dicer (DCR-1) ribonuclease initiates chromosome fragmentation when it is cleaved by CED-3 and is converted from an RNase to a DNase. Inactivation of the AKT survival pathway is accomplished by cleavage of CNT-1 by CED-3, which activates a potent PIP3-binding activity that inactivates AKT. Although loss of each CED-3 downstream pathway results in subtle cell death defects, simultaneous inactivation of multiple CED-3 downstream pathways blocks close to 50% of the cell deaths. These data indicate that the CED-3 caspase cleaves limited critical substrates to activate downstream pathways and to promote apoptosis, despite the model that cells die by a thousand cuts by caspases.

Recent Publications:

1. Nakagawa A, Shi Y, Kage-Nakadai E, Mitani S, and Xue D. Caspase-dependent conversion of Dicer ribonuclease into a death-promoting deoxyribonuclease. Science (2010) 328, 327-334.
2. Ge X, Zhao X, Nakagawa A, Gong X, Skeen-Gaar R R, Shi Y, Gong H, Wang X, and Xue D. A novel mechanism underlies caspase-dependent conversion of the dicer ribonuclease into a deoxyribonuclease during apoptosis. Cell Res (2014) 24, 218-32.
3. Nakagawa A, Sullivan K D, and Xue D. Caspase-activated phosphoinositide binding by CNT-1 promotes apoptosis by inhibiting the AKT pathway. Nat Struct Mol Biol (2014) 12, 1082-90.