



Regulating programmed cell death by activating the autophagic pathway

The Challenge: While the manipulation of programmed cell death has been considered for therapy of cancer, neurodegenerative and immunological disorders, almost all targets for cell death therapy are focused on regulators that mediate apoptosis. However, the autophagic pathway can be used as an alternative to apoptotic cell death and as a source of therapeutic targets. In mammalian systems, autophagy is thought to be involved in many physiological processes including, cell survival in response to starvation, cell growth control, anti-aging mechanisms, and innate immunity; whereas, the deregulation of autophagy has been proposed to play a role in certain diseases including, cancer, cardiomyopathy, muscular diseases, and neurodegenerative disorders.

UMBI Solution: A UMBI investigator has demonstrated that the ATG genes (ATG7 and Beclin 1) that regulate the cell survival mechanisms can be induced to activate programmed cell death. The investigator has characterized a new molecular pathway in which activation of the receptor interacting protein (RIP) and Jun N-terminal kinase (JNK) induces cell death with the morphology of autophagy. Further, it was observed that RIP is cleaved and inactivated by caspase 8 providing a mechanism to prevent autophagic cell death. Moreover, products that inhibit caspase 8 will allow RIP to transmit the signal needed to kill the cell through the autophagic pathway. Non-apoptotic cell death appears to provide a compensatory mechanism for cell killing when apoptotic regulators are compromised. Thus, combination therapies that address both the apoptosis and autophagic pathways may prove much more effective than targeting a single pathway.

Commercial Applications:

- Therapeutics - Alternative to apoptosis modulation for therapies manipulating programmed cell death for cancer, neurodegeneration and immunological disorders.
- Targets for drug development – Method for determining pharmaceutical compounds that induce the autophagic pathway.
- Increase effectiveness of apoptosis therapies – Apoptosis therapies may be contravened by autophagy, requiring combination approaches to therapy.

Advantages:

- Alternative to apoptosis for programmed cell death
- Provides a mechanism to both induce as well as prevent autophagic cell death
- Identified human autophagy genes, ATG7 and Beclin 1, as probes for pathway characterization and potential drug targets.

Patent Status: United States Patent Application, Publication Number 20050276809. December 15, 2005, "Function of autophagy genes in cell death."

Licensing Potential: UMBI is seeking non-exclusive and exclusive licensees to all or part of this technology. The UMBI inventor would welcome the opportunity to work with any licensee to further refine or extend the capabilities this invention.

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Relevant Publications:

1. Yu L, Wan F, Dutta S, Welsh S, Liu Z, Freundt E, Baehrecke EH, Lenardo M. 2006. Autophagic programmed cell death by selective catalase degradation. Proc Natl Acad Sci U S A. 103(13):4952-7.
2. Baehrecke EH. 2005. Autophagy: dual roles in life and death? Nat Rev Mol Cell Biol. Jun;6(6):505-10. Review.
3. Yu L, Lenardo MJ, Baehrecke EH. 2004. Autophagy and caspases: a new cell death program. Cell Cycle. Sep;3(9):1124-6. Review.
4. Yu L, Alva A, Su H, Dutt P, Freundt E, Welsh S, Baehrecke EH, Lenardo MJ. 2004. Regulation of an ATG7-beclin 1 program of autophagic cell death by caspase-8. Science 304(5676):1500-2.

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