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## Humanin: A Multifactorial Anti-death Agent

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### Commentary

Necrosis is one mode of cellular demise which historically was considered to be an uncontrolled process, but findings from recent years showed that necrosis is a well-regulated process [1,2]. Necrosis is associated with severe diseases and pathological conditions such as neurodegenerative disease, stroke, myocardial infraction, and many others for which currently there is no drug-based therapy. Thus, the need for a novel anti-necrotic therapy is of high importance.

Humanin (HN) is a 24-amino acid mitochondrial peptide, which was discovered in 2001 by Hashimoto thanks to its protective effect against amyloid beta toxicity in Alzheimer's disease [3-5]. HN was known for its' anti-apoptotic activity, which is mediated by HN binding, amongst others, to *Bcl-2*-associated X protein (Bax), a member of the B-cell lymphoma-2 (*Bcl-2*) family which regulates cellular survival [6,7]. Additional functions of HN include improving insulin sensitivity in type 2 Diabetes Mellitus via interaction with insulin-like growth factor-bindingprotein-3 (IGFBP-3) thus regulating its induction of insulin resistance [8]. Furthermore, it was discovered in 2003 that humanin can elevate cellular ATP levels even when there is no apparent lack in ATP [9].

Studies of humanin derivatives provided a variety of peptides with higher pro-survival activity, which later was showed to be mediated by inhibition of various cell death mechanism such as apoptosis and necroptosis and finally necrosis. Derivatives such as HNG, where the serine in position 14 was replaced with glycine conferred pro-survival activity at 1000 fold lower concentrations than native humanin. Additional activity enhancement was achieved by replacing the cysteine residue in position 8 with an arginine. Replacing arginine and phenylalanine in position 4 and 6 respectively resulted in some protease protection. Finally shortening the peptide to the 17 most essential residues resulted in the most active derivative – AGA (C8R)-HNG17 [10,11].

In a paper published in 2015, our group showed that HN and most efficiently its' derivative AGA (C8R)-HNG17 can confer protection against necrotic cell death [12]. This was demonstrated in neuronal cell lines PC-12 and NSC-34 where necrosis was induced in glucose free medium by either chemohypoxia or a shift from apoptosis to necrosis [1,13]. We also showed that humanin's mitigates a necrosis-associated decrease in ATP levels. Further, we demonstrated the peptide's direct enhancement of the activity of ATP synthase activity, isolated from rat-liver mitochondria, suggesting that AGA (C8R)-HNG17 targets the mitochondria and regulates cellular ATP levels. These findings provide an insight into the peptide's mechanism of action.

In addition we showed HN's anti-necrotic activity in a mice model of traumatic brain injury, where necrosis is the main mode of neuronal cell death. This was demonstrated by a decrease in a neuronal severity score as determined by neurobehavioral studies and by a reduction in brain edema as measured by MRI.

Humanin advantage as a potential anti-necrotic agent is based on three pillars:

1. Humanin is naturally found in the human body as a mitochondrial derived peptide.
2. Humanin levels decrease with age, which suggests that humanin can serve a treatment for age associated diseases such as Alzheimer's disease.
3. Humanin acts against different cell death mechanisms (i.e., apoptosis, necroptosis and necrosis). Thus further studies are required to investigate its efficacy against other necrosis-related diseases.

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