Mechanisms of neuronal apoptosis and neurodegeneration

https://neurodegenerationresearch.eu/survey/mechanisms-of-neuronal-apoptosis-and-neurodegeneration/

Title of project or programme

Mechanisms of neuronal apoptosis and neurodegeneration

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
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Source of funding information

Medical Research Council

Total sum awarded (Euro)

9833050.33

Start date of award

01-04-2005

Total duration of award in months

60

The project/programme is most relevant to

- Huntington’s disease
- Neurodegenerative disease in general

Keywords

Research abstract in English

Chemical agents and endogenous noxious stimuli can cause neurotoxic effects by several mechanisms. Ultimately, impairment of neuronal signalling, synaptic activity and intracellular protein

trafficking can result in neurodegeneration and neuronal demise. Establishing social contacts is the raison d'etre of neurons throughout their entire life span. To form and retain functional connections, neuronal differentiation and death are ruthlessly regulated in development and kept strictly under control in post-mitotic systems. Derangements in neural networks affect neuronal populations at large. Therefore failure to retain synaptic connectivity is linked to dysfunction and often followed by neuronal death. Neuronal cell death is not an obligate requirement for neural dysfunction at the level of distributed circuits or local circuits. Nevertheless, more or less widespread neuronal loss can occur after acute insults such as brain ischemia or invasion of the brain by pathogens, but also at the end-stage of neurodegenerative and psychiatric diseases.

Our research is centred on the mechanisms leading to neurotoxicity in chemical injury and disease states. The identification of molecular switches that decide the type of cell death neurons undergo following injury has been one of our major interests in the past few years.

We have characterized the metabolic requirements for cell death by apoptosis, and the role of different death sub-routines in the appearance of apoptosis or necrosis after excitotoxic injury.

In addition, we are studying the relative roles of loss of connectivity versus neuronal apoptosis in the onset of chronic neurodegenerative conditions.

Our major achievements include:

– The understanding of one of the major mechanisms that causes the excitotoxic Ca2+ overload in neurons during brain ischemia.

– The finding that statins can protect neurons from excess synaptic activity as found in excitotoxicity, but impair synaptic function and protein internalization in cortical neurons.

– The discovery that synaptic damage triggers two independent degenerative programmes in central neurons by a process that recapitulates the main features of CNS neurodegenerative disorders.

– The discovery that aggregate formation in a cellular model of Huntington's disease impairs protein recycling through the vesicular recycling centre and thereby alters synaptic protein homeostasis.

Lay Summary