Mechanisms of endogenous antigen processing by the MHC class II pathway: studies with viral and cellular proteins

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Title of project or programme

Title of PI	Mechanisms of endogenous antigen processing by the MHC class II pathway: studies with viral and cellular proteins

Principal Investigators of project/programme grant

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Source of funding information

Medical Research Council

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522030.74

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01-10-2009

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36

The project/programme is most relevant to

- Motor neurone diseases
- Huntington’s disease
- Spinocerebellar ataxia (SCA)

Keywords

Research abstract in English

While exogenously-acquired proteins are the main source of antigens presented to CD4+ T cells, it is known that many proteins expressed endogenously within MHC class II-positive cells can also access the MHC II presentation pathway. This proposal seeks to further our understanding of different pathways that govern the processing of such proteins, in particular the influence that intracellular location might have on processing route.

Firstly, I plan to build on my recent work studying the processing for CD4+ T cell recognition of Epstein-Barr virus (EBV) antigens within EBV-transformed lymphoblastoid cell lines (LCLs). I have CD4+ T cell clones to a range of epitopes in the virus-coded nuclear antigens EBNAs, in the latent membrane proteins LMPs 1 and 2, and in a cytoplasmic protein BHRF1 now known to be a latent cycle antigen. Our evidence shows that EBNA 2 and the EBNA3 proteins are processed via the inter-cellular transfer of as-yet-poorly-defined antigenic species, whereas EBNA1, the LMPs and BHRF1 are processed by different intracellular pathways. We have found that nuclear-localised EBNA1 is only processed by the intracellular macro-autophagy (MA) pathway when it is experimentally relocalised into the cytoplasm. The work will focus on determining the relative importance of MA, chaperone-mediated autophagy (CMA) and plasma membrane recycling to the endo/lysosome system as MHC II access routes for these proteins, and the effect of antigen or epitope re-location on that process.

Secondly, I shall move on to study the processing of cellular proteins of medical importance. I will investigate the processing of WT1 and STEAP, two tumour-associated antigens expressed in a wide range of malignancies that are good CD4 targets and compare their processing with the EBV proteins. I will go on to study antigen processing in the context of neurological diseases caused by poly-glutamine (polyQ) containing proteins forming toxic aggregates within cells. Degradative pathways such as MA, which can clear such aggregates, are of interest as potential therapeutic interventions for such conditions. In animal models disease severity is reduced when naturally nuclear-resident polyQ proteins are relocalised out of the nucleus. The objective will be to test the notion that MA cannot clear nuclear-localised aggregates and determine whether CMA can act as a substitute pathway to clear nuclear-localised aggregates.

Lay summary
In which category does this research fall?

- Basic research