

Humanizing Regulators of the Complement Cascade to Improve Research Relevance

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USA

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Humanizing Regulators of the Complement Cascade to Improve Research Relevance

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3

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Research Abstract

? DESCRIPTION (provided by applicant): Activation of the complement cascade occurs in development, aging and a wide variety of human disease including neurodegenerative diseases, autoimmune diseases and in response to infections. Much of our understanding of the complement cascade has come from animal models. However, there are critical species differences between these models and humans that make data generated inadequate. This

important difference hinders our ability to understand the complex role of the complement cascade and its key regulators in health and disease. In particular, there is no true functional equivalent of complement receptor 1 (CR1) that modulates the activity of complement components C1q, C3 and C4, key molecules in the complement cascade. Regulators of the complement cascade are also good targets for developing new therapies for diseases that involve complement activation. The closest functional equivalent to the human CR1 protein in mice is an isoform produced by the Cr2 gene, but its expression pattern differs substantially. Previous modeling of human CR1 in mice has been restricted to a limited number of cell types. Therefore, to overcome this major limitation of mice in modeling complement regulation, we have targeted mouse embryonic stem (ES) cells to express the human CR1 gene, driven by the human CR1 promoter and upstream sequences, and the human CR2 gene in place of the mouse Cr2 gene. We have further engineered these ES cells to enable site-specific recombination to generate two of the most common alleles of the human CR1 gene, the longer and the shorter forms. Correct targeting was confirmed, chimeric mice generated and germline transmission confirmed. Expression of CR1 and CR2 in both the blood and the brain was shown by RTPCR. In this proposal, we will fully determine the potential of this new strain to understand activation and regulation of the complement cascade in health and disease. We have two aims. In Aim 1, we will perform site-specific recombination to show we can generate an allelic series of CR1 and CR2 transcripts, including the common isoforms of human CR1. In Aim 2, we will use flow cytometry, immunofluorescence, RNA in situ hybridization and RT-PCR to determine the expression patterns of human CR1 and CR2 proteins. We will assess expression of CR1 and CR2 in specific cells in the blood, as this will be crucial in understanding the role of CR1 and CR2 in neuroinflammatory and immune disorders. Further, given the recent association of a region encompassing the CR1 gene in Alzheimer's disease (AD), we will determine the expression of CR1 transcripts and proteins in the brain. This validated mouse strain will lay the foundation for our work studying the role of complement in neurodegenerative disorders, particularly AD. It will also be made available without restrictions as we anticipate it being used by many to investigate the broader role of complement regulators in health and disease.

Further information available at:

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United States of America

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