LETTER

Reply to Woodruff et al.: C1q and C3-dependent complement pathway activation does not contribute to disease in SOD1 mutant ALS mice

Three initiating pathways of the complement system of the innate immune system are generally recognized as the classic (activated by C1q), alternative, and lectin pathways. C3 is a central component common to all three pathways (1). Because induction of complement components had been identified in amyotrophic lateral sclerosis (ALS) patient samples and multiple rodent models that develop paralysis from each of three ALS-causing mutations in superoxide dismutase (SOD1), these discoveries led to our study (2) assessing the contribution to disease of two complement components in SOD1 mutant mice. We focused initially on C1q because our laser-microdissection had identified C1q induction within motor neurons during disease of multiple ALS mice. We then applied a more general test, determining the effects on disease from deletion of C3. The outcomes were unambiguous: neither C1q nor C3 deletion ameliorated disease course in two lines of ALS model mice.

On the basis of new evidence included with their letter (3), Woodruff et al. take issue not with the outcome of our evidence, but with our use of the term "global" (which we used in the title of our article "C1q induction and global complement pathway activation do not contribute to ALS toxicity in mutant SOD1 mice") to describe our test of the three widely accepted C3-dependent pathways. Woodruff et al. (3) claim there is a "well-described" pathway of complement activation that is independent of C3. Initial evidence for such a pathway came from a report of active C5a generated via components of the blood coagulation system following C3 deletion (4). The proposed fourth activation pathway for complement [which Woodruff et al. (3) refer to as "extrinsic"] is neither as "well-described" nor widely accepted as the authors would have it. For example, the senior author of the founding report of C3-independent activation did not include this pathway in the detailed overview diagram in his recent review of the complement system (1). Nor did Woodruff and colleagues refer to it in their published ALS-related work, including their most recent report in which they describe C3 as "the central component common to all [complement] pathways" (5).

Be that as it may, Woodruff et al. (3) now report a new finding that deletion of the complement C5a receptor (CD88) provides a small (<10 d) extension of survival in the SOD1 mutant mouse line in which we found deletion of C3 to have no effect. The authors use this finding to argue that the very modest survival benefit (presented without evidence for the slowing of disease progression claimed in their title) may reflect a C3-independent mechanism of complement activation. Perhaps it does. However, more important is what biological significance should be attributed to such small survival benefits. Many therapeutic manipulations have produced claims of similarly small effects in ALS model mice, but none has proved effective when taken to clinical trial. These disappointing failures have led many to question the validity of conclusions concerning mechanistic contributors to ALS pathogenesis that are drawn from similarly small effects identified in a single SOD1 mutant mouse line.

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The authors declare no conflict of interest.

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