Comment on "Mannan-Binding Lectin-Associated Serine Protease (MASP)-1 Is Crucial for Lectin Pathway Activation in Human Serum, whereas neither MASP-1 nor MASP-3 Is Required for Alternative Pathway Function"

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Comment on “Mannan-Binding Lectin-Associated Serine Protease (MASP)-1 Is Crucial for Lectin Pathway Activation in Human Serum, whereas neither MASP-1 nor MASP-3 Is Required for Alternative Pathway Function”

W e have several concerns regarding the article by Degn et al. (1). In this article, the authors clearly showed that MASP-1 is essential for the activation of MASP-2 using deficient human serum in both MASP-1 and MASP-3. We are in agreement with this; however, we disagree with the following point, in which they claimed that MASP-1/3−/− serum was able to activate the alternative pathway, although we reported that in mice MASP-1 and MASP-3 are crucial to alternative pathway function through activation of proenzyme factor D (profD) (2, 3). We would like to raise the possibility that MASP-1/3 is still the main enzyme to activate profD in the human system because no data were shown in the Degn study (1), in which MASP-1 did not cleave the profD. Furthermore, concerning the activation of human profD shown in Fig. 2D of the Degn study, they did not show the profD in Western blotting and thought that all the fD were the active form. Also, it is possible that under the deficient condition of both MASP-1 and MASP-3, the other enzymes such as thrombin, kallikrein, and plasmin could act as the backup enzymes, resulting in cleavage of profD. Here, we show that human rMASP-1 (CCP-CCP-SP) can activate human recombinant profD (Fig. 1). Therefore, it is probable that MASP-1 and MASP-3 are not essential for the alternative pathway activation, but have some role in its activation. Actually, in Fig. 2A, Degn showed that alternative pathway activation was not detected in a 1:16 dilution of MASP-1−/− serum, although normal serum could considerably activate complement at the same conditions.

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Response to Comment on “Mannan-Binding Lectin-Associated Serine Protease (MASP)-1 Is Crucial for Lectin Pathway Activation in Human Serum, whereas neither MASP-1 nor MASP-3 Is Required for Alternative Pathway Function”

W e welcome the comment from Takahashi and colleagues addressing important aspects brought up in our investigation. We are happy that they agree with the main conclusion of our article, the requirement of MASP-1 for the activation of the lectin pathway (1). The contentious issue is the possible role of MASP-1 or MASP-3 in the activation of the alternative complement pathway. In our study, employing serum from an individual genetically deficient in both MASP-1 and MASP-3, we found the pres-
ence of a functional alternative pathway. We examined this as carefully and with as many controls as possible, and did not detect any requirement of MASP-1 or MASP-3 for alternative pathway activity. Takahashi and colleagues demonstrate in their comment that bacterially expressed human MASP-1 catalytic fragment (CCP-CCP-SP) is able to cleave recombinant human profactor D in vitro. However, MASP-1 is a very aggressive trypsin-like enzyme, displaying activity even in gelatin zymography (2). We have not examined whether profactor D or mature factor D was present in the MASP1-deficient serum, but merely conclude that functionally active factor D must be present and, hence, by inference mature factor D. The activity of the alternative pathway is very dependent on the concentration of serum used in the various assays. We have examined the activity at high serum concentrations. Regarding the slightly lower hemolytic activity observed in the MASP1-deficient serum at 1:16 dilution compared with serum from normal and heterozygous individuals, we note in the article that there is a rather broad normal range of alternative pathway activity within any given population, making it impossible for us to claim a lower than normal activity based on this single individual. Overall, the only conclusion we can draw from our data is that neither MASP-1 nor MASP-3 is crucial for alternative pathway activity in the human scenario. We have shipped samples of the sera used in our study to our Japanese colleagues for examination by them for the presence of profactor D, which they have reported to be present in the Masp1 knockout mice.

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