Humoral Innate Immunity and Acute-Phase Proteins

TO THE EDITOR: In their review article on humoral innate immunity, Mantovani and Garlanda (Feb. 2 issue)[1] do not mention the mast cell, a unique tissue immune cell that is considered to be the master orchestrator of the immune response by secreting numerous proinflammatory molecules, especially chemokines and cytokines.[2] With respect to Covid-19, mast cells were found to be degranulated in the lungs of deceased patients with severe disease.[3,4] Other investigators have reported elevated serum levels of the mast cell–derived proteolytic enzymes chymase and tryptase in patients with Covid-19.[5,6]

Our own preliminary results show that nanomolar levels of recombinant full-length SARS-CoV-2 spike protein can stimulate the secretion of interleukin-1β from cultured human mast cells from the Laboratory of Allergic Diseases R cell line (LADR) (Fig. 1). We also found that this effect was substantially augmented by costimulation with the alarmin interleukin-33, which is secreted from damaged cells. Taken together, this evidence suggests that mast cells, especially in the lungs, can be triggered by SARS-CoV-2 to secrete inflammatory molecules that contribute to the cytokine storms that are associated with high morbidity and mortality. Thus, addressing mast-cell activation may be an important approach to treating or minimizing the sequelae of infection with SARS-CoV-2.

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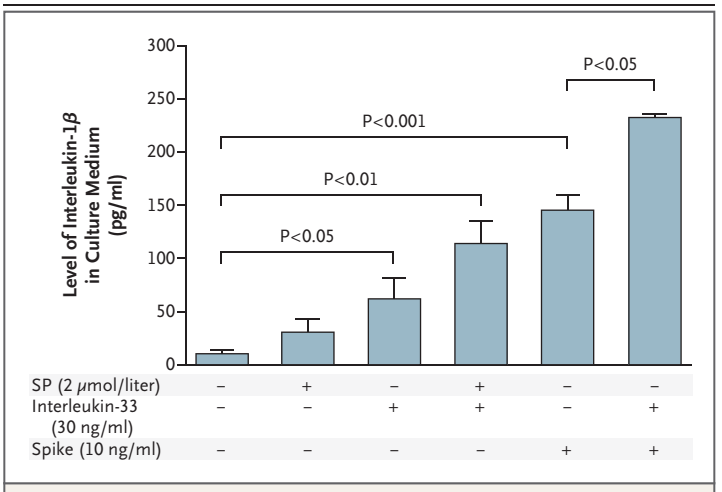

Figure 1. Release of Interleukin-1β from Human Mast Cells after Stimulation with Recombinant SARS-CoV-2 Spike Protein.

Mast cells from the Laboratory of Allergic Diseases R cell line (LADR) were stimulated either with substance P (SP, Sigma) or with recombinant full-length SARS-CoV-2 spike protein (Abcam) and interleukin-33 (R&D Systems) singly and in combination for 24 hours. Stimulation of interleukin-1β secretion was measured by means of enzyme-linked immunosorbent assay (R&D Systems) produced by 1 million cells per milliliter in culture. Results are presented as means; T bars indicate standard errors.

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THE AUTHORS REPLY: Theoharides and Tsilioni raise the important issue of mast cells as a component of innate immunity. We concur that the cellular arm of innate immunity is complex and includes mast cells, which are a source of cytokines, chemokines, and diverse mediators. In our review article, we focused on the humoral aspect of innate immunity. In addition to mast cells, we did not highlight other cellular components, such as the diversity of macrophages, platelets, and more.

As far as mast cells and mediators are con-

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cerned, we are not aware of carefully controlled studies involving patients with Covid-19 that were conducted in different institutions with validation cohorts, were independently confirmed, and showed strong prognostic significance with hard end points such as mortality. The correspondents found that the spike protein induced the release of interleukin-1β by mast cells and had a less-than-additive effect when combined with interleukin-33. As they mention, these data are preliminary. Indeed, one should carefully assess the possible involvement of contaminants, conduct dose–response experiments, and use different sources of the spike protein to verify their results.[1] We cannot forget that data have shown that toll-like receptor 4 is activated by protein ligands, yet such findings have not been substantiated.[2]

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Since publication of their article, the authors report no further potential conflict of interest.

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Bivalent Boosters against Severe Omicron Infection

TO THE EDITOR: Lin and colleagues (Feb. 23 issue)[1] report the vaccine effectiveness of bivalent Covid-19 vaccines in a large cohort of more than 6 million persons. The authors conclude that bivalent boosters provided substantial additional protection in persons who had previously been vaccinated.

As reported lately, the cost of a single dose of bivalent vaccine is expected to rise to $120 (U.S. dollars).[2] On the basis of the reported vaccine efficacies,[3] we estimated the number needed to vaccinate and the associated cost to avoid one severe Covid-19 outcome (hospitalization or death) or one death (Table 1). Because most Covid-19–related hospitalizations and deaths occurred in persons 65 years of age or older, the numbers needed to vaccinate and associated costs were lowest in this age group. However, the values for persons 18 to 64 years of age (number needed to vaccinate, 20,407, and associated cost, $2,448,804, for any severe event; 100,304 and $12,036,495, respectively, for death) appear to be much higher and seem unsustainable. These results lead us to question the value of the Centers for Disease Control and Prevention policy to provide bivalent boosters to all persons 6 months of age or older[4] and prompt prioritization to those at the highest risk for severe disease.[5]

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHOR REPLIES: Arbel and colleagues present an interesting application of the data from our research letter. Their findings have important implications. Unfortunately, the data that we reported were not sufficient to accu-

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