Commentary: The cell without qualities?

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Central Message

In order to qualify as a potential therapeutic target, a better understanding of the function of double-negative T cells during ischemia-reperfusion injury is needed.

See Article page e81.

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The Man Without Qualities, by Robert Musil, is considered one of the most significant novels of the 20th century. The main character, Ulrich, a young intellectual, is indifferent toward life and reality and lacks moral sense—he is referred to as a man of no qualities. Embedded in the complex social network of the sinking Austrian-Hungarian monarchy, Ulrich plays an important role in planning the 70th throne jubilee of Emperor Franz Joseph I.

The work published by Hsu and colleagues[1] in this issue of the *Journal* strongly reminds us of Musil's novel. Hsu and colleagues[1] investigate the role of double-negative T cells in a model of ischemia and reperfusion of the lung. Double-negative T cells lack surface expression of both CD4 and CD8. They thus are deficient in the classic qualities discriminating T cells into helper and effector cells.

What is currently known about double-negative T cells? They account for fewer than 5% of the cells in the circulating T cell pool, but they play a key role in a variety of diseases, such as acute kidney injury, graft-versus-host disease, and type 1 diabetes.[2-4] The pathophysiologic effect of double-negative T cells seems to vary with the surrounding. In some diseases, they promote an anti-inflammatory response. In others, such as ischemic stroke, double-negative T cells are a driving factor of neuroinflammation, and they exacerbate brain injury.[5] In the examined model of ischemia-reperfusion injury, double-negative T cells possess anti-inflammatory properties and release large amounts of interleukin 10.

Ischemia-reperfusion injury includes a plethora of signals, and through the years, our knowledge of the network of involved pathways has become more and more complex.[6] Oxidative stress and shifts in the electrolyte compartments activate cell death signaling. This cellular damage subsequently triggers a proinflammatory cascade. Immune cells home to the site of injury and further amplify the damage. Ischemia-reperfusion injury clinically translates into primary graft dysfunction, which remains a major hazard for perioperative mortality. As a variety of immune cells modulate ischemia-reperfusion injury, a considerable number of animal studies targeting the immune reaction has been published. So far, all of these approaches have failed to translate into clinical lung transplantation.

The findings of Hsu and colleagues[1] raise a number of questions, and the role of double-negative T cells in lung transplantation requires further investigation. What is the effect of T cell–depleting induction therapies on double-negative T cells? What is the role of these cells during acute cellular- or antibody-mediated rejection? Can they induce graft tolerance?

The work of Hsu and colleagues[1] is extremely interesting and provides a fresh view on ischemia-reperfusion injury. Further efforts are needed, however, to unravel the qualities of double-negative T cells. Only then might they qualify as a potential novel therapeutic target.

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