Commentary: The cell without qualities?

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Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Sept 16, 2019; revisions received Sept 16, 2019; accepted for publication Sept 17, 2019; available ahead of print Oct 3, 2019.

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J Thorac Cardiovasc Surg 2021;161:e93

0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2019.09.107>

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 colleagues¹ in this issue of the *Journal* strongly reminds us of Musil's novel. Hsu and colleagues¹ 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

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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.

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published. So far, all of these approaches have failed to translate into clinical lung transplantation.

The findings of Hsu and colleagues¹ 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 colleagues¹ 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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