Milestone 15

The discovery of regulatory T cells

In 1995, Japanese scientist Shimon Sakaguchi described a distinct cell population that served as a crucial brake on the body's immune system. The cells — which became known as 'regulatory T cells' — prevented the immune system from over-reacting to tissues of the body. For decades, some researchers had doubted whether these cells existed, but Sakaguchi's findings proved otherwise. His discovery opened up a new landscape of treatment possibilities for autoimmune conditions such as multiple sclerosis, lupus, diabetes and cancer.

Scientists began to suspect the presence of an unusual immune system wrinkle more than 50 years ago. In 1969, a Japanese team found that when the thymus gland of neonatal mice were removed, their circulating immune cell counts dropped (Milestone 1). The end result was a runaway autoimmune reaction, causing widespread inflammation and tissue damage. (Only later would researchers learn that this was because regulatory T cells form in the thymus, and thymectomy prevented this developmental process from occurring.)

Yale researchers led by Richard Gershon built on this finding the next year, reporting that when thymectomized mice were injected with large numbers of thymus cells, they mounted a lower immune response to foreign cells than thymectomized mice that had not received the initial thymus cell treatment. The team theorized that a set of cells they called 'thymic lymphocytes' might be producing a 'shut-off substance' that dampened immune responses in the treated mice.

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When researchers scrutinized mouse immune genes more closely, however, they did not find regions coding for molecules that would allow T cells to suppress immune function, and could not figure out what made the thymic lymphocytes distinct from other T cells. That lack of progress sent the field into suspended animation for more than two decades. During this time, even the concept of 'suppressor T cells' was considered rather taboo.

The narrative abruptly resumed in 1995, when Sakaguchi finally pinpointed what made the mysterious thymic lymphocytes unique: they expressed a surface marker molecule called CD25. In experiments, Sakaguchi showed that when mice received T cell suspensions that lacked cells with the CD25 marker, they developed autoimmune conditions of the thyroid, pancreas and other organs. However, when some of these mice received a suspension rich in $CD2^+$ cells soon after the first infusion, the fresh $CD25^+$ cell dose stopped their incipient autoimmune conditions from progressing.

Sakaguchi's discovery of the CD25 identifier finally allowed researchers to isolate and work on regulatory T cells for the first time. After his finding, other research teams began to identify subpopulations of regulatory T cells with different kinds of immune-suppressing properties.

In 2003, three key papers were published from independent groups. Shohei Hori working with Sakaguchi, as well as the labs of Alexander Rudensky and Fred Ramsdell identified FOXP3 as the elusive transcription factor that programmed the differentiation and immune-modulating functions of regulatory T cells. Collectively, the studies found that FOXP3-deficient mice developed a fatal autoimmune condition in which the aggressive function of non-regulatory T cells spiralled out of control. Researchers began referring to FOXP3 as a master controller that governs the behaviour of regulatory T cells, activating genes that direct the production of anti-inflammatory factors.

With the basic principles of regulatory T cell function established, researchers started exploring their potential therapeutic uses. In 2012, a Polish team administered regulatory T cells to children with type 1 diabetes and found that their pancreatic function improved to the point that some were able to decrease their insulin dose. Researchers at the University of California in 2015 completed a similar proof-of concept trial of the cells in adults with diabetes. Other trials are evaluating the ability of regulatory T cells to treat ulcerative colitis, autoimmune hepatitis and graft-versus-host disease, underscoring the cells' promise as game-changing therapeutic agents.

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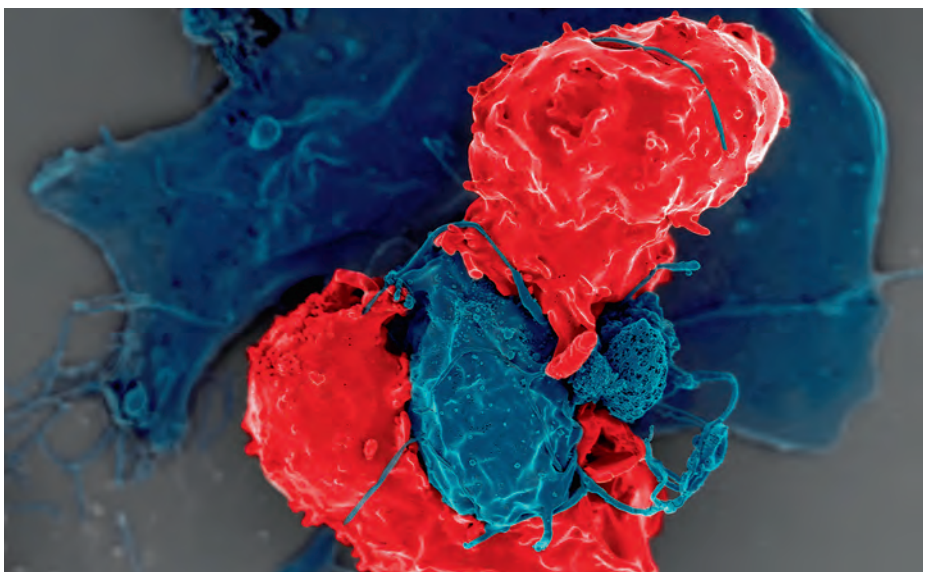

Regulatory T cells interacting with antigen-presenting cells

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Milestone study

Sakaguchi, S., Sakaguchi, N., Asano, M., Itoh, M. & Toda, M. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). *J. Immunol.* **155**, 1151–1164 (1995)

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