Tomio Tada 1934–2010

Masaru Taniguchi

Tomio Tada died 21 April 2010 of complications of prostate cancer. He was 76 years old. Tada was an emeritus Professor of the University of Tokyo who made major contributions to immunology both in his native Japan and at the international level.

Tomio Tada was president of the Japanese Society for Immunology (1985–1988) and served as an executive board member, vice-president (1991–1994) and president (1994–1997) of the International Union of Immunological Societies. He was an honorary member of the Medical and Science Academy of Romania (1997) and an honorary doctor of the Poland Copernicus Medical University (1998). He was awarded the Hideyo Noguchi Prize (1976), the Emil Adolf von Behring Prize (1980), the Cultural Merit Award from the Emperor (1984), and the Order of the Sacred Treasure, Gold and Silver Star from the Emperor (2009), one of Japan's highest honors.

Tada began his research career as an immunology fellow (1964–1966 and 1968) in the laboratory of Teruko and Kimishige Ishizaka at the Children's Asthma Research Institute in Denver, Colorado. The Ishizakas are famous for their discovery of immunoglobulin E. Tada identified this immunoglobulin isotype in the monkey.

In 1971, Tada made perhaps his greatest contribution to immunology by establishing the concept of immune suppression, which despite its rather tortuous history has become a fundamental tenet in the field. Tada provided evidence for the existence of suppressor T cells, which negatively regulate antibody responses. At that time, the idea that T cells help antibody responses had just been firmly established on the basis of classical experiments using hapten-carrier conjugates and adoptive transfer of T cells and B cells; thus, the notion that T cells could be suppressive was both novel and controversial. At around the same time as Tada's groundbreaking studies, Richard Gershon (Yale University) also demonstrated the involvement of T cell-mediated suppression in immunological tolerance. Later, Tada and Gershon both established the new paradigm of peripheral tolerance, the idea that immune homeostasis is regulated by suppressor T cells. This was very different from the widely accepted model of central tolerance, which results in the deletion of highly autoreactive T cells in the thymus. Although there were extensive efforts to identify the mechanisms by which suppressor T cells regulate immune responses, they were mostly unsuccessful, and this area of research lay dormant until its rebirth in the guise of regulatory T cells, which have become a topic of great interest among many immunologists.

Two lines of research have been heavily influenced by Tada's original work, the concept of immune regulation. One is of course regulatory T cells, which negatively regulate autoimmune disease development, originally described by Yasuaki Nishizuka and Teruyo Sakakura; this was followed by the discovery of Foxp3⁺ regulatory T cells by Shimon Sakaguchi in 2003. Although it is believed that *Foxp3* is a master gene for this regulatory function, *Foxp3* expression itself is negatively controlled

by RORγt, the master transcription factor that regulates the generation of pathogenic interleukin 17-producing helper T cells. Foxp3 expression determines regulatory function, but RORγt expression suppresses *Foxp3* expression and can turn regulatory T cells into pathogenic T cells. Thus, regulatory T cells and pathogenic T cells are interchangeable; their fate hinges on expression of a particular transcription factor, which is controlled by environmental factors such as cytokines.

The second line of research connected to Tada is the natural killer T (NKT) cell, a connection that is probably less well known but intriguing nonetheless. NKT cells are a unique subset of lymphocytes characterized by expression of the invariant α-chain variable region 14 (Vα14) T cell antigen receptor. Before anything was known about NKT cells, investigators were producing T cell hybridomas from the antigen-specific suppressor T cells being studied by Tada. Interestingly, 12 of 13 of these hybridomas selectively used the invariant Vα14 receptor. Thus, this invariant Vα14 NKT cell receptor is in a sense a unique marker for the suppressor T cell. NKT cells are bifunctional, with their phenotype being determined by their environment. They can mediate negative regulatory functions, suppressing autoimmune disease development and maintaining transplantation tolerance by producing interleukin 10, but also have protective functions, enhancing antitumor and antipathogen responses by producing interferon-γ. It thus seems likely that the regulation of immune responses, particularly as it is related to peripheral tolerance, is heavily influenced by environmental factors, and identification of the effector mechanisms remains an important future goal.

After a stroke in 2001, Tada was half-paralyzed and unable to speak, but he continued to write by typing with his left index finger and communicated with a voice synthesizer. Despite this new obstacle, Tada's strong spirit persisted. His apartment near the University of Tokyo remained a focal point for gatherings and spirited discussions with his former colleagues and students. Tada also published several essays, such as "A Reticent Giant," which described his second life after his stroke, and was awarded the Hideo Kobayashi Prize (2008). Despite his stroke, Tada created five original Noh dramas, dealing mainly with his spiritual and philosophical exploration, although new Noh dramas are rare and most were written several hundred years ago. These are *The Hermit Isseki*, which concerns Albert Einstein's theory of relativity; *The Well of Ignorance*, on the topic of brain death and heart transplantation; *Resenting Lament*, about cultural prejudice against the people who were forcibly taken from Korea to Japan during World War II; *The Mourning of Atomic Bombing*, about the victims of the atomic bombing in Hiroshima; and *The Virgin Mary in Nagasaki*, for the repose of the souls of victims of the atomic bombing there.

Tada is survived by his wife, Norie, his children, Chris, Ko and Aya, and five grandchildren. His life and work continue to inspire all who knew him.

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