Rejecting a Swedish phone number as a call centre scam, you might miss a Nobel Prize

Of the three winners of the 2025 Nobel Prize for Physiology and Medicine for clarifying why our immune system might turn against us and why not, only one of the prize winners could be informed in time.

The Science Journal from the 9th of October this year shows a photograph of Ms. Mary Brunkow in Seattle, USA, visibly overcome by her emotions. In the morning, an AP photographer visited her at home and had to justify his seemingly initially absurd request to photograph her by explaining that she had won a Nobel Prize. She didn't pick up the phone as she explained later, when she saw a Swedish number, thinking, "that's just, that's spam of some sort" (1). She was not the only one missing the call from Stockholm. From the two additional winners, Fred Ramsdell was on holiday in his homeland, at the Rocky Mountains, so only Shimon Sakaguchi, from Japan, could be reached before the Prize announcement was made public.

Scientists in the field of autoimmune diseases are delighted

Particularly pleased that Mary Brunkow is being recognized was Thomas Boehm, an immunologist at the Max Planck Institute of Biology, who remarked that she has not always got the credit she deserves. Another reason for contentment is that a female scientist was awarded the Prize in autoimmune diseases, a group of illnesses that particularly affect women, as noted previously (2, 3). Other scientists, including those studying genomic responses that regulate autoimmune expression in inflammatory bowel disease and immune responses against cancer cells, praise the work of the award winners, highlighting prospective approaches to treat autoimmune diseases. To date, about 200 clinical trials in this field are registered (1, 4).

Significance of the prize

The implication of this year's Nobel Prize for Medicine, of course, is not the episode that the world's wide call centre scam somehow blogged the Nobel Prize committee's communication in time, nor the fact that a female prize winner was named. Still, no clinical trials have yielded widely adopted therapies; however, the prize winners elucidated that, though complicated, a defined mechanism that regulates an otherwise life-saving system can fail: under certain conditions, it can turn against the organism. The positive aspect of the findings is the recognition that not everyone suffers from autoimmune diseases, although everyone relies on the immune system for survival (4, 5).

The immune system in view of a short textbook

The immune system is essential not only to humans but to all living organisms, since all are challenged by other organisms, sometimes to their benefit, but often in ways that can be harmful or even lethal to the ones attacked. No wonder the system is highly sophisticated, and no part of the body is left unexamined for proper function. This is done by immune cells, mainly produced in the bone marrow. Those studying and working in health sciences are aware of the textbook knowledge of the first line of defence, the innate immune system, followed by the adaptive (acquired) immune system (6). The

functions of different immune cells are expressed on their cell membranes. The cells contain numerous receptors involved in cell-cell interactions, metabolic functions, and immune responses (7).

The former hypothesis why autoimmune diseases could occur

Another rule of life is that what is beneficial can turn out to be harmful. This also applies to the immunological system, as well, which has the potential to attack the cells of the 'host', causing frightening autoimmune diseases. They are a challenge for physicians in clinical practice, are difficult to diagnose, were formerly often named after the physician who first described the syndrome, and involve multiple organ systems, occurring in men at a younger age than in women (8). Despite intensive research, the mechanism that triggers the attack on itself remained uncertain and has given rise to several hypotheses.

An explanation was nicely outlined in a recent review exploring sex differences in tissue-specific immunity and immunology; the introduction hinted at the 'disproportionally' higher susceptibility of males to infectious diseases. Contrary to females who have a 'generally stronger overall immune response to infectious diseases, and hence to a greater 'susceptibility to certain inflammatory conditions,' (9).

First hints towards the role of the thymus in controlling the immune system

Another author followed the widely given explanation for the occurrence of autoimmunity, or as it was otherwise termed as 'gain-of-function mutation.' In a review of the immune system, he referred to specific cells identified in the 1970s as 'inflammasome' (7). He might have indicated to a publication in 1976 about thyroiditis in T cell-depleted rats, which were made 'lymphogenic within the spleen and cervical lymph nodes, resulting in the 'autoallergic response' similar to the human autoimmune disease thyroiditis. When given lymph nodes and spleen cells intraperitoneally from normal females of the same strain to the 'thymectomized' and irradiated rats, 'thyroid changes were prevented' (10).

In fact, as early as 1969, two Japanese investigators identified the thymus's role in autoimmunity by removing the organ from newborn mice three days after birth. This affected the development of the ovary but not the testes, and the occurrence of the autoimmune diseases, gastritis and thyroiditis (11). The 2025 Nobel Prize winner from Japan appeared on the scene with his colleagues in 1982, demonstrating that spleen cells from thymectomized, diseased mice, when injected into healthy mice, severely damaged their ovaries. In another attempt, spleen cells from normal female mice, when injected intraperitoneally into diseased mice, prevented oophoritis. The technique known as 'adoptive transfer' and the specific fraction of immune cells from healthy mice were identified as Lyt-1 T cells (CD5 Lyt-1 T cells and $CD45RB^{low}$ cells) (12, 13).

Those interested in the potential therapeutic fractions of T cells may consult the original publications listed here. An additional publication reported in 1990 that euthymic rodents developing under the influence of particular T cells ($CD45RB^{high}$ CD4+ T cells), severe wasting and death with inflammatory infiltrations in the liver, lung, stomach, thyroid and pancreas. This could be prevented by $CD45RB^{low}$ CD4+ T lymphocytes (14).

A rodent model for immunological research

The findings, so far, resulted in the belief that 'immune tolerance' is achieved by getting rid of 'harmful immune cells in the thymus' and a 'central tolerance mechanism prevents autoimmune diseases (4). Simon Sakaguchi and coworkers challenged this hypothesis in a 1995 publication. At that time, specific laboratory animal strains were commonly used for immunological research, such as BALB/c nu/+ mice. The animals lacked fur, i.e., were nude; they were heterozygous, with one functional copy and one mutant copy, resembling phenotypically normal but genetically distinct from the wild type. Their lymph nodes were anatomically normal, but their immune cell profile showed increased mast cells and altered T-cell functions. These strains are intended for studying gene effects on immune function without complete immunodeficiency.

The work of the Japanese prize winner and his group, regulatory T-cells (TREGs) is in charge

It is known that 10% of CD4+ cells (helper T cells that coordinate the adaptive immune response) and less than 1% of CD8+ cells express the interleukin-2 (IL-2) receptor alpha-chain (CD25). A BALB/c mouse-derived suspension was 'depleted' of CD25+ cells and inoculated into BALB/c athymic nude (nu/nu) mice, which all developed a wide range of histologically and serologically defined autoimmune diseases. 'Reconstitution' of CD4+CD25+ cells prevented the diseases. It was concluded that CD4+CD25+ cells contribute to 'maintaining self-tolerance by down-regulating the mechanism to cause autoimmunity (15).

A mini review helping to find the way through the genomics involved

In a mini-review published twenty-five years ago, Sakaguchi reflects on his and his coworkers' work in the context of relevant results in autoimmunity, including cancer, partly caused by autoimmune mechanisms, and transplantation. His review points out that the group of CD4+ T cells, on the one hand, can cause and or prevent autoimmune diseases. The difference is related to CD25, the alpha chain of interleukin (IL)-2 expressed on activated T cells, and CD45HB/RC (a protein tyrosine phosphatase expressed in almost all hemopoietic cells). A subpopulation of CD4+ T cells suppresses pathogenic self-reactive T cells, which are produced in the thymus and function as regulatory T cells in the periphery. Among the subpopulations are $CD5^{high}$, $CD45RB/RC^{low}$, RT6.1+, and CD25+. Surface markers for regulatory CD4+ T cells remain under investigation. Cytokines are of great interest because they are associated with regulatory T cells (16). The publication seems to have initiated naming regulatory T cells as TREGs cells, and they became an integrated immunological research tool (16).

The final proof, or the contribution of the US prize holder

So far, TREGs have become known to be involved in preventing autoimmune diseases without specific proof that they are directly engaged in the protection of a particular disease (6). This changed with the publication of a group of investigators working at the US biotech Celltech Chiroscience, where Brunkow and Ramsdell collaborated at that time (1). As mentioned above, autoimmune diseases particularly affect women (2). The group chose to work on a model of male mice suffering from scurfy. Probably the decision to work especially on a very rare male autoimmune disease was not influenced by the gender ideology, enabling the authors to avoid meddling around cismen, sex bias, etc., but the X chromosome in XY, as related to the disease, is clearly defined in this case. The animal has scaly, crusted skin on eyelids, ears, tail, and paws, and other malformations and deformities. Among the

internal abnormalities are systemic inflammation, severe anaemia, enlarged spleen and lymph nodes. They die about three or four weeks old.

FOXP3 might become a household name in the field of autoimmune diseases

It was found that the pathology results from dysregulated CD4+SD8-T-cell activity caused by a mutation in the transcriptional regulator Foxp3, which is otherwise essential for normal immune homeostasis (17). The equivalent disease in human males is known as polyendocrinopathy and enteropathy X-linked syndrome (IPEX). The disease typically presents in the first year of life, with malabsorption and watery diarrhoea. Associated diseases are commonly T1DM and eczematous dermatitis. Not uncommon are additional autoimmune diseases of the blood, liver, and kidney, splenomegaly, and several other immune dysregulations. The boys usually die within the first or second year of life. In milder cases, they might survive into the second or third decade (18). The group led by Brunkow and Ramsdell demonstrated that IPEX syndrome is associated with mutations in the human gene FOXP3 (19). Through this work, it was possible to link FOXP3 for the first time to an autoimmune syndrome.

The finding of the Japanese group fits what was found by the US investigators

The Sakaguchi group, which first reported the finding in 1995, confirmed that FOXP3 is expressed in naturally arising CD4+ regulatory T cells. Furthermore, they could show that FOXP3 converts naïve T cells into regulatory T cells, similar to naturally occurring CD4+ regulatory T cells (20).

Reflection:

Based on how the two leading scientific magazines, Science and Nature, announced the 2025 Nobel Prize in Medicine, the scientific community appears most impressed by the opportunity to develop therapeutic interventions for autoimmune diseases and cancer, and to advance transplantation using Tregs (1, 5). The finding that a specific genomic system has now been revealed, thereby solving the mystery of why not more autoimmune diseases afflict humanity, since it depends on it for survival, isn't discussed in the forefront. Future research in this direction will likely shed more light on why the overwhelming majority of us overcome infections and parasite attacks without side effects.

Last, not least: If the scientific community in Thailand were to follow up on each Nobel Prize in greater detail, as is done here, why is no one asking why Thailand has not yet produced even one? The answer should not be that Thailand's resources don't allow high-groundbreaking science.

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Grammarly software was used to improve English, but the AI function was disabled.