New Drugs That Have Changed Medicine

4. Cyclosporine

Makoto Shiragami
Fusayo Shiragami

Challenge of organ transplantations

If we could replace damaged parts of the human body (= organs) which cannot be repaired (= treated) with new ones like a machine, we could continue our healthy lives forever. This idea is nothing short of wonderful. iPS cells may make this dream come true, but it will probably take a little more time. We have tried to replace human organs with artificial organs such as artificial kidney or heart, and such attempts have been successful to some extent, but artificial organs cannot be a complete substitute of organ function.

Many doctors and scientists have worked hard to realize this dream of "what if we could replace organs that cannot improve by treatment with new organs…" since more than a century ago. Experimental animal-to-animal organ transplantations have been performed repeatedly. In 1906, French surgeon Jaboulay transplanted goat and pig kidneys into humans. This is called xenotransplantation, but the experiment ended in failure. In 1936, Ukrainian surgeon Voronoy transplanted the kidneys of a deceased donor into the thigh of patients with acute renal failure. This was the first attempt of human-to-human allograft, but the patient died after 36 hours.

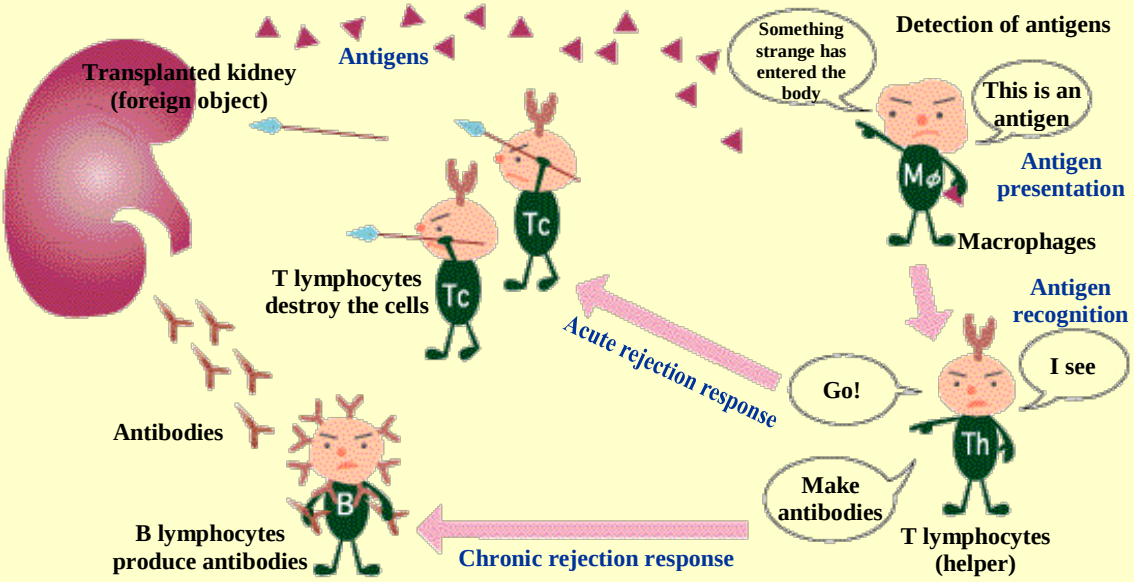
Even if organs of animals or other humans are transplanted into recipients, they will not work unless engraftment is achieved. Graft failure occurs because of the recipient's immune function against the transplanted organs, which is called the rejection response. To improve the outcome of organ transplantation, we had to wait for the development of immunosuppressive drugs to prevent rejection response.

Rejection response

To protect our bodies from foreign enemies, our body has a mechanism to eliminate foreign objects when they enter our body (= immunity). Transplanted organs are foreign to recipients' bodies. Therefore, the action of immunity is to remove these organs, which is called the rejection response. There are two types of rejection: acute and chronic rejection. Acute rejection occurs within 3 months after transplantation, and chronic rejection occurs thereafter.

Let us now discuss the mechanism of the rejection response (Fig.1). Macrophages, which are a type of white blood cell, recognize transplanted organs as foreign objects and then provide this information to lymphocytes called helper T cells, another type of white blood cell. The helper T cells then activate cytotoxic T cells to make them attack the transplanted organs. This is called acute rejection. Helper T cells also activate B cells (lymphocytes) to produce antibodies. These antibodies attach to the blood vessels of the transplanted organs and destroy them. This is called chronic rejection.

Figure 1. Mechanism of the rejection response



Tokyo Women's Medical University, the Department of Renal Surgery website
(http://www.twmu.ac.jp/KC/Surgery/ktx6.html)

The discovery of cyclosporine

In 1961, British surgeon Calne confirmed the immunosuppressive effects of azathioprine. In 1978, he successfully transplanted a kidney of a deceased donor (cadaveric kidney transplantation) using azathioprine.

The discovery of a new immunosuppressive drug, cyclosporine, increased the success rate of organ transplantation dramatically. Cyclosporine is a substance produced by a fungus and that was discovered by Swiss Sandoz Pharma (now Novartis Pharma) in a soil sample obtained from Hardangervidda, in Norway in 1970. In 1972, Sandoz researcher Borel discovered that cyclosporine has potent immunosuppressive effects. In 1978, British surgeon Calne used cyclosporine to perform cadaveric kidney transplantation successfully.

Action of cyclosporine

Cyclosporine prevents acute rejection because it interferes with the growth of cytotoxic T cells by suppressing substances called lymphokines that are produced by helper T cells. Immunosuppressive drugs do not only reduce rejection but also the action of the immune system, which is intended to protect the body from foreign invaders. It may therefore sometimes cause serious infectious diseases. While azathioprine suppresses all cells responsible for immunity, cyclosporine only suppresses cells that are directly associated with rejection, resulting in relatively minor deterioration of immunity. In addition, cyclosporine can reduce the dose of steroids used with immunosuppressive drugs by less than one-third, leading to a dramatic reduction of the side effects of steroids, including obesity, moon face, diabetes mellitus, and cataract. However, cyclosporine is known to have such side effects as renal toxicity, high blood pressure, hypertrichosis, neurotoxicity, and

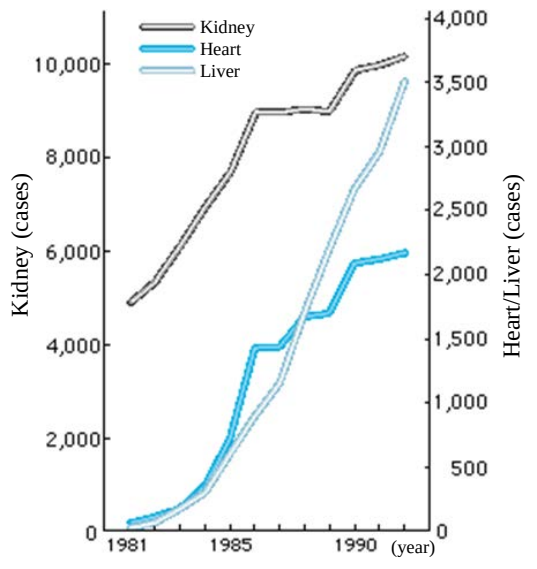
hepatotoxicity.

By the way, do recipients have to continue to receive immunosuppressive drugs after transplantation? Yes, recipients have to receive immunosuppressive drugs as long as transplanted organs are functioning. However, after 3 months of transplantation, the frequency of rejection decreases, and the doses of immunosuppressive drugs can be reduced.

Achievements of cyclosporine

There are numbers showing how innovative cyclosporine is for organ transplantation. According to a 1980 report from the United States, the one-year survival rate of liver transplantation was 38% with azathioprine. However, it increased to 78% with the use of cyclosporine. At the same time, cyclosporine was reported to increase the one-year survival rate of heart transplantation to more than 80%. As cyclosporine was commercialized in various countries since around 1983, the number of transplantation cases increased dramatically. This caused the problem of a shortage of organ donors (Fig 2).

Figure 2. Changes in transplantation cases in the US



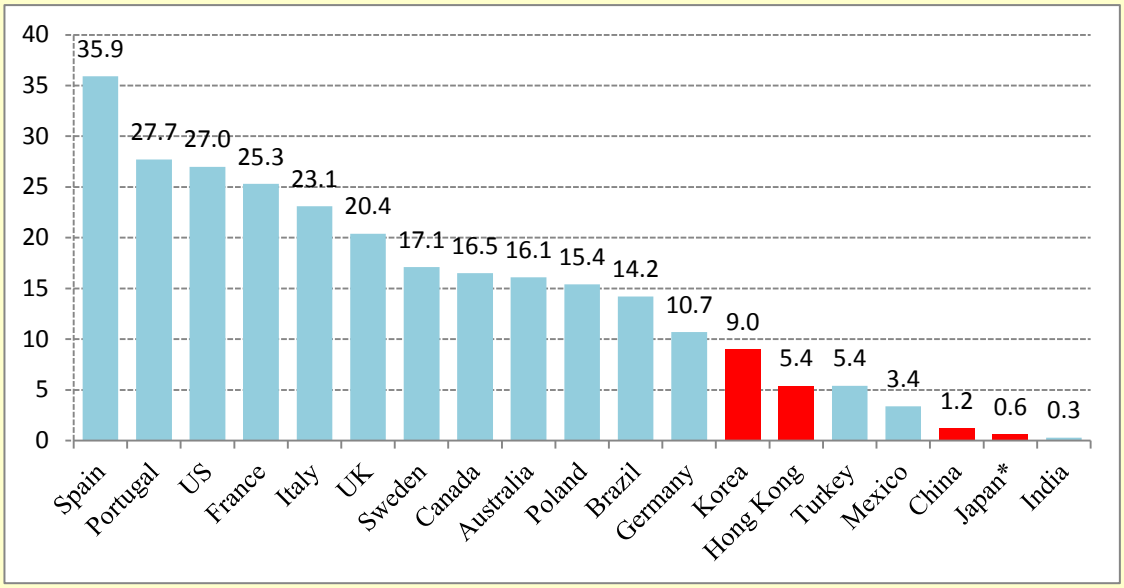
Hiroshi Takagi, "The advent of cyclosporine and the development of transplantation." The facts about cyclosporine. Hiroshi Takagi eds., International Medical Publishers, page 7

Current status of organ transplantation in Japan

Although cyclosporine was launched in Japan in 1986, organ transplantation did not increase as dramatically as in other countries. It was because there was not agreement on recognizing brain death as human death in Japan. Therefore, kidneys and livers have been transplanted from living related donors. In 1997, it was allowed to transplant organs from brain dead donors who had given prior written consent under a new law. Subsequently, it became possible to donate organs with family consent, even if the individual's intentions are unclear. Cases of organ transplantation have since been increasing in Japan. However, organ donations are not as common as in Western countries (Fig 3). To promote medical transplantation, it is important to enhance interests and deepen the understanding of the

people of Japan

Figure 3. Numbers of organ donors in the world in 2014 (per million population)



INTERNATIONAL REGISTRY OF ORGAN DONATION and TRANSPLANTATION Final numbers for 2014 (Dec 2015)

Current status of cyclosporine

Cyclosporine had the problem that it is poorly soluble in water. Therefore, the use of cyclosporine was limited based on individual differences in absorption and side effects such as renal toxicity. To address such problems, a microemulsion formulation of cyclosporine was developed to improve its water solubility. This formulation improved the outcome of organ transplantations. Cyclosporine is still widely used as an essential drug in organ transplantation although 30 years have already passed since its development.