Laudatio

von

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anlässlich der Verleihung

des Paul Ehrlich- und Ludwig Darmstaedter-

Preises

2023

an

Prof. Dr. Frederick W. Alt

und Prof. Dr. David G. Schatz

Paulskirche, Frankfurt am Main

14. März 2023

Anrede,

About 100 years ago, Karl Landsteiner, a Viennese doctor immunized rabbits with two different chemical preparations of tartaric acid representing the two stereoisomers of the same molecules as shown earlier by Louis Pasteur. Stereoisomers are chemically identical, yet they differ in the three-dimensional orientations of their atoms in space, like your two hands are identical yet cannot be superimposed. What Landsteiner found was quite astonishing: Immune sera derived from the immunization with the lefthanded form recognized the original version, but not the right-handed form, and vice versa. He concluded that immune system distinguishes the most subtle chemical difference imaginable, a rather surprising achievement. He went on to show that this is true for many other chemical structures he named antigens. Landsteiner and many generations of immunologists after him wondered how the immune system would be able to achieve this extraordinary level of chemical discrimination. The big question was: How is it possible to store the instructions for billions of discriminatory antibodies in our genetic information? There simply wouldn´t be enough room in our chromosomes to code for all of these different proteins.

Yet, you all know how wonderful the system works. Immunization, vaccination has dramatically reduced the burden of disease, and we all have benefitted from the ability of our body to generate immunity against newly emerging pathogens, such as SARS-CoV-2. But as you all know, discriminatory power can also be a problem, especially when a virus for instance changes it protein structures and thus escapes immune recognition. This creates an eternal arms race between the body´s defenses and the pathogens. I mention this to explain to you why it is so important to understand how antibodies, and the antigen receptors of T cells, representing another important cell type of our immune system, are made.

The first breakthrough towards understanding to this problem came, when Susumu Tonegawa discovered in the 70's that the genetic blueprints for antibodies are in fact not laid down in a linear fashion in our chromosomes, but rather are broken up into small regions that are scattered over a large stretch of the DNA molecule. These elements that can be viewed as LEGO bricks that assemble to form the final antibody product. Much to his and everybody´s surprise, he found that these small pieces are stitched together – in some mysterious way – into complete genes. Because this happens in a combinatorial fashion, this led him to propose that the body could make many antibodies from a very small number of individual elements.

You are very familiar with this principle, when you try to guess the correct combinations of numbers in the lottery; if you have to pick 6 numbers from 49, you have a 1 in 140 000 000 chance to hit the correct combination. So, the immune system has enacted a general solution to encode many different antibodies using only a modest number of individual genetic elements. This saves a lot of space on the chromosomes and leaves room for all the other important parts of genetic that we need to build an entire body.

But, as important as this discovery was, it generated two additional problems. First, how would it be possible to efficiently recognize and fuse these small elements together? And second, once it was recognized that even combinatorial diversity wasn´t enough to produce the astounding diversity of antibodies, and that imprecise fusion of elements was an important element of generating diversity, how could this be achieved?

These two fundamental problems were solved by this year´s laureates. Together, **David Schatz** and **Fred Alt** have transformed our understanding of antigen receptor formation in the immune system. Let me give you a few elements of their biography first, before explaining in a bit more detail what they have done.

David Schatz completed his PhD in 1990 at Massachusetts Institute of technology with David Baltimore, then after a postdoc, he moved to Yale school of medicine to establish his lab where he has been since. David Schatz is a member of the National Academies of science and of medicine and he is a fellow of the American association for the advancement of science. He has been a Howard Hughes Medical Institute Investigator for many years and has received numerous awards.

Frederick Alt is a professor at Harvard medical school. He completed his PhD at Stanford in 1977, was a post doc of David Baltimore, then went on to develop his own lab at Columbia University before moving to Boston in 1991. Fred Alt is also a member of the National Academies of Science and Medicine, a fellow of the American association for the advancement of science and a member of EMBO. He is a Howard Hughes Medical Institute Investigator since 1987 and has also received number of prestigious awards.

Schatz identified the enzyme at the heart of antigen receptor diversity. His idea was as elegant as it was effective. The plan was as follows. First to identify the cells in which the recombination process was most active, second, to transfer the genetic material from these cells into cells that would not normally be able to carry out this critical process in order to endow them with this unique property, and finally, to identify the mysterious recombination activation gene. We of course do not know whether David Schatz had any hopes of succeeding, but, against all odds, he did. The recombination activation gene, actually a tandem of genes RAG-1 and RAG-2 was

thus identified. A sharp mind, fearless attitude, and superb experimental abilities came together to deliver this breakthrough. Thanks to this discovery we now know the molecular basis of some immunodeficiency syndromes in patients unable to mount proper immune responses and are thus prone to fatal infections unless their immune system is replaced through bone marrow transplantation, a topic dear to my heart!

But David Schatz didn´t stop there. In the years that followed he made many more important discoveries, he even worked out the evolutionary roots of the recombination activating machinery so that we now have a much clearer picture of how vertebrates enacted a revolutionary type of immune system about 500 million years ago. He also provided a detailed picture on the mechanisms by which these RAG proteins bind and cleave DNA during the recombination process of the bricks of immunoglobulin genes. Further diversification of antibody diversity occurs later in lymph nodes following antigen recognition. This process is based on the induction of somatic mutations by the activation induced deaminase (AID). Schatz has shown how his reaction is regulated and targeted to the right region of the immunoglobulin genes. Finally, he has successfully studied how the rest of the genome is protected against this dangerous reaction that can cause B cell cancer (lymphomas).

Frederick Alt also played an important part in the story of somatic diversification of antibodies and the equivalent receptors by which T cells recognize antigens. In a quite dramatic discovery, Alt first showed that the very same recombinase that Schatz had implicated in the assembly of antibodies was also required for the assembly of the T cell receptors. This finding not only had a major impact on our thinking about the overall structure of our immune system, but it also clarified the big unknown about the evolutionary relationship of antibody mediated immune defense and the defenses mounted by killer T cells that you all have heard of. It is now clear that the receptors, although different in detail, all come from the same ancient receptor that has evolved in the first vertebrates that emerged on the planet. The next big question tackled by Fred Alt was how extra diversity could be generated at the fusion points of elements during the recombination process. As I mentioned before, it was soon found that combinatorial assembly isn´t everything; the immune system has evolved a special type of DNA synthesizing enzyme that operates at the broken ends of the genetic elements before they become fused to make complete antibody or T cell receptor genes. Alt used elegant mouse genetics to identify this special enzyme and thereby unraveled a second secret of antigen receptor diversity. But a third problem remained. How could during the recombination process the relevant genetic elements be brought together, over such large distances on a chromosome. A bold hypothesis was proven by breathtaking experimental confirmation. So became evident a spectacular example of

chromosomal gymnastics including bending and twisting exercises. Chromosomes are grabbed by a special protein complex and pulled together for the recombinase activation enzyme to cut and paste them together.

In these few minutes I could not give justice to the many additional discoveries made by this year´s laureates. Their work has transformed our understanding of the inner workings of the immune system and fills many pages of all immunology textbooks. They have illuminated the ingenious mechanisms invented by nature to achieve the discriminatory power on which our lives depend when fighting the constant threat of pathogens. We congratulate them on their achievements and look forward to many more discoveries.