Rede

von Dr. Rino Rappuoli

anlässlich der Verleihung

des Paul Ehrlich- und Ludwig Darmstaedter-Preises

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an

Prof. Dr. Andrew Fire

Prof. Dr. Craig Mello

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Es gilt das gesprochene Wort!

Few years ago we were in this cathedral to celebrate Craig Venter, the man who linked his name to one of the most important milestones in science: the sequence of the human genome. We all believed that the sequence of the human genome was going to provide all the information necessary to understand the blueprint of man. We had finally achieved a dream that scientists had followed for years, we thought we had in our hands all necessary information.
Today we know that we understand very little of the information which is present in the human genome and we believe that understanding the information on the genome may take most of the present century. The scientists we celebrate today discovered a new secret of the human genome. They discovered that in addition to the genes that code for the building blocks of the human body, the genome expresses small double stranded RNAs, often named small interfering RNAs or siRNAs. These RNAs are used by the human genome to regulate gene expression during growth, aging, tumor formation, and also as a defense against nucleic acids of invading microorganisms such as viruses. The information coding for these RNAs is present in non coding regions of the genome, often in such small regions that are totally dismissed by the algorithms available today.

In addition, it became evident very early that the discovery of Andrew Fire and Craig Mello was not just a new, fundamental finding of basic science, but is was also very easy to apply in the laboratory to solve quickly problems that took years with previous technologies. For instance, it was found that it could be used in large scale to inactivate genes in order to understand their function. In fact, it was sufficient to transfect human cells with chemically synthesized double stranded RNAs to silence the gene of interest. Previously, the gene had to be physically deleted from the nucleus, a procedure, which took several months and could not be used in large scale.
Perhaps, even more importantly, it was discovered that the same technology could be used as drugs for therapy. Administration of double stranded small interfering RNAs to whole organisms was found to successfully cure many experimental diseases including cancer and neurodegenerative diseases, decrease the blood level of cholesterol, and cure viral infections such Hepatitis C, hepatitis B, parainfluenza virus, the avian influenza virus. No known drug has the broad potential application of small interfering RNAs.

The discovery we celebrate today derives from the work of scientists that in the 1990's were trying to use antisense RNAs to block the synthesis of viral gene products in plants in order to make them resistant to viral infection. In parallel to the work in plants, the role of small RNA in gene regulation was studied in the small animal model Caenorhabditis elegans. The idea was that blocking the synthesis was going to help understand the role of the genes and could be useful to cure those diseases caused by the expression of harmful genes. The antisense RNA although could achieve some success in the laboratory, never achieved the goals people had expected. Even more important, people could not imagine that nature had developed a system which was by far more efficient than the antisense and that this system had been used during evolution to regulate gene expression and as a defense against nucleic acids of invading microorganisms such as viruses. In fact nature had developed a protein named DICER, which recognizes the double stranded RNA and destroys the messenger RNA of the gene complementary to the small RNA. The first idea that the antisense RNA was not the real mechanism used by nature came in 1997 when it was found that RNA-mediated gene downregulation could be obtained independently with both sense and antisense RNA. The real discovery came when it was shown that it is double-stranded RNA which causes specific genetic interference. While using the previously described sense and antisense RNA-mediated inhibition of gene expression to identify a number of genes involved in the Wnt signaling in C. elegans, Craig Mello in 1997 used for the first time the name RNA-mediated interference (RNAi) to describe the phenomenon that he did not understand yet. Only one year later Andrew Fire and Craig Mello discovered that double-stranded RNA was more effective in introducing interference of gene expression in C. elegans than either strand individually. They also described that the interference was not only evident in the animals injected with a double-stranded RNA, but also on their progeny, suggesting a mechanism not working by stochiometric interference with endogenous

mRNA, but rather a catalytic or amplification process triggered by the double-stranded RNA. Their discovery was confirmed in 2001 by G. Hannon, who identified the enzyme (dicer), which recognizes and cuts double-stranded RNA in 22 base-pairs fragments thus amplifying the system. The discovery gained popularity and in the year 2002 was selected as the breakthrough of the year by Science magazine and mentioned as one of the highlights of the year by Nature. I believe that the biologically active small RNAs, the most popular of which are the interfering mRNAs represent the most novel and surprising biological event described during the last few years, which have potentially huge therapeutic applications.

In conclusion, RNA interference is a novel biological mechanism that is likely to find practical applications and be the basis for a new class of therapeutic agents for infectious diseases and cancer.