The Nobel Prize in Physiology or Medicine 1986

Presentation Speech

Presentation Speech by Professor Kerstin Hall of the Karolinska Institute

Translation from the Swedish text

Your Majesties, Your Royal Highnesses, Ladies and Gentlemen,

We have all been small infants who have grown tall. It is growth hormone, released from the pituitary gland, which regulates growth after birth. Lack of this hormone during infancy results in growth retardation, and a growth hormone deficient man is a minicopy of his potential self. The pituitary growth hormone, however, has no direct growth promoting effect on cells, and growth before birth occurs independently of growth hormone.

We are all derived from one single cell which carries the genetic material coding for all the different characteristics expressed in the thousands of billions of cells present in adult man. This first cell divides into two identical daughter cells. These daughter cells grow and then they too divide. During the cell divisions which follow, the cells begin to express specific characteristics, in other words, they differentiate. The newborn infant already has all the different types of cells found in the adult.

The pattern of growth and differentiation has long been established, but the mechanisms regulating prenatal development remained unknown - growth hormone does not control these events. The discovery of growth factors in tissues other than the pituitary led to a new understanding - growth and differentiation are regulated by signal substances released from cells and acting on neighbouring cells. The first such signal substances to be identified were nerve growth factor (NGF) and epidermal growth factor (EGF). The discovery of NGF by Rita Levi-Montalcini and EGF by Stanley Cohen initiated a new era in the research area of growth and differentiation and was followed by the identification of several other growth factors released by different types of cells.

It all began when the Italian developmental biologist Rita Levi-Montalcini was invited to Viktor Hamburgers laboratory in St. Louis, Missouri. There she repeated a previously performed study, but the conclusion she reached was different. When transplanting

mouse tumour to chick embryos she found an outgrowth of certain nerve fibres in the chicken. The nerve outgrowth was similar when the transplantation was performed without direct contact between the tumour and the chick embryo. Rita Levi-Montalcini concluded that the tumour released a substance which promoted nerve growth. She developed a bioassay using cultured nerve cells for identification of the factor.

The biochemist Stanley Cohen joined the research group in the early 1950s. He observed that saliva and salivary gland from the male mouse contained far more NGF than the mouse tumours. He purified NGF from salivary glands and raised antibodies against NGF.

The discovery, identification and isolation of NGF created a breakthrough in the research field of developmental neurobiology: For the first time a chemically well-characterized substance became available for use in studies of nerve growth. Rita Levi-Montalcini showed, in a series of brilliantly performed studies, that NGF is not only necessary for the survival of certain nerves but also regulates the directional growth of the nerve fibres. The nerve cells die when NGF is blocked by antibodies. NGF is produced by the target cells which lure the nerve fibres to grow in the direction. Injections of NGF into the brain cause the outgrowth of specific nerve fibres. This neurotropic effect of NGF offers an explanation of how nerve fibres can find their way through the tangle of nerves in the brain.

Stanley Cohen, who purified NGF, is also the discoverer of epidermal growth factor or EGF. While investigating the effects of NGF he observed that injection of salivary gland extracts to newborn mice accelerated their development. They displayed precocious opening of their eyelids and early eruption of their teeth. Stanley Cohen realized that the salivary gland extracts contained some additional growth factor apart from NGF. He isolated, characterized and established the amino acid sequence of this factor and showed that it accelerated the healing of corneal wounds.

EGF has proven to be a general growth factor with action not only on epithelial cells but also on a large variety of other cells. A prerequisite for its action is the presence of specific binding sites, termed receptors, on the surface of the target cells. Stanley Cohen isolated and characterized the EGF-receptor. He discovered that the receptor consisted of one part on the outside of the cell membrane, which captures EGF, and the other part on the inside of the cell which displays enzyme activity. When EGF binds to the receptor on the outside of the cell it activates this internal enzyme activity. Gradually a new concept has emerged - this type of enzyme activity is a general pathway by which the action of growth factors is initiated. Furthermore, some viral oncogenes cause tumour growth code for proteins with the same kind of enzyme activity as the EGF receptor.

NGF and EGF were discovered in mice, but since then one has moved from mouse to man. The chemical structures of human NGF and EGF are established today, and recombinant human NGF and EGF are produced by DNA-technology. This has opened the way for the use of NGF and EGF in clinical medicine. Deficiency or overproduction of these growth factors may be of importance in the pathogenesis of malformations and

errors of development, degenerative changes with regeneration defects, delayed wound healing and tumour diseases. The role of NGF in diseases of the central nervous system, such as senile dementia, and the possibility of using NGF after damage to peripheral nerves are currently being explored. Application of EGF has already been shown to enhance the healing of wounds of cornea, skin and intestine. Autotransplantation of skin rapidly cultivated outside the body with the help of EGF can be used to cover burns.

Rita Levi-Montalcini and Stanley Cohen were the first to discover and isolate growth factors. Their pioneering contributions stimulated the search for other growth factors and several such substances have been characterized today. Their work has opened up a research field of potential importance to future medicine. Rita Levi-Montalcini and Stanley Cohen have advanced our knowledge from a stage when growth and differentiation could only be described as phenomena and growth factors were unknown, to a situation today when the role of growth factors in cell proliferation, organ differentiation, and tumour transformation is generally recognized. Rita Levi-Montalcini is the great developmental biologist who showed how the outgrowth of the nerves was regulated. Stanley Cohen is the brilliant biochemist who purified the first growth factors and improved our understanding about how a growth signal from the outside is relayed into the cells.

As a representative of the Nobel Assembly at the Karolinska Institute, I convey to you the sincere congratulations of the Assembly and ask you now to receive your Prize from the hands of His Majesty the King.

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