Dankesrede

von

Prof. Dr. David Wallach

anlässlich der Verleihung

des Paul Ehrlich- und Ludwig Darmstaedter-Preises

2018

in der Paulskirche Frankfurt am Main

14. März 2018

Es gilt das gesprochene Wort!

Honorable guests,

To be awarded a prize that bears the name of a scientist as exceptional as Paul Ehrlich is a great honor.

To be awarded this prize for research on molecular signaling in immunology seems to me especially significant, because it places this research within the historical context of a pathway pioneered by Paul Ehrlich—exploring immunology in terms of molecular recognition.

Paul Ehrlich's work was an inspiration to my laboratory during those years in which we attempted to identify inhibitors of TNF in body fluids.

In this search, we eventually found that such inhibitors do indeed exist in human sera. To our surprise, we found that these inhibitors are actually soluble forms of two cell-surface TNF receptors. Recalling Ehrlich's description of antibodies as soluble and cell-bound receptors, we felt that we were following in his footsteps. My students pasted Ehrlich's famous illustrations of soluble and cell-bound 'side chains', as Ehrlich had called them, on their workspaces, alongside illustrations of the soluble and cell-bound TNF receptors.

But we were also aware that our findings were contributing to a new point of view of how molecular recognition participates in immune defense and in pathology.
While in Ehrlich's time, pathology was viewed as the result of harm caused to our cells by external agents such as infecting bacteria, we now know that pathological changes are to large extent self-inflicted. They might well be fully mediated by our body's own components.

The discoveries that cytokines—immunoregulatory extracellular mediators that our own cells produce—often cause us harm, and that the cytokine TNF makes a major contribution to this harm, was an important step in the realization that pathological changes in our body can be self-inflicted.

What we have learned since then about the mechanisms by which TNF and other cytokines act has further nailed down this notion.

Let me illustrate what we have learnt by referring to a term that was widely used by Ehrlich and his peers, and was also used in the field of TNF research—the term 'toxins'.

The immunologists of Ehrlich's generation directed much of their attention to the response of the body to bacterial toxins such as those causing diphtheria and tetanus. At that time, disease and immune defense were viewed as opponents engaged in a mortal duel between opposing destructive effects—a duel in which the pathogens employ toxins to destroy their host cells and the threatened host cells fight back by generating antibodies to block those toxins and, with the help of complement proteins and macrophages, also kill the pathogens.

Toxins, or rather 'cytotoxins' and 'lymphotoxins', were also the names that were initially bestowed on TNF and on its closely related cytokine LTα.

Those names were given to TNF because until TNF was eventually isolated, its only known cellular effect was the killing of cells. Its very name, TNF, standing for 'tumor necrosis factor', also reflected a view of this protein as a purely destructive entity. The same applies to the term 'necrosin', which was coined much earlier and probably also referred to the protein that we now call 'TNF'. The choice of

these names reflected the misguided belief that TNF acts very much like the bacterial toxins—the mistaken belief that it damages cells via some intrinsic harmful activity.

At the time that I joined this field, more than 30 years ago, it was still being suggested that TNF kills cells via some enzymatic activity that it possesses, or possibly by forming pores in the cell membranes.

Since then, we have come a long way.

We now know that TNF has numerous effects on cell function, and that only some of them result in cell death.

We now also know of many receptors and ligands that are structurally and mechanistically related to TNF and to its receptors. These members of what we now call the 'TNF superfamily' control practically all aspects of immunity.

We know too that none of the effects of the TNF superfamily, or of any of the other cytokines, are exerted in the way that diphtheria or other such toxins work. Neither TNF nor any other cytokine has any intrinsic enzymatic activity. They all affect cells only by binding to cell-surface receptors, and in that way they trigger the functions of specific components of the affected cells.

In fact, we now know that even some of those pathogen components that were called 'toxins' do not have any intrinsic toxic activity. Instead, they act by activating harmful cellular functions.

Exploring the way in which TNF inflicts pathological changes has occupied my laboratory and many others over the past three decades. Allow me to list some of the members of my laboratory who have taken part in the initiation of this research:
Talia Hahn and Helmut Holtmann, for their role in clarifying that TNF is not a cytotoxic molecule but rather a multifunctional cytokine, allowing it to orchestrate inflammation, as well as for the initial evidence that the body employs specific mechanisms to restrict potentially harmful effects of TNF;
Hartmut Engelmann, Dan Aderka, Daniela Novick and Yaron Nophar, for their search for proteins that contribute to the restriction of potentially harmful effects of TNF, for identifying the soluble and the cell-bound forms of the TNF receptors in this search, and for isolating and cloning them;
Cord Brakebusch, for identifying the region within the TNF receptor that we now call the 'death domain';
Mark Boldin, Igor Mett and Eugene Varfolomeev, for the discovery of one of the main molecular pathways of programmed cell death—the extrinsic cell death pathway—and for the cloning of its components;
and Nikolai Malinin, Andrew Kovalenko and Si Qing Zhang for the discovery of signaling proteins that mediate induction inflammation and other immune functions, as well as resistance of cells to death, by activating transcription factors of the NF-κB family.

Let me now add a few words about the important therapeutic implications of this research and about the directions it might take in the future.
Paul Ehrlich believed that identifying molecular mechanisms which contribute to pathology would offer clues to therapy. This vision has clearly been realized in the TNF field. Millions of patients who suffer from chronic inflammatory diseases can now benefit from the therapeutic effects of antibodies and soluble receptors that target the recognition of TNF by its cell-bound receptors.

Moreover, emerging evidence indicates that blocking or enhancing the activation of other receptors of the TNF superfamily can potentially provide therapy in various other kinds of diseases.

There is one radical difference, however, between these achievements and the vision of Ehrlich.

Ehrlich, who sought to target the molecular recognition of pathogens, had reasons to believe that he could design a drug that would harm the pathogen while having no effect at all on the host. In describing this absolute specificity, he used the term ‘magic bullet’.

However, today when physicians attempt to arrest pathology by targeting molecules such as TNF, reaching such absolute specificity is not possible. Since these molecules are integral constituents of the host they also have beneficial effects that we do not wish to block.

We can, however, get closer and closer to such specificity by identifying the specific molecular interactions that contribute to each of the different individual effects of the TNF superfamily. To elucidate the intricacies of these molecular interactions has been and will continue to be a long and arduous undertaking. Many scientists have already contributed to it, and many more will contribute further. The more the advances achieved in this research, the greater will be the specificity of the drugs to be designed in the future.

I feel privileged that we have had the chance to take part in the initiation of this long road, and I thank you for this sign of recognition of our contributions.