Laudation for Andrea Ablasser

Assistant Professor at the Swiss Federal Institute of Technology, Lausanne, Switzerland.

Winner of the Eppendorf Award for Young European Investigators 2018

The laudation was held by the Eppendorf Award Jury Chairman Prof. Reinhard Jahn (Director at the Max Planck Institute for Biophysical Chemistry, Göttingen, Germany) at the prize ceremony at the EMBL Advanced Training Centre in Heidelberg on June 21, 2018.

» One of the main jobs of our immune system is to detect and eliminate potentially noxious external agents, most importantly pathogenic microorganisms such as viruses and bacteria. Indeed, our immune system is critical for surviving in an environment where we are constantly under attack by pathogens. How the immune system manages this complex task never fails to fascinate me – as a neuroscientist I like to state that the brain is our most complex organ but I am coming to believe that the immune system is at least of similar complexity.

Mammals possess two kinds of immune responses termed innate and adaptive immune response. The adaptive immune system is tailored to cope with each hostile organism on a individual basis, thus providing a very high degree of specificity. Due to these extraordinary features, the adaptive immune system has been in the focus of immunological research in the past decades. Impressive progress was made not only in understanding the basic principles but also in exploiting its properties to fight diseases such as cancer. However, this immune response requires some time to become effective, and if this were our only protection from pathogenic agents, we could be quickly overwhelmed by fast replicating organisms. Therefore, the innate immune system, with its much shorter response time, is our first line of defense.

In contrast to the high specificity of the adaptive immune system, the innate immune response is relying on a standing arsenal of defense weapons that are ready to fire any time. It is

activated by general features that are common to many pathogens. In fact, the only condition is that these features can be distinguished from endogenous host molecules. Due to its rather basic nature, for many years the innate immune system received less attention but its remarkable properties, together with its fascinating ability to distinguish friend from foe, have increasingly become appreciated. Targets recognized are, for example, surface proteoglycans shared by many bacteria. Surprisingly, it has become apparent in the past decade that various nucleic acids including double-stranded DNA – completely independent of their sequence – can also trigger the system. At a first glance this does not seem to make sense – as every living organism our cells contain DNA, so how can this be functioning as a signal for microbes? The specificity here lies in compartmentalization: In a healthy cell, double-stranded DNA is confined to the nucleus. Thus, any dsDNA in the cytoplasm is likely to originate from a pathogen (particularly from viruses that otherwise have few distinguishing features), and since DNA is essential for every organism it cannot be concealed by chemical modification and mutagenesis, a common strategy of viruses for escaping the adaptive immune response.

How is DNA recognized and how is the response triggered? Since several years, proteins are known that recognize dsDNA either in the endomembrane system or in the cytoplasm. It is also known that the cells react with an inflammatory response – they release a cocktail of cytokines and interferones that alert surrounding cells and activate a defensive immune response. However, how DNA-binding proteins tell the cell to synthesize and release cytokines has been uncovered only recently, and it is here where Andrea Ablasser, the winner of this year's Eppendorf Young Investigator Award, has made seminal contributions. Before Andrea tells you more about her work, I would like to briefly introduce her.

Andrea grew up in a family of medical doctors and became fascinated by science already during her early high school years. In the family tradition studying Medicine was probably the obvious choice. However, she was unsure which direction to take as she was also attracted to physics where she enrolled in some courses. While pursuing a medical degree, she became more interested in the scientific foundation of Medicine and was frustrated by their superficial treatment in her practical education. For these reasons, she was looking for an interesting research project immediately after her Intermediate Exam. She therefore joined the Department for clinical pharmacology, headed by Stefan Endres, where her passion for basic science increased. Here she met a postdoctoral scientist – Veit Hornung – whom she followed for a brief stint to the University of Massachusetts before she joined his team after Veit established his own laboratory in Bonn.

In the lab, they were hot on the trail of DNA recognition, trying to identify the missing link between DNA sensing and cytokine activation. Then they apparently had a bit of bad luck – two reports from another laboratory, the group of Jason Chen, identified an unusual second

messenger known from bacteria – the cyclic dinucleotide GMP-AMP, referred to as cGAMP as the key intermediate. They also showed that this molecule is synthesized by a novel and hitherto uncharacterized DNA binding protein, now termed cGAMP synthetase (cGAS) as the biosynthetic enzyme. Problem solved?

Being scooped is tough luck for every scientist. However, instead of giving up, the team immediately set out to work on the new pathway, and then the surprises kept coming. Andrea's first major discovery was that the structure of cGAMP was chemically distinct from its bacterial relatives, and more importantly, that these specific differences were absolutely crucial for the ability of the second messenger to activate the downstream target. This target is a homodimeric membrane protein: ER-resident protein stimulator of IFN genes (STING), which is the central activator of the inflammatory response. Then Andrea found out that the novel second messenger cGAMP does not only activate intracellular mechanisms but spreads to other cells, i.e. it serves as a fire siren that alerts the neighbors. These and other discoveries resulted in an extremely impressive list of high-ranking publications from her postdoc that I have seen only very rarely! For this work she has received already several Awards such as the Max von Pettenkofer Prize, the Jürgen Wehland Prize, the Paul Ehrlich and Ludwig Darmstaedter Prize for young researchers, and the GlaxoSmithKline Award for basic medical research.

In 2014, Andrea Ablasser became tenure-track Assistant Professor at the EPFL in Lausanne. Since then, her performance as a group leader has been at least as remarkable as before, and despite the short period of time, she has already made seminal contributions. First, she showed, that the GAS-STING pathway is also activated in senescent cells by its own DNA, when nuclei or chromosomes become unstable and escape into the cytoplasm, resulting in a much acclaimed and commented publication in Nature Cell Biology. In addition, her team has recently identified the first inhibitor for the central mediator STING, with remarkable clinical potential, a discovery that is now in press in Nature (the journal where several of her previous papers were published which I am sure will please our sponsors from Nature…). However, let us Andrea tell by herself what she has done – let's welcome this year's winner of the Eppendorf Young Investigator Award, Andrea Ablasser! «