Andrea Ablasser wins the 2018 Eppendorf Award for Young European Investigators

Andrea Ablasser, Eppendorf Award winner 2018

This year's award ceremony took place at the EMBL Advanced Training Centre in Heidelberg, Germany, on 21 June 2018. Science writer Geoff Marsh talks to the 2018 winner Andrea Ablasser, Assistant Professor at the Swiss Federal Institute of Technology, Lausanne, Switzerland, about her contributions to a key step in the innate immune response, which triggers a frontline defense when cells are attacked by microorganisms.

Geoff Marsh: First and foremost, I would like to say congratulations on behalf of Nature Research, part of Springer Nature, for winning the prize.

Andrea Ablasser: Thank you. It is a big honour to receive this award and is an appreciation of the work of the many people involved.

GM: At a very basic level, how does the innate immune system work to spot pathogens in and around our cells?

AA: The innate immune system has evolved so-called 'pattern recognition receptors' that recognize specific microbial products. The sensing of these microbial products triggers inflammation and innate immune effector responses that fight the pathogen. At the same time, the pattern recognition receptors can also sense damage by sensing self-DNA products, which can also indirectly alert the immune system to the presence of pathogens.

GM: So the work in your laboratory is aimed at elucidating the exact mechanism by which this deoxyribonucleic acid (DNA) recognition works in our cells?

AA: Yes. We are interested in understanding how DNA is sensed, and how this sensing is translated into the induction of effector responses.

GM: Why did you ask that question?

AA: I was intrigued by the finding that double-stranded DNA can elicit very strong immune responses. Double-stranded DNA is the basic building block of life itself so it is kind of a paradoxical situation.

GM: You and your team have been looking at a prime suspect behind DNA recognition. What is it?

AA: We know that one of the predominant mechanisms to sense double-stranded DNA is an enzyme called 'cGAS', which stands for 'cyclic GAMP synthase'. It senses double-stranded DNA in a sequence-unspecific manner, and then produces a cyclic nucleotide second-messenger molecule. The second-messenger molecule activates a second receptor called STING and that triggers downstream signalling and inflammation. What we have contributed to the understanding is to describe the chemical nature of the second-messenger molecule. We have gone on to show that this signalling pathway has some very interesting features. It is not connected through protein–protein interaction, but through a soluble second-messenger molecule that has a signalling function, so it can be horizontally transferred between cells and alarm neighbouring cells.

GM: Does that mean that a cell can pass on its antiviral immunity to neighbouring cells without eliciting the transcription of any genes?

AA: That is correct. CGAMP itself functions as a signalling molecule that can relay information in between cells.

GM: How does it get between cells?

AA: Gap junctions. These are channels that connect neighbouring cells. Because

Andrea Ablasser, Reinhard Jahn (Jury Chairman), Jürg Dübendorfer (Eppendorf AG)
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Left to right: Axel Jahns[1], Maria Leptin[2], Andrea Ablasser, Reinhard Jahn[2], Laura Machesky[2], Martin Lohse[2], Jürg Dübendorfer[1], Dieter Häussinger[2]

[1]Eppendorf AG
[2]Eppendorf Award Jury

CGAMP is a very small molecule it can be passed through gap junctions and become distributed in a local tissue environment between neighbouring cells.

GM: Do we know how this system is regulated?

AA: This is still incompletely understood in the field. Are there enzymes that cleave it off? One enzyme has been described but there is probably still a lot more to discover because there must be tight regulation of this pathway to avoid aberrant stimulation or inappropriate activation of immune responses.

GM: And does that occur? Is there sometimes an erroneous detection of 'self' molecules?

AA: Yes. That is actually a major focus of my lab right now. What we know today is that there are very rare genetic disorders that involve defects in DNA metabolic enzymes. cGAS is a driver of these diseases and can contribute to very severe auto-inflammatory syndromes. What we are also beginning to realize is that cGAS, through its self-DNA sensing function, is involved in many more complex disorders and diseases, such as myocardial infarction. Two papers last year described the activation of cGAS through self-DNA as a contributor to the detrimental outcomes following myocardial infarction.

GM: Does our more detailed understanding of this mechanism offer opportunities for therapeutic interventions for these diseases?

AA: STING and cGAS are emerging as very attractive targets for diseases. In the context of stimulating these pathways, for example in tumour immunotherapy, to block pathways in autoimmune diseases such as lupus, and also in more complex diseases.

GM: There is another more recent strand to your work, separate from pathogenic infection, and that is in relation to senescence.

AA: Yes. That is also an effector response that is triggered by cGAS due to sensing aberrant self-DNA. What we found is that during cellular senescence, when cells get older, they show disruption of the nuclear envelope architecture. This leads to chromatin herniation into the cytosol and this can activate cGAS, thereby contributing to an inflammatory response to aged cells. What we are currently following up is whether cGAS and STING may contribute to ageing or age-related diseases. It is intriguing because the mechanisms that help us to clear pathogens and that save our lives when we are young might be detrimental when we get older.

To listen to the full interview, visit: https://go.nature.com/2mcqrgo

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Presented in partnership with *Nature*, the Eppendorf Award for Young European Investigators recognizes outstanding work in biomedical science. Besides a prize money of € 20,000, it provides the opportunity for European researchers to showcase their work and communicate their research to a scientific audience.

The winner is selected by an independent jury of scientists under the chairmanship of Reinhard Jahn, Director at the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany. *Nature* and Eppendorf do not influence the selection.

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