One more reason to swear off tobacco: The inflammatory trap induced by nicotine

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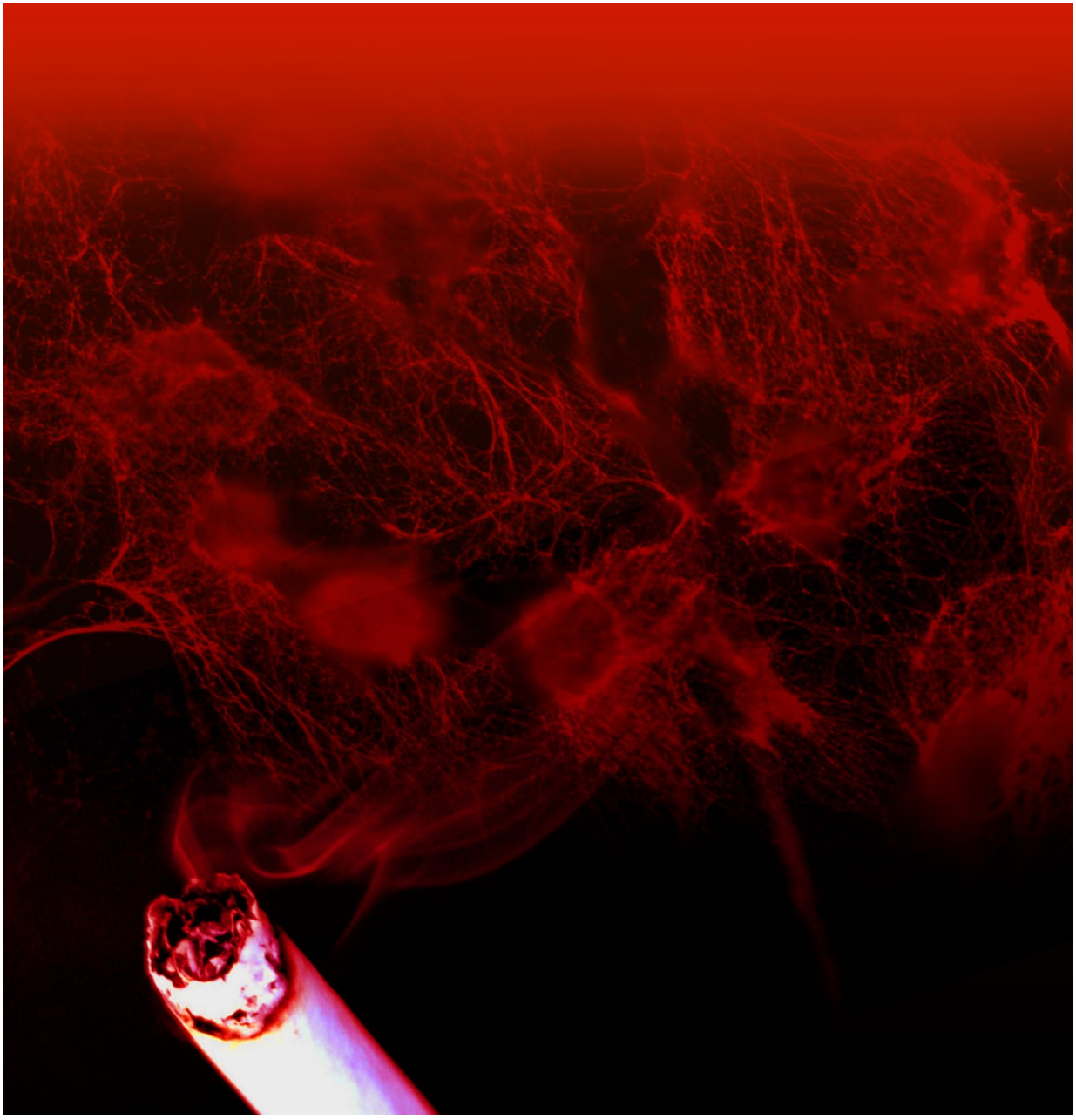

The image illustrates how smoke from a cigarette transforms to neutrophil extracellular traps which eventually reach blood vessels. The fibril meshwork depicted in red is taken from a microscopic image of activated neutrophils that have released NETs. Each fibre is one or more strands of DNA loaded with antimicrobial enzymes and inflammatory molecules Credit: Ava Hosseinzadeh, Umeå University

An Umeå-based team in collaboration with US researchers reveals a new link between nicotine and inflammation. They report that nicotine strongly activates immune cells to release DNA fibres decorated with pro-inflammatory molecules, so called neutrophil extracellular traps (NETs). The continuous exposure to these NETs can harm the tissue and could explain the hazardous consequences of tobacco consumption for human health.

Tobacco use causes death of nearly six million people annually according to WHO. Nicotine is the major addictive and toxic component in tobacco products. In cells, nicotine signals via nicotine acetylcholine receptors to mediate dangerous effects on the consumer's body. Nicotine is a major cause of inflammatory diseases among smokers and also non-smokers by passive inhalation, such as for instance chronic obstructive lung disease (COPD). COPD is widely spread and affects more than 10 percent of the adult population in westernised countries. The molecular mechanisms underlying this inflammatory activity of nicotine are not well understood.

In a recently published article in the *Journal of Leukocyte Biology*, researchers at the Laboratory for Molecular Infection Medicine Sweden (MIMS) at Umeå University reveal a novel link between nicotine and inflammation. They found that nicotine activates neutrophils, in an

undesirable fashion.

Neutrophils are the most abundant type of white blood cells that circulate in the blood stream ready to attack invading microbes with an arsenal of antimicrobial compounds. Neutrophils are essential to prevent infection by engulfing invading microbes, or by releasing reactive oxygen species as well as DNA fibres from their own nuclei, termed neutrophil extracellular traps (NETs). NET release is a mixed blessing. Loaded with antimicrobial enzymes and pro-inflammatory molecules NETs are harmful to invading microbes, however, they can also potently harm the host's own tissue, if not controlled in the right manner. In recent years, NETs have been attributed to be mediators of tissue damage in several inflammatory diseases, such as for instance small vessel vasculitis, arthritis and cancer.

For the first time, Ava Hosseinzadeh and colleagues at MIMS show that nicotine triggers NET release. The signal to trigger NETs is mediated by a specific acetylcholine receptor found on neutrophils and further signalled into the cell via a protein kinase known as Akt.

"This particular finding explains the missing piece of the puzzle of tobacco usage and inflammation," says Ava Hosseinzadeh, who worked on this project during her doctoral dissertation. "This novel finding opens new avenues to understand the consequences of tobacco usage for human health and should be seen as one more convincing argument to quit nicotine usage in any form."

"The next evident step is to demonstrate the NET-inducing capacity of nicotine in animal models and human samples," says Constantin Urban, associate professor and project leader at Umeå University. "Such 'in vivo' studies will enable us to attract new funders and potentially interest of the pharma industry. Our finding could hopefully lead to novel anti-inflammatory therapies of tobacco usage related diseases."

More information: A. Hosseinzadeh et al, Nicotine induces neutrophil extracellular traps, *Journal of Leukocyte Biology* (2016). DOI: 10.1189/jlb.3AB0815-379RR