



Emerging Evidence Supports the Hypothesis that Neutrophil Extracellular Traps are a Major Factor in Genesis and Progression of Chronic Obstructive Pulmonary Disease

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ABSTRACT

Since their discovery about fifteen years ago, neutrophil extracellular traps (NETs) have been recognized as an intrinsic part of vertebrate innate immunity and inflammatory response. Consisting of entangled strands of extracellular DNA decorated with histones, elastase, myeloperoxidase and other proteins, NETs entrap and kill pathogens, but are increasingly also found to contribute to acute and chronic inflammatory disease due to their toxicity to host cell and autoimmunity induction. Chronic obstructive pulmonary disease (COPD) turned out to be among the major disorders involving overshooting formation of NETs and associated adverse effect. In the present review, we summarize the progress in knowledge on the role of NETs in COPD pathology made since our first reports on this subject. We highlight recent substantial advances and discuss possible cause-and-effect relationships, connections with common comorbidities and interactions with drugs, also to illustrate the importance of NETs as a future diagnostic tool and target for new medication strategies.

COPD is a progressive inflammatory airway disease, usually following long-term exposure to environmental insults. The main causal factor for developing COPD is inhaled tobacco smoke¹. COPD affects around 10% of the adult population in industrialized countries² and has substantial impact on the quality of life and life expectancy³. It is the third leading cause of death on the global scale⁴ and the sixth leading cause of death in countries with high socio-demographic index⁵. The disease varies in clinical presentation, often involving recurrent bacterial infection, massive neutrophil infiltration, and emphysematous alveolar wall destruction⁶. COPD is frequently still characterised into distinct 'phenotypes' based on varying criteria⁷⁻⁹ (caveats defined by Agusti¹⁰). In many cases, periods of stable condition alternate with episodes of worsening (exacerbations), leading to increasing small airway obstruction and lung function impairment. Lung function decline is also a key basis of disease assessment according to international guidelines¹¹.

Extracellular traps (ETs) consist of entangled threads of DNA with dimensions down to 2 nm, associated with histones, elastase, myeloperoxidase (MPO) and other proteins that are antimicrobially effective, but also potentially cytotoxic^{12,13}. ET formation (ETosis) by phagocytes is an intrinsic part of vertebrate innate pathogen defense and inflammatory response¹². In humans, ETs are most frequently formed by neutrophils, then being abbreviated as NETs. Evidence on the existence of NETs is quite recent, first traces (although not explicitly designated) dating back to 1996¹⁴, followed

