Tours, September, 2019

ABSTRACT

Neutrophil Serine Proteases In Health And Disease

Polymorphonuclear neutrophils are the first cells recruited to inflammatory sites and form the earliest line of defense against invading microorganisms. Neutrophil elastase, proteinase 3 and cathepsin G are three hematopoietic serine proteases maturated by cathepsin C (CatC). CatC is a highly conserved tetrameric lysosomal cysteine dipeptidyl aminopeptidase. The best characterized physiological function of CatC is the activation of pro-inflammatory granule-associated serine proteases, including neutrophil serine proteases. These proteases are synthesized as inactive zymogens containing an N-terminal pro-dipeptide, which maintains the zymogen in its inactive conformation and prevents premature activation, which is potentially toxic to the cell. The activation of serine protease zymogens occurs through cleavage of the N-terminal dipeptide by CatC during cell maturation in the bone marrow. Active serine proteases are stored in large quantities in neutrophil cytoplasmic azurophilic granules. They act in combination with reactive oxygen species to help degrade engulfed microorganisms phagolysosomes. These proteases are also externalized in an active form during neutrophil activation at inflammatory sites, thus contributing to the regulation of inflammatory and immune responses. As multifunctional proteases, they also play a pathogenic role in genetic, auto-immune or chronic inflammatory diseases. Mutations in the *ELA2/ELANE* gene, encoding neutrophil elastase, are the cause of human congenital neutropenia. Proteinase 3 serves as the major autoantigen in granulomatosis with polyangiitis, a systemic autoimmune vasculitis. All three proteases are involved in chronic inflammatory lung diseases including chronic obstructive pulmonary disease (BPCO) (*reviewed in* Korkmaz et al., 2010, Pharmacol. Rev.)

In vivo data suggest that pharmacological inhibition of pro-inflammatory neutrophil serine proteases would suppress or attenuate deleterious effects mediated by these proteases in inflammatory/auto-immune disorders. The pathological deficiency in CatC is associated with Papillon-Lefèvre syndrome. The patients however do not present marked immunodeficiency despite the absence of active neutrophil serine proteases in immune defense cells. Hence, the transitory pharmacological blockade of CatC activity in the precursor cells of the bone marrow may represent an attractive therapeutic strategy to regulate activity of serine proteases in inflammatory and immunologic conditions. A variety of CatC inhibitors have been developed both by pharmaceutical companies and academic investigators, some of which are currently being employed and evaluated in preclinical/clinical trials (*reviewed in* Korkmaz et al., 2018, Pharmacol.Ther.).

During the lectures from 21th-31st October 2019, the physicochemical functions of neutrophilic proteases, toward a goal of better delineating their role in human diseases and identifying new therapeutic strategies based on the modulation of their bioavailability and activity will be described.

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