Therapeutic targeting of cathepsin C : *from pathophysiology to treatment*

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Biosketch: Dr. Brice Korkmaz's scientific interest focus on physiopathological functions of neutrophilic serine and cysteine proteases. Dr Korkmaz has been recruited by INSERM (*French National* Institute *of* Health *and* Medical *Research*) in 2009 after post-doctoral stays in France (INSERM U618), USA (Seattle, University of Washington, Medical genetics) and Germany (Munich, Max Planck Institute of Neurobiology). He has extensive expertise in biochemistry/enzymology and in neutrophilic chronic inflammatory/autoimmune diseases. He is responsible of a research group (therapeutic targeting of neutrophilic proteases) in team 2 of INSERM-U1100 since 2012.

Abstract: 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 stored in large quantities in neutrophil cytoplasmic azurophilic granules. They act in combination with reactive oxygen species to help degrade engulfed microorganisms inside phagolysosomes. These proteins 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 regulatory role in noninfectious inflammatory diseases. *ELA2/ELANE* gene, encoding neutrophil elastase, are the cause of human congenital neutropenia. Neutrophil membrane-bound proteinase 3 serves as an autoantigen in granulomatosis with polyangiitis, a systemic autoimmune vasculitis. All three proteases are affected by mutations of the gene (*CTSC*) encoding cathepsin C (dipeptidyl peptidase I), a protease required for activation of their proform before storage in cytoplasmic granules. Mutations of *CTSC* cause Papillon-Lefèvre syndrome. Because of their roles in host defense and disease, elastase, proteinase 3, and cathepsin G are of interest as potential therapeutic targets. Dr B. Korkmaz and his collaborators are studying the physicochemical functions of these 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.

References:

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