Title: Molecular basis for Ehlers-Danlos syndrome and search for new therapeutic strategies in the forms linked to a defect in glycosaminoglycan biosynthetic genes

Research Project
The research activities of our group are centered on the study of connective tissue disorders with special attention to arthropathies, a major thematic area of our laboratory. We are mainly interested in the extracellular matrix of cartilage that is composed of complex and fascinating biomacromolecules, namely proteoglycans, that comprise a core protein on which are attached a variable number of glycosaminoglycan (GAG) chains. Proteoglycans, together with collagens and different glycoproteins, are essential to the functional and structural integrity of extracellular matrices of connective tissues. Our research project in the field of rare diseases is dedicated to the study of Ehlers-Danlos syndrome (EDS) variants due to mutations of genes coding for enzymes involved in the synthesis of GAG chains of proteoglycans. Indeed, a growing number of glycobiochemical studies have described genetic diseases caused by disturbances in GAG assembly (see ref 1 for review). We previously studied the molecular basis of the defect of GAG synthesis due to mutations of β4GalT7, a glycosyltransferase implicated in the formation of the tetrasaccharide region, that serves as a primer for both heparan and chondroitin sulfates, the two main types of GAG saccharide chains (2). We recently identified, in collaboration with the Center for Medical Genetics (Ghent, Belgium), several mutations of a new gene coding for β3GalT6, the second galactosyltransferase involved in the formation of the tetrasaccharide linkage region of GAGs, causing a severe and pleiotropic connective tissue genetic disease with autosomal recessive inheritance (3). The phenotype of affected patients overlaps with several Ehlers-Danlos syndrome (EDS) variants and spondyloepimetaphyseal dysplasia with joint hyperlaxity. We showed by a combination of biochemical and glycobiochemical approaches that the identified mutations produce a major default in both heparan and chondroitin sulfate synthesis. These defects contribute to the alteration of collagen fibril organization and wound healing delay, key clinical features of the syndrome. Our current project is to molecularly characterize the mutants of β3GalT6 using recombinant enzyme expression systems developed in our laboratory, and to provide further insight into the pathogenesis of this new EDS variant involving GAG defects. A growing body of evidence indicates that EDS syndromes are not only due to mutations of genes coding for collagen or their biosynthetic enzymes but also to defaults affecting “regulators” of extracellular matrix assembly such as proteoglycans. We therefore wish to carry on further genetic studies of connective tissue disorders such as EDS, that may be associated with or may result from abnormal GAG synthesis. We also aim to test, in first instance by using in vitro and animal models, whether small molecules called xylosides that are able to restore GAG biosynthesis, bypassing the use of the core protein of proteoglycans, would possibly correct some symptoms associated with these defects. We aim by this project to provide new diagnostic tools for some forms of rare genetic diseases characterized by connective tissue disturbances for which the causative genes are not yet identified, and to facilitate the development of therapeutics to counteract GAG alterations and their clinical consequences.