Serpinopathies Foreword

Advances in medical knowledge have traditionally focused on archetypal examples, as with Sir William Osler's dictum in the late nineteenth century, that "He who knows syphilis knows medicine." Similarly, with the commencement of the molecular era of medicine in the 1960's, hemoglobin became a paradigm for the way in which genetic variations in the structure of a protein could result in a range of diverse diseases. The power of this model resulted from the solving of the structure of hemoglobin, but what impressed me as a participant at that time was the realization that the structure not only provided a template for studying diseases of hemoglobin, but also for the study of the consequences of variations in the globin family as a whole. An opportunity to apply the same approach, using structure-based homologies, to diseases arising from mutations in other protein families, was initiated by the work of Carl-Bertil Laurell, in Malmo Sweden in 1963. His finding that a mutation commonly present in the plasma protein α1-antitrypsin was associated with lung degeneration, identified the function of this otherwise unknown and atypical protease inhibitor. The subsequent amino acid sequencing of α1-antitrypsin with my colleagues in New Zealand to determine the position of the common mutations in the molecule, also led to the recognition of its close homology with another plasma protease inhibitor, antithrombin in 1979. However, two swallows do not make a summer and the recognition that we were looking at a new protein superfamily came from the additional alignment with ovalbumin by Hunt and Dayhoff in 1980.

Interest in this newly identified family was transformed by the determination of the structure of α1-antitrypsin by Huber and colleagues in Martinsried Germany in 1984. Their structure provided a template on which to align other members of the family and because the α1-antitrypsin crystallized in Martinsried was in a protease-cleaved form, the structure also revealed the ability of this family of protease inhibitors to undergo a

profound conformational change. By this time, other members had been added to the family, including the plasma proteins such as antiplasmin, PAI-1, C1-inhibitor, angiotensinogen and the hormone-binding globulins. Each of these was in turn associated with diverse familial disorders and it was soon apparent that most of the underlying mutations were closely sited together in what became recognized as the hinges and mobile regions of the template molecule. In this new family, we had a paradigm to supplant that of hemoglobin, not just as a model of genetic disease, but also as a model of the way that changes in molecular shape and fold could lead to dysfunction and to what became known as conformational diseases. Yet, how could these new ideas and concepts be communicated on the basis of what was denoted by Hunt and Dayhoff as the *ovalbumin-antithrombin-III-alpha 1-proteinase inhibitor superfamily*? A simpler name was needed. My thoughts immediately turned to the globins and hence to the acronym for this novel family of serine protease inhibitors, the serpins. James Travis who had led studies on the functional and biochemical properties of α1-antitrypsin readily agreed to join in proposing the new name, which was soon adopted by the wider field because of its convenience.

The prime reason though for the choice of name, *the serpins*, was to encourage the study of the family as a whole and it has been rewardingly successful in this. The flowering of these studies is seen in this volume, which documents the ubiquitous distribution of the serpins and their diverse functions. It is no exaggeration that the conformational mechanism of the serpins has provided a template for adaptation that has been critical to the evolution of higher organisms. As the authors each show in this book, the clearest evidence of the way this adaptation has allowed tissue-specific functions and modulation comes from the diseases that resulted from mutations in the individual serpins. The diversity of these serpinopathies, as brought together in this volume, covers the whole range of molecular and conformational pathologies. This timely book establishes the basis for what could be a dictum for the 21st century, "He who knows the serpins knows molecular medicine."

Robin Carrell
University of Cambridge (June 2006)

Molecular and Cellular Aspects of the Serpinopathies and Disorders in Serpin Activity

Gary A. Silverman and David A. Lomas

Preface

In 1980, Lois Hunt and Margaret Dayhoff identified a new protein superfamily containing ovalbumin, antithrombin III, and α_1-proteinase inhibitor.[1] Although provisionally named the ovalbumin–antithrombin superfamily, Robin Carrell and James Travis utilized the acronym *serpins* to describe this expanding superfamily, as the members were predominately serine proteinase inhibitors.[2] Since the 1980s, the serpin field has virtually exploded in terms of family size and our knowledge of their roles in biological systems.[3–6] Inspection of the nucleotide repositories provides evidence for over 2000 family members, including 37 in humans (http://www.ncbi.nlm.nih.gov/Genbank/index.html; http://www.ensembl.org/index.html). Serpin citations and structures deposited in PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) and the PDB (http://www.rcsb.org/pdb/) exceed 43,000 and 80, respectively. Once considered unique to metazoans and most *Poxviridae*, serpins have now been detected in all domains of life such as *Archaea*, *Prokarya*, and *Eukarya*.

Strict conservation of the serpin fold throughout evolution attests to the critical relationship between the potential energy stored in the native structure and the dynamic inhibitory function that distinguishes serpins from the canonical peptidase inhibitors. In essence, serpins are finely tuned molecular machines that undergo a major conformational rearrangement

to irreversibly trap their target peptidase. For reasons that have yet to be fully appreciated, nature has sought to retain this more complex inhibitory machine relative to the simpler canonical inhibitors and to place serpins at critical checkpoints in a variety of intra- and extra-cellular proteolytic cascades. However, like the moving parts of any finely tuned machine, serpin function can be severely impaired by amino acid variants positioned within any one of the several structural elements that affect protein folding or overall motility. Indeed, similarly placed mutations in the serpin scaffold of different serpin genes have led to the emergence of a new class of conformational disorders, the serpinopathies.[7–10]

The major goal of this text is to summarize our recent understanding of how serpin mutations and amino acid variants can lead to significant human diseases such as α_1-antitrypsin deficiency, hereditary angioedema, familial presenile dementias, and thrombophilia. While some of the serpin disorders serve as prime examples of conformational disorders (serpinopathies), others are due to the more classical type 1 (decreased steady-state amounts of a functional inhibitor) or type 2 deficiencies (normal steady amounts of protein, but the inhibitor is dysfunctional), or reactive site loop "change-in-function" mutations.

While most serpins are irreversible inhibitors of serine and cysteine peptidases, several family members serve other functions whose normal and pathological roles in biological systems have yet to be fully elucidated. As a prelude to understanding the pathogenesis and the broad biological implication of serpin disorders, we first present an overview of the serpin superfamily with an emphasis on their distribution, evolution, structure, and inhibitory mechanism. Next, insight into the spectrum of biological systems regulated by serpin gene activity is provided by several prokaryotic and eukaryotic model organisms. The roles that serpins play in defined physiological process such as cell death and tumor invasion are explored in the third section. Finally, lessons from all of these studies are used to better understand the relationships between serpins in human health and disease.

The editors are grateful to the contributing authors for providing their collective expertise in bringing this text to fruition. We are also grateful to our wonderful colleagues in the serpin and peptidase community who provided their thoughtful insights into many of the biological and biochemical issues discussed in these pages.

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