

# **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  $\alpha_1$ -proteinase inhibitor.<sup>1</sup> 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.<sup>2</sup> Since the 1980s, the serpin field has virtually exploded in terms of family size and our knowledge of their roles in biological systems.<sup>3–6</sup> 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.<sup>7–10</sup>

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  $\alpha_1$ -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.

## Acknowledgments

The editors and contributing authors dedicate this text to Robin Carrell and James Travis, whose scientific insight and thoughtful mentoring have helped inspire the study of serpin biology.

## References

1. Hunt LT and Dayhoff MO (1980) A surprising new protein superfamily containing ovalbumin, antithrombin-III, and  $\alpha$ 1-proteinase inhibitor. *Biochem Biophys Res Commun* **95**(2):864–871.
2. Carrell R and Travis J (1985)  $\alpha$ 1-Antitrypsin and the serpins: Variation and countervariation. *Trends Biochem Sci* **10**:20–24.
3. Gettins PG (2002) Serpin structure, mechanism, and function. *Chem Rev* **102**(12):4751–4803.
4. Potempa J, Korzus E and Travis J (1994) The serpin superfamily of proteinase inhibitors: Structure, function, and regulation. *J Biol Chem* **269**(23):15957–15960.
5. Silverman GA, Bird PI, Carrell RW, *et al.* (2001) The serpins are an expanding superfamily of structurally similar but functionally diverse proteins: Evolution, mechanism of inhibition, novel functions, and a revised nomenclature. *J Biol Chem* **276**(36):33293–33296.
6. Silverman GA, Whisstock JC, Askew DJ, *et al.* (2004) Human clade B serpins (ov-serpins) belong to a cohort of evolutionarily-dispersed intracellular proteinase inhibitor clades that protect cells from promiscuous proteolysis. *Cell Mol Life Sci* **61**:301–325.
7. Davis RL, Shrimpton AE, Holohan PD, *et al.* (1999) Familial dementia caused by polymerization of mutant neuroserpin. *Nature* **401**(6751):376–379.
8. Lomas DA and Mahadeva R (2002) Alpha1-antitrypsin polymerization and the serpinopathies: Pathobiology and prospects for therapy. *J Clin Invest* **110**(11):1585–1590.
9. Lomas DA and Carrell RW (2002). Serpinopathies and the conformational dementias. *Nat Rev Genet* **3**(10):759–768.
10. Carrell RW and Lomas DA (2002) Alpha1-antitrypsin deficiency—a model for conformational diseases. *N Engl J Med* **346**(1):45–53.