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SERPINE2/Protease Nexin-1 *in vivo* multiple functions: Does the puzzle make sense?

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Keywords

Development / Nervous system / Cancer / Vasculature / Protease inhibition / Injury / Cell surface receptors / Genetically modified mice

Abstract

Cultures of glial cells and fibroblasts allowed and lead to the identification SERPINE2/Protease Nexin-1 (SERPINE2/PN-1). Cellular, biochemical, immunological and molecular characterization substantiated its variable expression in many organs as a function of development, adult stages, pathological situations or following injury. It is not a circulating serpin, but as other members of the family, its target specificity is influenced by components of the extracellular matrix. The challenges are to identify where and when SERPINE2/PN-1 modulatory action becomes crucial or even possibly specific in a mosaic of feasible *in vivo* impacts. Data providing correlations are not sufficient to satisfy this aim. Genetically modified mice, or tissue derived thereof, provide interesting *in vivo* models to identify and study the relevance of this serpin. This review will highlight sometimes-intriguing results indicating a crucial impact of SERPINE2/PN-1, especially in the vasculature, the nervous system or the behavior of cancer cells *in vivo*. Data presently available will be discussed in an attempt to define general trends in the diversity of SERPINE2/PN-1 modes of action *in vivo*.

1. Introduction

Originally two different *in vitro* experimental models lead to the characterization of SERPINE2/Protease Nexin-1 (SERPINE2/PN-1). Cultured glial cells release a protein promoting neurite outgrowth in neuroblastoma cells[1]. The purification of this factor indicated its interactions with serine proteases and its sequencing established it as a serpin[2,3]. In another tissue culture system, human fibroblasts release a potent thrombin inhibitor called Protease Nexin-1 (SERPINE2/PN-1)[4]. Its sequencing established its identity with the glia-derived neurite promoting factor[5].
Multiple *in vivo* functions of SERPINE2/PN-1 have been suggested over the years by biochemical measurements or tissue culture experiments. They have recently been well reviewed by Arocas and Bouton[6]. This chapter does not aim to duplicate such a detailed review but to rather focus on *in vivo* impacts identified by the use of genetically modified mice and to highlight some reports providing indications on distinct or common mechanisms underlying these functions.
With time, SERPINE2/PN-1 was shown to inhibit many different serine proteases with an especially high affinity and potency for thrombin[6]. Expression of SERPINE2/PN-1 is detected at different levels in different organs and regulated during development[7]. It is thus important to establish the nature of its organ-specific biological impact and whether it relies on similar on distinct modes of action.