JOURNAL OF PROTEOMICS 72 (2009) 200–209

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Review

# Timeline of key events in snake venom metalloproteinase research

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ARTICLE DATA

*Article history:*
Received 13 January 2009
Accepted 14 January 2009

*Keywords:*
Snake venom metalloproteinases
Hemorrhagic toxins
Proteomics
ADAMs
Disintegrins
Extracellular matrix

ABSTRACT

It is reasonable to state that snake venom toxinology has been actively pursued for at least the past 400 to 500 years. Early on it was appreciated that the venoms of the Viperidae produced profound local effects, notably hemorrhage. For the past 100 years, with the advent of modern chemistry and biochemistry significant progress has been gained regarding the function, structure and role of the snake venom metalloproteinases (SVMPs) in viperid venom pathogenesis. In this review we provide a concise, chronological presentation of the key significant studies that have led to our current understanding of these intriguing toxins.



## Contents



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1874-3919/$ – see front matter 
doi:10.1016/j.jprot.2009.01.015

## 1. Introduction

It is likely that snake venoms have been a topic of general public fascination since man first observed a snake envenoming either as in pursuit of prey or as an act of defense. In general, the first scientific observations and experimentations on venomous snakes can be attributed to Francesco Redi, who in 1664 wrote a tract entitled "Osservazioni intorno alle vipere (microforma)." Interestingly, this spawned additional scientific comment in 1673 from Moyse Charas who wrote a tract entitled "New experiments upon vipers (microform): with exquisite remedies that may be drawn from them, as well for the cure of their bitings, as for that of other maladies: also A letter of Francisco Redi, concerning some objections made upon his observations about vipers, written to Monsieur Bourdelot and Mr. Alex. Morus: together with the sequel of new experiments upon vipers, in a reply to a letter written by Signore F. Redi." What makes this work so interesting is that it in effect highlights many issues regarding Toxinology which are currently being investigated such as use of venoms for pharmaceuticals and treatments for snake envenoming as well as noting that snake venom research then as now can be somewhat contentious.

In 1765 the naturalist Felix Fontana published an incredibly interesting work entitled (translated from Italian) "Treatise on the venom of the viper; on the American poisons; and on the cherry laurel, and some other vegetable poisons." Some of the chapters in this treatise include: "The venom of the viper is not a poison to the viper itself"; "The venom of the viper is not a poison to every species of animals"; "What causes the death of animals that have been poisoned by the viper"; and "On the action of the venom of the viper on the blood of animals." As one can observe, these aspects of toxinology are still under research today which may cause some skeptics to question whether any progress in this field has indeed been realized. To this we can offer a resounding response that in the case of snake venoms, particularly over the past 40 years incredible advances have been made in the understanding of the composition of venoms, and the biochemistry and molecular mechanisms of action of individual toxins. The overwhelming challenge facing toxinologists now is to understand, in an integrative, systems approach the mechanism by which venoms affect tissues and ultimately the organism which has been envenomed.

As an example of the advances made, we have generated a concise review of key investigations on the snake venom metalloproteinases found in venoms which have been experimentally shown to be involved the pathologies associated with snake envenoming (Fig. 1). We hope that this will serve as an exemplar of how toxinology, as applied to a specific toxin class found in many venoms, evolves from a point of speculation to a rich and deep level of understanding of snake venoms in general and the multitude of toxins of which they are comprised.

## 2. Venoms Are Proteolytic

As early as 1881 it was noted that bothropic species of snakes were suggested to be proteolytic [1]. In the early 1900s it was recognized that venom could coagulate blood but there was some uncertainty as to the whether the mechanism involved proteolysis. In a review by Kellaway the toxic actions observed in snake venoms were considered, in part, to be the result proteolytic enzymes [2]. By 1949 Rocha et al. more specifically recognized the potential of venoms as

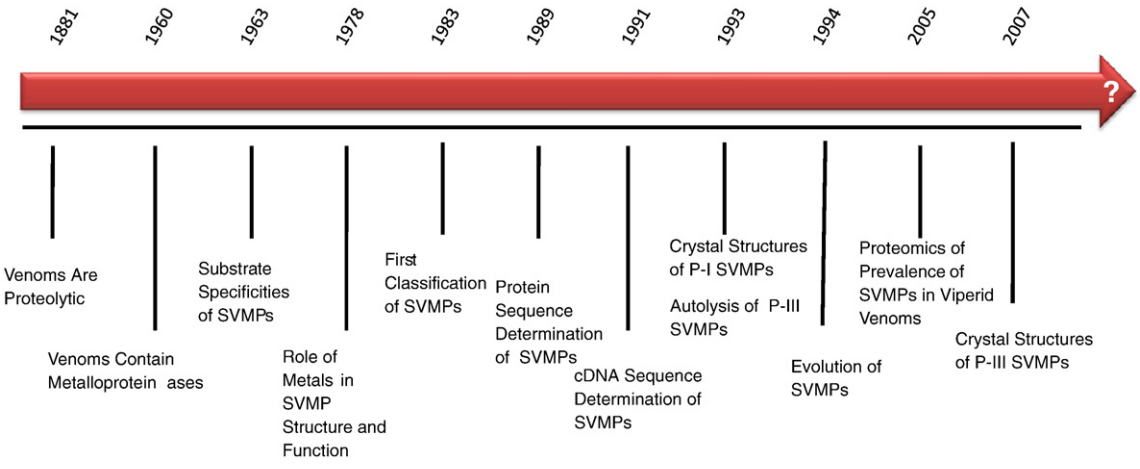


**Fig. 1 – Timeline of key events in SVMP research. The dates correspond to the publication year of the first article related to the event.**