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A rational nomenclature for naming peptide toxins from spiders and other venomous animals

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ABSTRACT

Molecular toxinology research was initially driven by an interest in the small subset of animal toxins that are lethal to humans. However, the realization that many venomous creatures possess a complex repertoire of bioactive peptide toxins with potential pharmaceutical and agrochemical applications has led to an explosion in the number of new peptide toxins being discovered and characterized. Unfortunately, this increased awareness of peptide-toxin diversity has not been matched by the development of a generic nomenclature that enables these toxins to be rationally classified, catalogued, and compared. In this article, we introduce a rational nomenclature that can be applied to the naming of peptide toxins from spiders and other venomous animals.

1. Introduction

Scientists and lay public alike have been interested in the secretions from venomous animals for many centuries. However, the modern era of molecular toxinology did not begin until the 1960s and it was driven primarily by a desire to purify and understand the mechanism of action of lethal components from medically important animals such as marine cone snails (Whysner and Saunders, 1966), stonefish (Deakins and Saunders, 1967), and snakes (Sato et al., 1969).

The pioneering work of Baldomero Olivera, Michael Adams, Lourival Possani and others in the late 1980s and early 1990s led to the realization that most animal venoms comprise a complex cocktail of peptide and protein components of which the lethal toxin often represents only a minor proportion (Olivera, 1997; Possani et al., 2000; Adams, 2004). Moreover, it gradually became clear that many of the non-lethal venom components have useful bioactivities that enable them to be deployed as research tools, such as in the characterization of ion channels (Adams et al., 1993; McIntosh et al., 1999a; King, 2007; King et al., 2008), or as leads for the development of pharmaceutical agents (Harvey, 2002; Lewis and Garcia, 2003) and insecticides (Tedford et al., 2004b; Bosmans and Tytgat, 2007). This realization, combined with the development of more sophisticated venom fractionation techniques, advances in mass spectrometry (Escoubas, 2006; Favreau et al., 2006; Escoubas et al., 2008), and the ability to directly analyze toxin transcripts from venom-gland cDNA libraries (Kozlov et al., 2005; Sollod et al., 2005), has led to a rapid increase in rate of peptide-toxin discovery during the past decade.

Unfortunately, this rapid expansion of the peptide-toxin database has not been matched by the development of a rational nomenclature for naming these toxins. In this article, we demonstrate that the number of peptide-toxin sequences being deposited in the protein and nucleic acid

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databases is growing exponentially, with the result that continued use of *ad hoc* naming schemes will introduce confusion and make it difficult to compare toxins and establish evolutionary relationships. We have therefore developed a rational nomenclature that imparts each toxin name with information about its origin and biological activity. We suggest that this nomenclature can be applied to the naming of peptide toxins from spiders and other venomous animals.

2. Results and discussion

2.1. Growth of the peptide-toxin database

We define peptide toxins as venom peptides with a molecular mass less than 10 kDa, which includes the vast majority of proteinaceous toxins from spiders, hymenopterans, cone snails, and scorpions (and a significant proportion of sea anemone and snake toxins). This cut-off value provides a clear distinction between the peptide toxins that dominate most animal venoms and larger enzymes and haemostatic factors from snakes, for which an established nomenclature already exists (Meier and Stocker, 1992).

We have used the Tox-Prot database (Jungo and Bairoch, 2005) in order to examine the rate of discovery of peptide toxins. While there are more comprehensive sequence databases available for peptide toxins from scorpions (Tan et al., 2006) and cone snails (Haas et al., 2008), the Tox-Prot database allows an objective historical comparison of the rate of discovery of peptide toxins from different venomous animals. Fig. 1 shows the growth in peptide-toxin discovery during the period 1967–2006. We have defined the year of discovery as the date in which a particular peptide sequence was first published, patented, or deposited in Swiss-Prot (Boeckmann et al., 2003). The number of peptide-toxin sequences isolated from sea anemones, cone snails, scorpions, and spiders has grown exponentially over the past decade (Fig. 1A–D), whereas the number of peptide toxins isolated from snakes has grown only linearly since 1970 (Fig. 1E).

If one considers only peptide toxins from sea anemones, cone snails, scorpions, and spiders, the cumulative total number of sequences has been growing exponentially since 1985 (Fig. 1F). Based on an extrapolation of this exponential rate of increase, the number of the peptide toxins isolated from these animals alone is expected to grow from 1111 in 2006 to ~4500 by 2015 and ~24,000 by 2025 (Fig. 2). However, these projections are likely to be underestimates and they fall well short of the millions of unique sequences projected to be present in the venoms of these animals (Table 1). The ability to sequence toxins directly from mass spectrometric analysis of venoms (Escoubas et al., 2008), as well as initiatives to sequence the genomes of venomous animals (Menez et al., 2006; Putnam et al., 2007), will further accelerate the rate of peptide toxin discovery over the next decade. Thus, in order to facilitate future cataloguing and analysis, it is imperative that a rational nomenclature be developed for naming these peptide toxins.

2.2. Extant schemes for naming peptide toxins

Several attempts have been made previously to develop a rational nomenclature for naming venom proteins. For example, in 1991, the International Society for Toxinology (IST) established a Nomenclature Committee to develop a standardized nomenclature for naming toxins from plants, bacteria, and venomous animals (Meier and Stocker, 1992). A survey of IST members carried out by this committee (Meier and Stocker, 1992) indicated that 98% of respondents favoured development of a standardized toxin nomenclature but, almost two decades later, no such system has been formulated. As a result, numerous different methods have been employed to name peptide toxins. As outlined in the following sections, these range from *ad hoc* schemes that contain no information about function or species of origin to more rational nomenclatures based on toxin origin, function, molecular scaffold, or some combination of these parameters.

2.2.1. Ad hoc *naming schemes*

The relatively small number of lethal proteinaceous toxins purified from venomous animals in the earliest period of molecular toxinology research were typically named in an *ad hoc* fashion, usually by concatenating some derivative of the genus or species name with the word "toxin". For example, the lethal peptide toxin from the Sydney funnel-web spider *Atrax robustus* was named robustoxin (Sheumack et al., 1985), whereas the toxic protein from the black widow spider *Latrodectus tredecimguttatus* was named α-latrotoxin (Tzeng and Siekevitz, 1978). While this *ad hoc* approach to naming toxins provides information about the biological origin of the peptide, it has the potential to cause confusion. For example, the lethal toxin from the Blue Mountains funnel-web spider *Hadronyche versuta* was named versutoxin (Brown et al., 1988), even though this peptide is an ortholog of robustoxin from *A. robustus* (34/42 residues are identical). Not surprisingly, these toxins have the same three-dimensional (3D) fold (Fletcher et al., 1997a; Pallaghy et al., 1997) and biological activity (Nicholson et al., 1994, 1998).

Many peptide toxins have been given trivial names based on their order of elution during a chromatographic separation procedure, such as DW13.3 (Sutton et al., 1998) and Tx4(6-1) (de Figueiredo et al., 1995). This type of naming scheme provides minimal information content with no clues about the animal from which the toxins were isolated nor their mode of action. In some cases, initials identifying the source genus and species have been attached to the toxin name, such as in the case of the ASIC1a blocker PcTx1 from the tarantula *Psalmopoeus cambridgei* (Escoubas et al., 2000). While this type of naming scheme helps with source identification, it provides no information about the molecular target of the toxin and begs the question of what name to use for other toxins isolated from the same animal, including possible paralogs.

2.2.2. Nomenclature based on primary structure and molecular target

The most comprehensive *sequence*-based toxin nomenclature is that developed by Tytgat et al. (1999), which is