Investigating Antivenom Function and Cross-Reactivity – a Study of Antibodies and Their Targets

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Snake Antivenom: an Essential Medicine – and a Black Box

Venomous snakebites are regarded as one of the World’s most neglected tropical diseases/conditions with up to 2.5 million victims every year1. The best-practice treatment for snake venom envenoming derived from the blood of large mammals (typically horses or sheep) immunized with venom of one or more snake species. The active toxin-neutralizing components in antivenom are complex mixtures of antibodies (or fragments thereof)2. The individual antibodies are adapted by the immune system of the production animal to bind specific to each toxin used in the immunization procedure. In many cases antivenom is also able to neutralize some – or even all – toxic effects of snakebites from related snake species3.

Proteomics-based studies aiming at quantifying the extent of such cross-protection of antivenoms against venoms from related snake species are referred to as antivenomics. The current state-of-the-art antivenomics protocol involves affinity chromatography of venoms with immobilized antibodies4. Although proven effective in clinical applications antivenomics fail to explain how this cross-reactivity is working at the molecular level and must be performed for one snake venom-antivenom pair at a time.

Knowledge of interactions between the immunoreactive parts (referred to as epitopes) of a toxin or macromolecule in general and the corresponding antibodies is a prerequisite to understand and predict neutralization potential of a given antivenom against any fully characterized snake venom. Although antivenom to snakebites is a more than 120 years old invention5, only little is known about the neutralizing antibodies or their epitopes6.

Ideas and Perspectives

- Identity linear peptides from snake toxins that can bind antibodies in antivenom using custom designed high-density peptide microarray technology6. See figure 1
- The microarrays in this study have shown five technical replicates of 93'261 15-mer peptides derived 966 toxins from pit viper snake species (sub-family Viperidae).
- Localize epitopes in peptide hits
- Characterizing important antibody-toxin interactions based on allowed variation of epitope
- Predict cross-reactivity of antivenoms on a protein family level and thereby expand the clinical applications of existing antivenoms to other snake species or suggest changes in immunization mixture to improve the medicine
- Learning from nature’s preferences for specific epitopes, it will be possible to estimate the number of antibodies needed to neutralize the critical toxins for any given snake species
- In the long run this may result in recombinant immunization mixtures and even lead to the first fully recombinant antivenom

References

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Figure 1 – Schematic overview of principle in peptide microarray experiments