



Research Article

Structural space of intramolecular peptide disulfides: Analysis of peptide toxins retrieved from venomous peptide databases[☆]

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ABSTRACT

Structural space of intramolecular peptide disulfides is the combination of arrangement of even number of cysteine residues in single polypeptide and the disulfide isomers resulting from differential connectivity between cysteine residues. In the current report, we are documenting theoretical analysis and derivation of general formula $[2 \times 4^{\{\frac{n}{2}-1\}}]$ to predict possible distinct cysteine patterns for given 'n' even number of cysteine residues in a sequence. Combined formula of predicting distinct cysteine patterns and different disulfide isomers can be used to deduce the truly available structural space of intramolecular peptide disulfides, which may be used in structural analysis of disulfide rich peptides and proteins. In this report, we have also analyzed cysteine patterns and disulfide connectivities of peptide toxins, which is the largest group of intramolecular peptide disulfide natural products, retrieved from publically available animal toxin databases. Observed 29 distinct cysteine patterns of toxins exhibited 61 unique intramolecular disulfide folds, with limitation of having up to eight cysteine residues in a sequence, compared to theoretically available 170 different cysteine patterns generating 13,946 distinct intramolecular disulfide folds. Database analysis of peptide toxins has also revealed the features of presence of same intramolecular disulfide motif in functionally divergent peptide toxins and adaptation of the same disulfide fold with similar functions in different venomous species. Calculations of relative accessible surface area of cystine and average value of non-cysteine residues in the representative intramolecular disulfide folds of peptide toxins has revealed the feature of poor accessibility of cystine to external agents and their dependency on number of disulfide bonds in the sequence. Implementation of new generation sequencing methods and novel disulfide mapping techniques will unravel hidden diversity of intramolecular disulfide motifs of toxins and current report points to the selection of disulfide motifs in peptide toxins.

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1. Introduction

Disulfide bond formation is the most common posttranslational modification of cysteine residues, strongest stabilizing force of conformations of polypeptide, and integral component of oxidative folding of peptide/protein (Bulaj, 2005; Fass, 2012; Borges and Lake, 2014). Disulfide bonds of peptide/proteins are broadly

classified as 'intramolecular disulfide' if disulfide occurs within the polypeptide and 'intermolecular disulfide' if disulfide occurs between the polypeptide. Even though later class of disulfide is more associated with oligomerization and quaternary structure formation, former class of disulfides are crucial in defining 3D-structure of polypeptide which is more apparent in multiple disulfide containing polypeptides (Mouhat et al., 2004; Reeks et al., 2015). Increase in the number of intramolecular disulfides in a sequence drastically increase number of disulfide isomers, imparting different 3D-structure to the same polypeptide (Gehrmann et al., 1998). Structural diversity resulting from differential disulfide connectivities is well documented in the literature with general formula to predict the possible number of disulfide isomers for given 'n' even number of cysteine residues (or) number

Abbreviations: IPDM, intramolecular peptide disulfide motif; ATAP, animal toxin annotation project; PDB, Protein Data Bank; RASA, relative accessible surface area; ICK motif, Inhibitory Cystine Knot motif.

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of disulfides in the sequence (Kauzmann, 1959; Benham and Jafri, 1993; Bhattacharyya et al., 2013). However, the true structural diversity of multiple disulfides containing polypeptides not only depends on disulfide connectivity but also on arrangement of even number of cysteine residues in the sequence which is often termed as 'cysteine pattern' or 'cysteine frame work'. In the current report, we are documenting the general equation to predict possible number of distinct cysteine patterns for given even number of cysteine residues in the sequence. Manual inspection and combination approach was employed to deduce the possible cysteine patterns for two, four, six and eight cysteine residues in a sequence which was eventually used to derive the formula to predict possible cysteine patterns for given even number of cysteine residues in a sequence. The combined formula of prediction of disulfide isomers and cysteine patterns can be used to deduce the truly available structural space of intramolecular peptide disulfide motifs (IPDMs).

Enormous diversity of IPDMs in venoms has raised curiosity to investigate the occurrence of cysteine patterns and disulfide isomers of peptide toxins derived from different venomous species. Intensive research in the area of venoms has revealed wealth of information about peptide toxins which are readily available in public databases such as Animal toxin annotation project of Uniprot (Jungo et al., 2012), ConoServer (Kas et al., 2012), ArachnoServer (Herzig et al., 2011), and Animal toxin database (He et al., 2008). We have manually scrutinized entries of toxins in the above databases and information is drawn with respect to cysteine pattern, disulfide connectivity, 3D-structure, and molecular target of peptide toxins containing up to four intramolecular disulfides in the sequence. The database analysis has revealed presence of 29 distinct cysteine patterns in peptides toxins. These patterns eventually resulted 61 different disulfide folds through disulfide connectivity. Interestingly, structural diversity resulting from differential disulfide connectivities was not prominent in peptide toxins. Analysis of disulfide folds in the databases has also revealed the features of presence of the same intramolecular disulfide folds in functionally divergent peptide toxins, as evident in the case of ICK motifs containing peptide toxins. Intramolecular disulfide folds of peptide toxins were further subjected to analysis through calculation of relative accessible surface area of cystines and average value of non-cysteine residues in native fold of toxin using ASA view tool (Ahmad et al., 2004). It is found that cystines in natively folded toxins are poorly accessible to external agents and this tendency is dependent on number of intramolecular disulfide bonds in the sequence. The results of present studies may be of interest for the growing field of venomics, must be viewed in future expansion of structural space of toxin disulfide folds and points to the selection of intramolecular disulfide folds in peptide toxins.

2. Materials and methods

2.1. Theoretically available structural space of intramolecular peptide disulfides

In the following section, we are deducing general formula to predict number of distinct cysteine patterns for given even number of cysteine residues in the sequence. Cysteine pattern can be defined as relative position of occurrence of cysteine residues within a sequence which may have variable number of non-cysteine residues between separated cysteines. To generate all possible patterns for given even number of cysteine residues, we have started with a pattern where all cysteine residues are together and then separated one, two, three, etc cysteines from left to right to achieve other different patterns. Unidirectional separation of cysteines was undertaken to avoid confusion like one cysteine separation from left will be the same as three cysteine separations from right in consecutive four cysteine residues in the sequence. Table 1 provides summary of generation of distinct cysteine patterns for given even number of cysteine residues in the sequence.

Distinct cysteine patterns for 'n' even number of cysteine residues in the sequence forms a series

$$=2, 8, 32, 128 \dots$$

$$=2 (1, 4, 16, 64 \dots)$$

Series 1, 4, 16, 64 . . . is a geometric progression with first term $a=1$ and common ratio $r=4$.

The n^{th} term of this geometric progression series is = $\left[2 \times 4^{\left(\frac{n}{2}-1\right)}\right]$

Note: Inclusion of term $\left(\frac{n}{2}\right)$ in the formula will eventually give positive integer greater than one.

Three different formulas were proposed to predict i^{th} number of ways intramolecular disulfide bridges can be connected to result distinct disulfide isomers.

$$i = \frac{(2n)!}{2^n \times n!}$$

where 'n' represents number of disulfide bonds (Kauzmann, 1959; Benham and Jafri, 1993).

$$i = \frac{n!}{\left(\frac{n}{2}\right)! \times 2^{n/2}}$$

where 'n' represents even number of cysteine residues (Bhattacharyya et al., 2013).

$$i = (n-1) \times (n-3) \times (n-5) \dots \dots 1$$

where 'n' represents even number of cysteine residues. Note: This formula requires manual intervention during prediction of disulfide isomers.

Total structural space of intramolecular peptide disulfides is combination of distinct cysteine patterns and possible number of disulfide isomers. We have chosen second formula in the above list

Table 1

Possible number of distinct cysteine patterns for given even number of cysteine residues in the sequence.

Even number of cysteine residues (No. of intramolecular disulfides)	Number of patterns for each separation of cysteine from cluster	Total number of distinct cysteine patterns
2 (1)	1 + 1	2
4 (2)	1 + 1 + 2 + 4	8
6 (3)	1 + 1 + 2 + 4 + 8 + 16	32
8 (4)	1 + 1 + 2 + 4 + 8 + 16 + 32 + 64	128

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