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In silico tools for the assessment of newly expressed proteins in GMOs

Toxicity

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Scientific Officers

Trusted science for safe food

efsa
European Food Safety Authority

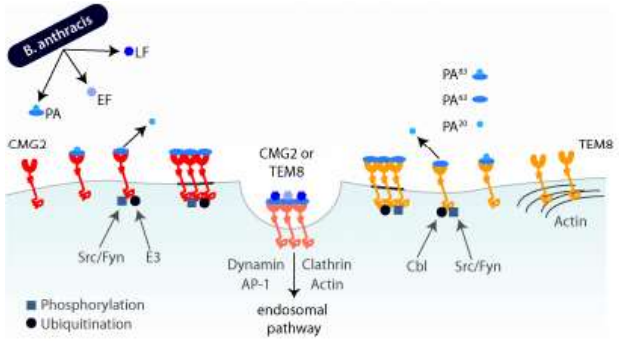
IN SILICO TOOLS - TOXICITY

- The present

- The current *in silico* investigations on proteins in GMO dossiers are based on comparisons of the protein sequence to company in-house databases

- Limitations

- Sequence similarity cannot be used as sole criterion for characterising a protein as a toxin:
  - 3D structures are relevant
  - complex formation
  - specific protein binding/active sites
  - databases comprehensiveness as regards experimentally validated toxins



Friebe,S et al., 2016 Toxins, 8, 69

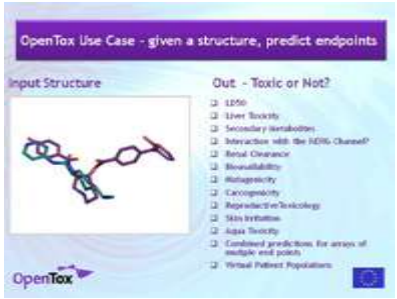
Is a better approach possible?
Are there protein predictive toxicity tools useful for GMO RA?

IN SILICO TOOLS - TOXICITY

- Predictive protein toxicity tools in RA

Differently from the small molecules area

- no fit-for-purpose tools
- incomplete knowledge on the determinants of pathogenetic effects



- The future

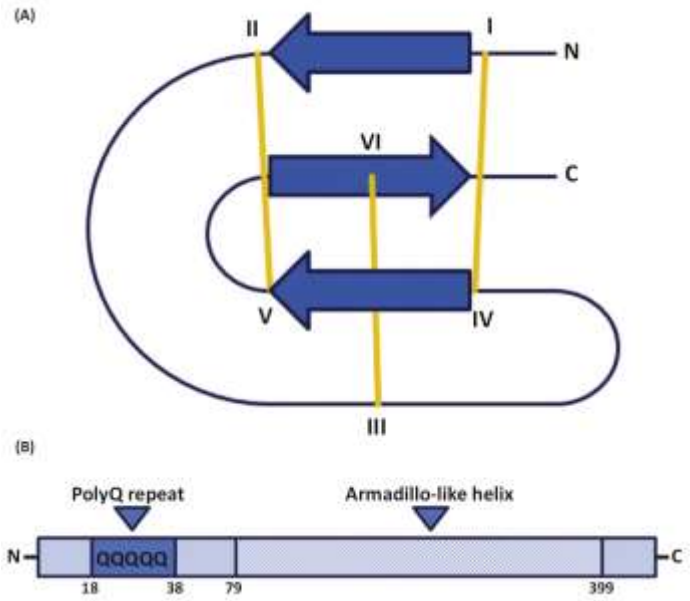
Extensive information is now available in public databases and can serve as the basis for establishing *in silico* tools to determine the potential for protein toxicity

- 3D structures
- protein biological function
- molecular pathways
- **"molecular signatures" (motifs, domains)**

EXAMPLES

Motif analysis

homologous proteins with similar function share similar motifs (critical region relevant for function and folding), even when the overall identity is low (20-30%).



A clear consensus sequence that can be reliably identified

Franceschi et al, 2017
Trends in Biotechnology, 2017, 35, 483

Structural Representation of the (a) Inhibitor Cystine Knot (ICK) and (b) Polyglutamine (polyQ) Motifs.

EXAMPLES

Domain analysis

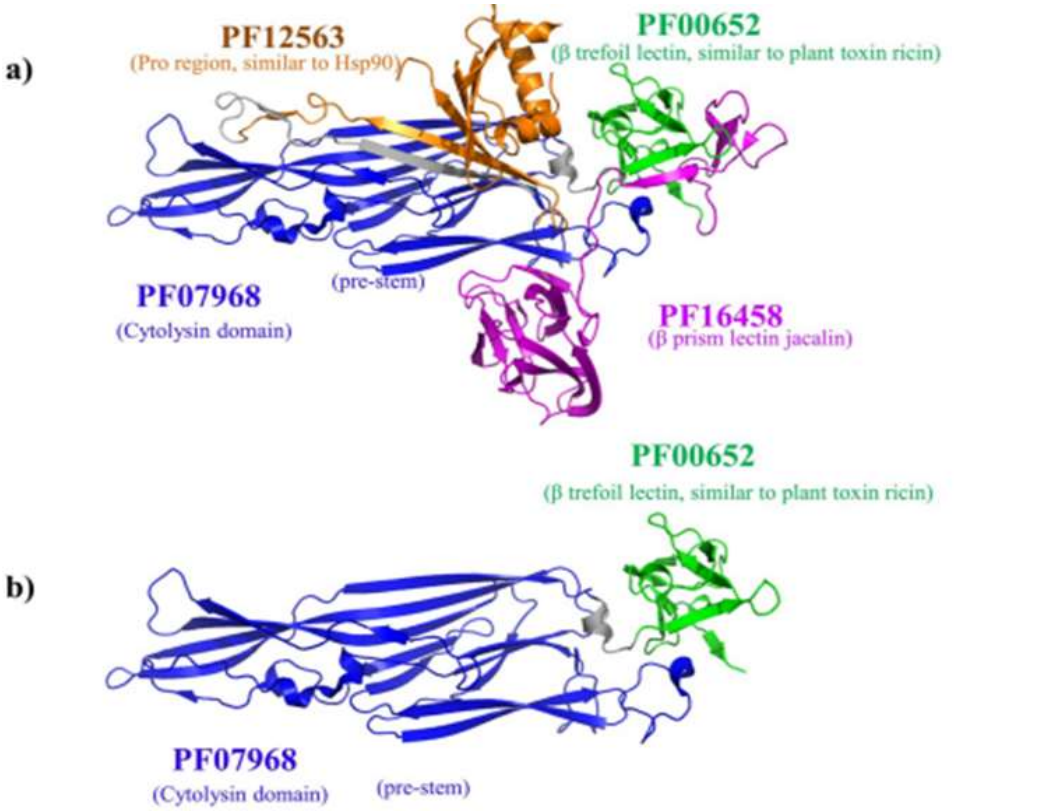


Figure 5. Domain structures of the hemolysins from *Vibrio cholera* (**a**) and *Vibrio vulnificus* (**b**). The membrane-active form of both is a heptameric, pore-forming structure.

Negi et al, 2017
Scientific Reports 7: 13940

IN SILICO TOOLS - TOXICITY

NP/EFSA/GMO/2018/01

Literature search – Exploring in silico protein toxicity prediction methods to support the food and feed risk assessment

1. Identifying, list and cluster proteins known to be associated with adverse effects in humans and animals
2. Identifying molecular signatures (e.g. motifs, domains) of these "toxic" proteins and the pathogenesis leading to adverse effects in humans and animals.
3. Identifying available databases and evaluate their relevance with respect to the scope.

Deadline: January 2020

QUESTIONS FOR DISCUSSION

- Would MS welcome the development of robust predictive toxicity tools, database/strategies supporting the GM protein safety assessment, improving the current strategy and (possibly) substituting animal studies?

- Is there any similar exercise currently undertaken or planned by MS?

- Proteins as chemicals - read across and TTC: a dream or a possibility?

- Any suggestions?

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