Digital development of peptides against Bax-induced apoptosis

Ioana M. ILIE, Bernadette Mayer, Tom Vlaar, Lars van der Heide

University of Amsterdam (van 't Hoff Institute for Molecular Sciences, University of Amsterdam, Science Park 904, Amsterdam, the Netherlands)
i.m.ilie@uva.nl

The proteins in the Bcl-2 family play crucial roles in regulating apoptosis. In particular, Bax is a proapoptotic protein that was linked to cellular death when it is activated and translocates to the mitchondria. Hence, targeting this protein represents an attractive therapeutic approach, which can aid in regulating apoptotic signalling and potentially contribute to the development of novel therapies against cancer and neurodegenerative diseases.

Here, we introduce a digital paradigm, which relies on rational design and computer simulations to develop and validate peptide-based agents that bind to Bax, thereby inhibiting its apoptotic properties. The peptides were rationally designed and optimized to bind to Bax starting from the crystal structures of affimers in complex with Bcl-2 proteins. Next, molecular dynamics simulations (MD) were employed to probe the stability of the Bax-peptide complexes and to estimate the binding free energies. Finally, the peptides were experimentally validated.

The results show that the designed peptides bind with high affinity to Bax, particularly in the canonical hydrophobic groove. Two of the designed peptides bind in the canonical hydrophobic groove (BH1 domain) of Bax and one peptide binds to the outside of the BH3 domain (α2-helix). Notably, the peptides restrict the flexibility of the α1-α2 loop, closing off the bottom trigger site associated with toxicity. Experimental validation shows the protective properties of the digitally designed peptides.

All in all, the results highlight the potential of these peptides as valuable tools for further exploration in modulating apoptotic pathways.