Nostatin A mode of action: New hypotheses suggesting possible mechanisms involved

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Nostatin A (NosA) is an extensively modified ribosomally synthesized and post-translationally modified peptide (RiPP) belonging to the classification of nitrile hydratase-like RiPP leader peptides (proteusins) derived from the terrestrial cyanobacterium Nostoc sp. NosA is characterized by a peptide core of 30 amino acids and exhibits a rare combination of structural elements not previously found in RiPP. These include the co-occurrence of oxazole and thiazole heterocycles, and dehydrobutyrine or dehydroalanine residues linked by a unique sanctipeptide linkage. Interestingly, NosA also has an isobutyl-modified proline residue, which is unusual in natural products.

NosA can inhibit the growth of several cancer cell lines at low nanomolar concentrations without inducing hemolytic activity. It causes the cell cycle arrest during the S-phase leading to mitochondrial apoptosis by a mechanism distinct from known tubulin binding and DNA damaging agents.

In my talk, I will focus on the methods used to find a specific molecular target of NosA or a pathway directly affected by its action. In particular, I will focus on omics methods that have yielded interesting insights into nostatin mode of action that helped us to formulate relevant working hypothesis.

Preliminary results suggest that NosA induces endoplasmatic reticulum (ER) stress in a very short time which is accompanied by significant changes in the lipidomic profile of tumor cell lines. However, it remains an interesting question whether, changes in the cellular lipidome cause ER stress or vice versa. Elucidating this question remains a major challenge for us.