Novel ribosomally synthetized and post-translationally modified peptide nostatin A with potent anti-cancer activity: current state and future.

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Aside from well known biactive peptides synthetized via nonribosomal peptide synthetazes procaryotes produces wide variety of ribosomall peptides that are heavilly moddified via postraslational modification (RiPPs). We have discovered a new cyanobacterial RiPP that we dubbed nostatin A based on its cytostatic mode of action and the producing organism *Nostoc* sp. C33. Along with the compound discovery we have also obtained the gene cluster responsible for nostatin A biosynthesis. The gene cluster featured a typical architecture for RiPPs possessing a leader peptide (recognition site for protease) and a precursor peptide (the future peptide product). The 30-AA sequence of the nostatin A precursor peptide is consistent with detailed inspection of the HRMS/MS data, when considering the predicted posttranslational cyclodehydration and dehydrogenation of the serine and threonine residues into oxazoles and thiazoles by means of encoded cyclodehydratase and oxazoline oxidase, and formation of dehydroalanine from serine by LanM-like dehydratase, as frequently reported in RiPPs. The specific feature of nostatin A is a modified proline residue which appears to be responsible for the compound bioactivity. The structure very likely also possess thioether crosslinks installed by the LanM-like enzyme making the structure multicyclic.

In this talk I will focus on the on the novel insight into nostatin A structure which is torturing our laboratory for past 5 years. I will also present the future research line which will be aimed on the discovery of nostatin A molecular target via methods of chemical proteomic and genome-wide CRISPR-Cas9 screen.