Molecular recognition in bitter taste GPCRs

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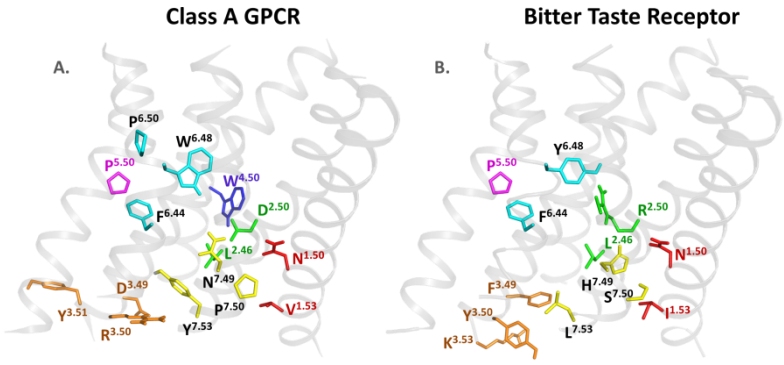

Bitter taste is one of the basic taste modalities and is typically considered as anti-ingestive signal against poison consumption. Bitter taste perception is mediated by bitter taste receptors (T2Rs), a subfamily of G-protein coupled receptors (GPCRs). [1] Recently T2Rs were shown to be expressed extraorally, emerging as potential novel drug targets, and a better understanding of molecular recognition of bitter compounds may be helpful not only for rational design of functional foods but also to discover novel drugs.

In this talk, I will present our research on exploring T2R molecular recognition and activation mechanisms using computational approaches. Integrating structure modeling and docking simulations with experimental mutagenesis studies, we found that the ligand binding pocket of T2Rs coincides with the canonical binding site of GPCRs. [1, 2] However, T2Rs similarity to Class A GPCRs is very low (13-29% for the TM domains) and this difference can be noticed not only in the binding site composition, but also in the regions of some typical Class A sequence motifs (shown above), such as the TM3 D[E]RY and the ECL2-TM3 disulfide bridge. [3] Since most of the conserved motifs are involved in GPCR activation mechanism, the differences in conserved residues suggest an alternative mode of regulating conformational states, with possibly a less stabilized inactive state for T2Rs compared to Class A GPCRs. Moreover, most of the known bitter ligands are agonists, with only a few antagonists documented thus far. The agonist-to-antagonist ratios of GPCRs are much lower than for T2Rs. We have previously found that GPCR promiscuity towards antagonists correlates with binding site exposure and hydrophobicity, [4] and similar features were also found to underlie the promiscuity of T2Rs towards their agonists. [5] Our findings show that, while promiscuity towards ligands is a general GPCR feature, T2Rs are unique in terms of their high agonist-to-antagonist ratio and overall low affinity towards ligands. [3] These characteristics may be related to the T2R sequence and structural motifs, but require further investigation.

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References:

[1] A. Di Pizio, M.Y. Niv, *Israel Journal of Chemistry*, **2014**, 1205-1218.
[2] R. Karaman R, S. Nowak S, A. Di Pizio, H. Kitaneh, A. Abu-Jaish, W. Meyerhof, M.Y. Niv, M. Behrens Y. *Chemical Biology & Drug Design*, **2016**, doi: 10.1111/cbdd.12734.
[3] A. Di Pizio, A. Levit, M. Slutzki, M. Beherens, R. Karaman, M.Y. Niv, *Methods in cell biology*, **2016**.
[4] A. Levit, T. Beuming, G. Krilov, W. Sherman, M.Y. Niv, *J Chem Inf Model*, **2014**, 184-194.
[5] A. Di Pizio, M. Y. Niv, *Bioorg Med Chem*, **2015**, 4082-4091.