KHNYN is a Zinc-Finger Antiviral Protein (ZAP) co-factor that degrades ZAP-bound RNA

Zoe Yeoh[1], Jennifer Meagher[2], Chia-Yu Kang[3], Jennifer Bohn[4], Paul Bieniasz[5], Melanie Ohi[6], Janet Smith[7]

[1]University of Michigan [2]University of Michigan, [3]Biophysics at Michigan, University of Michigan, Ann Arbor, MI, USA, [4]Laboratory of Retrovirology, The Rockefeller University, New York, NY, USA, [5]The Rockefeller University - HHMi, [6]University of Michigan, [7]Life Sciences Institute, University Of Michigan
zyeoh@umich.edu

The human genome is CpG-suppressed due to the methylation and subsequent deamination of cytosines to uracil in open chromatin, leading to the conversion of the complementary nucleotide to an adenine by DNA repair pathways. This leads to CpG-poor mRNA, which is used as a molecular marker by host cells to distinguish between self mRNA and CpG-enriched viral RNA during infection. A protein called Zinc finger Antiviral Protein (ZAP) binds CpG dinucleotides, leading to degradation of viral RNA1–3. However, ZAP has no intrinsic RNase activity. It is thought that this activity is provided by KHNYN, a ZAP co-factor4. KHNYN has three domains – a KH (K-Homology) domain with predicted RNA binding activity; an NYN (N4BP1, YacP-like Nuclease) domain with predicted RNase activity; and a C-terminal domain (CTD). However, how KHNYN and ZAP act together to promote RNA degradation is not understood and is the focus of these studies.

We are using biochemical and structural approaches to address the function of three KHNYN domains and to test whether KHNYN acts as an RNase for ZAP. Our biochemical and structural results show that the KH domain does not bind RNA. We also found that while the KHNYN NYN domain is a poor RNase on its own, when complexed with ZAP it rapidly hydrolyzes RNA irrespective of the CpG content. Finally, the KHNYN CTD is essential for binding to ZAP. Together, these results support a model where ZAP and KYNYN form a complex that facilitates the binding and degradation of single-stranded RNA.

References:
Gao et al. Science 297, 1703-1706 (2002).
Takata et al. Nature 550, 124-127 (2017).
Meagher et al. PNAS 116, 24303-24309 (2019).
Ficarelli et al., eLife, 8, e46767 (2019).