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MPI-NAT SEMINAR SERIES

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Deciphering the cnidarian antiviral immune system sheds light on the early evolution of animal immunity

The fast co-evolution of viruses and host antiviral systems can result in blurry homology or even in shifts of whole defense mechanisms between species. In vertebrates such as mammals and fish, the antiviral immunity is heavily based on the interferon pathway whereas in the case of invertebrates the antiviral immunity is believed to be based mostly on an RNA interference (RNAi). Until now, the recognition mechanism and mode of action of such systems were studied mostly in vertebrates (human and mouse), insects (*Drosophila*) and nematodes (*C. elegans*). From this limited phyletic sampling, it is impossible to deduce what was the original mode of action of these systems in their last common ancestor and how antiviral immunity was triggered in early animals. To attain novel insights into the evolution of this system, we study it in an outgroup: the sea anemone *Nematostella vectensis*, which represents Cnidaria, a phylum that separated from the rest of animals 600 million years ago. We harness the genetic and molecular tools available for this species to decipher the cnidarian system for battling RNA viruses and answer the outstanding questions regarding the evolution of antiviral immunity and its ancestral state in animals. We showed that like bilaterian animals *Nematostella* reacts transcriptionally to the viral hallmark of long (200-7000 bp) double-stranded RNA (dsRNA). However, unlike vertebrates and nematodes, *Nematostella* is not differentially-responsive to short and long dsRNA carrying or lacking the viral hallmark of 5′-triphosphate group. Our transcriptomic and proteomic results for long dsRNA challenge put in question the textbook dichotomy between the antiviral immune systems of vertebrates and invertebrates as we find upregulated components of both systems in *Nematostella*. These findings support the intriguing scenario that the ancient intracellular antiviral innate immunity system which was present in the last common ancestor of Cnidaria and Bilateria was in several aspects more complex and diverse than the systems found in extant vertebrates and protostomes such as arthropods and nematodes. To gain further mechanistic insight into the cnidarian antiviral system we generated by applying CRISPR/Cas9 in *Nematostella* mutants for genes suspected based on homology to take key roles in dsRNA detection and activation of the cnidarian immune system. These include two RIG-I-Like Receptors (RLRs), Mitochondrial antiviral-signaling protein (MAVS) and oligoadenylate synthase (OAS). Transcriptomic analyses of mutants challenged with dsRNA reveal that indeed these components are crucial for the cnidarian response and that some of the components specialize in regulating different arms of the immune system.

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