Pan-Phylum Characterisation of Helminth Endocannabinoid Signalling Systems

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Parasitic helminths are responsible for a range of debilitating neglected tropical diseases (NTDs) and agricultural infections, inflicting a significant global burden on human, plant and animal health. Overreliance on a handful of frontline anthelmintics has accelerated the threat of drug resistance, highlighting an urgent need for novel drug target identification and validation. Endocannabinoid signalling (ECS) is currently a hot topic in vertebrate medicine where ECS therapeutics are becoming attractive options for the treatment of many conditions. Our knowledge of helminth ECS systems is limited; in nematodes data is primarily derived from the model species *Caenorhabditis elegans,* where the ECS appears to modulate several facets of neurobiology (e.g., motility, growth, lifespan and fertility). Most interestingly, homologues of the mammalian EC G-protein coupled receptors (EC-GPCRs) CB1 and CB2 appear absent in nematodes including *C. elegans*, instead the nematode-specific EC-GPCRs NPR-19 and NPR-32 have been implicated in nematode EC signalling. We have no information on ECS system presence or function in flatworms. To broaden our understanding of helminth ECS systems and identify putative novel targets for helminth control we employed publicly available genome and transcriptome data and *in silico* bioinformatics approaches to examine the presence, conservation and life-stage specific expression profiles of ECS pathway proteins (biosynthesis/degradation enzymes and EC receptors) in all helminths that possess genome/transcriptome information (93 nematode spp, 33 flatworm spp (134 and 44 genomes respectively). The data demonstrate that: (i) Nematode ECS pathways exhibit increased complexity in comparison to vertebrate systems; (ii) ECS signalling effectors display broad patterns of conservation across phylum Nematoda and Platyhelminthes, including in therapeutically and agriculturally important species; (iii) Flatworms possess a putative novel EC-GPCR that is broadly conserved pan phylum (present in 82% of 33 flatworms investigated), has key EC-binding domains and displays ~40% homology to vertebrate CB1; (iv) EC-effectors are expressed in therapeutically relevant parasitic nematode life stages (i.e. infective larval and intra-mammalian life stages) suggesting a role for the ECS in parasite host-seeking, invasion and infection biology. These data have informed our understanding of the complexity of helminth ECS pathways and will seed follow-on functional studies underpinning ECS drug target validation in parasitic helminths of importance.