Two Virus-Induced MicroRNAs Known Only from Teleost Fishes Are Orthologues of MicroRNAs Involved in Cell Cycle Control in Humans

MicroRNAs (miRNAs) are similar to 22 base pair-long non-coding RNAs which regulate gene expression in the cytoplasm of eukaryotic cells by binding to specific target regions in mRNAs to mediate transcriptional blocking or mRNA cleavage. Through their fundamental roles in cellular pathways, gene regulation mediated by miRNAs has been shown to be involved in almost all biological phenomena, including development, metabolism, cell cycle, tumor formation, and host-pathogen interactions. To address the latter in a primitive vertebrate host, we here used an array platform to analyze the miRNA response in rainbow trout (Oncorhynchus mykiss) following inoculation with the virulent fish rhabdovirus Viral hemorrhagic septicemia virus. Two clustered miRNAs, miR-462 and miR-731 (herein referred to as miR-462 cluster), described only in teleost fishes, were found to be strongly upregulated, indicating their involvement in fish-virus interactions. We searched for homologues of the two teleost miRNAs in other vertebrate species and investigated whether findings related to ours have been reported for these homologues. Gene synteny analysis along with gene sequence conservation suggested that the teleost fish miR-462 and miR-731 had evolved from the ancestral miR-191 and miR-425 (herein called miR-191 cluster), respectively. Whereas the miR-462 cluster locus is found between two protein-coding genes (intergenic) in teleost fish genomes, the miR-191 cluster locus is found within an intron of a protein-coding gene (intragenic) in the human genome. Interferon (IFN)-inducible and immune-related promoter elements found upstream of the teleost miR-462 cluster locus suggested roles in immune responses to viral pathogens in fish, while in humans, the miR-191 cluster functionally associated with cell cycle regulation. Stimulation of fish cell cultures with the IFN inducer poly I:C accordingly upregulated the expression of miR-462 and miR-731, while no stimulatory effect on miR-191 and miR-425 expression was observed in human cell lines. Despite high sequence conservation, evolution has thus resulted in different regulation and presumably also different functional roles of these orthologous miRNA clusters in different vertebrate lineages.