STAT6 NEGATIVELY REGULATES TBK1-TRIGGERED IFNΦ1 ACTIVATION IN ZEBRAFISH

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ABSTRACT

Mammalian STAT6 plays a crucial role in lymphocyte differentiation and proliferation in adaptive immunity, and recently, studies have showed that it can be regulated by TBK1 to promote the transcriptions of CCLs in innate immunity. Whether STAT6 is involved in innate immunity in lower vertebrates is unclear. In this study, we reported that zebrafish STAT6 suppressed TBK1 phosphorylation, resulting in the decrease of IFN expression. Firstly, a typical ISRE motif was found from the promoter region of zebrafish *stat6*, whereas it is absent in human *stat6*; and the transcription of zebrafish *stat6* was upregulated significantly in the early stage after virus infection. These indicated that fish STAT6 might be involved in host defense to virus. Subsequently, overexpression of STAT6 impeded the IFNφ1 promoter activity induced by SVCV or poly I:C; Furthermore, TBK1-, but not MITA-mediated activation of IFNφ1 promoter was impaired by STAT6. Co-IP and Western blot experiments indicated that MITA and IRF3 were significantly phosphorylated by TBK1, and the N-terminal kinase domain of TBK1 was indispensable. Meanwhile, STAT6 could bind the kinase domain of TBK1, which dephosphorylated TBK1 and then resulted in the reduction of IFNφ1. Finally, zebrafish STAT6 distributed in both nucleus and cytosol, suggesting that it may play roles not only as a transcriptional factor, but also in cytoplasmic signaling transduction. Taken together, these data demonstrated that fish STAT6 can attenuate the kinase activity of TBK1, leading to the suppression of IFNφ1 expression, indicating that a novel function of STAT6 exists in lower vertebrate.

KEYWORDS

STAT6; Negative regulator; Interferon; TBK1; Zebrafish

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