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# Identification and characterization of a tumor necrosis factor receptor like protein encoded by Singapore grouper iridovirus



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#### ABSTRACT

Virus encoded tumor necrosis factor receptors (TNFRs) have been demonstrated to facilitate virus to escape from apoptosis or other host immune response for viral replication. Singapore grouper iridovirus (SGIV), a large DNA virus which belongs to genus *Ranavirus*, is a major pathogen resulting in heavy economic losses to grouper aquaculture. Here, SGIV ORF096 (VP96) encoding a putative homolog of TNFR was identified and characterized. Multiple sequence alignment indicated that SGIV-VP96 contained two extracellular cysteine-rich domains (CRDs) with conserved four or six cysteine residues, but lacked the transmembrane domain at the C-terminus. SGIV-VP96 was identified as an early (E) gene and localized in the cytoplasm in transfected or infected cells. Overexpression of SGIV-VP96 *in vitro* enhanced cell proliferation, and improved cell survival against SGIV infection. Furthermore, virus infection induced apoptosis and caspase-3 activity were inhibited in SGIV-VP96 expressing FHM cells compared to the control cells. Taken together, our results suggested that SGIV might utilize virus encoded TNFR like genes to modulate the host apoptotic response for effective virus replication.

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#### 1. Introduction

Apoptosis is an important event in the normal development and homeostasis of multicellular organisms, and considered to be a host defense mechanism against viral replication. Apoptosis was also utilized for viruses to evade the host immune system to ensure viral replication, propagation, and persistent infection (Rahman and McFadden, 2006). Increasing evidences revealed that viruses could encode TNFR homologs and hijack the cellular TNF/TNFR pathway to favor viral infection by regulating the host apoptotic response (Benedict et al., 2003). Several viral TNFR homologs have been identified in the genomes of large DNA viruses, including poxvirus, herpesvirus, iridovirus and African swine fever virus (ASFV) (Arav-Boger et al., 2006; Poole et al., 2006; Saraiva et al., 2002; Sedger et al., 2006). To escape from the host immune response, these vTNFR homologs mimicked function by sequestering host cytokines in distinct ways and at different stages of the immune response. The Myxoma virus T2 protein (M-T2) could inhibit TNF $\alpha$ -mediated cytotoxicity and virus-induced lymphocyte apoptosis (Sedger and McFadden, 1996). CrmE protected cells only from the cytolytic activity of human TNF (Reading et al., 2002). To our knowledge, information concerning the function of vTNFR homologs from lower vertebrate virus remains largely unknown.

Iridoviruses are large DNA viruses, and the family iridoviridae are currently divided into five genera: Ranavirus, Lymphocystivirus, Iridovirus, Chloriridovirus and Megalocytivirus (Jancovich et al., 2011). It has been reported that typical apoptosis was evoked by iridovirus infection, including Chilo iridescent virus (CIV), red sea bream iridovirus (RSIV), lymphocystis disease virus (LCDV), Rana grylio virus (RGV), soft-shelled turtle iridovirus (STIV), frog virus 3 (FV3) and grouper iridovirus (GIV) (Chitnis et al., 2008; Huang et al., 2011a,b, 2007a; Pham et al., 2012; Imajoh et al., 2004; Hu et al., 2004; Chinchar et al., 2003). Singapore grouper iridovirus (SGIV), a novel ranavirus, was isolated from diseased grouper (Oin et al., 2001). Previous studies demonstrated that SGIV infection induced typical apoptosis in Fathead minnow (FHM) cells (Huang et al., 2011a,b). Based on the elucidation of SGIV genome, some potential viral gene products were predicted to be associated with apoptosis, including a lipopolysaccharide-induced TNF-a factor (LITAF) homolog and three TNFR homologs (Huang et al., 2008; Song et al., 2004). Whether SGIV TNFRs could regulate apoptosis during SGIV infection remains unknown.

In the present study, we firstly described a TNFR like gene encoded by SGIV ORF096 (VP96). SGIV-VP96 was able to increase the cell proliferation, and suppressed virus infection induced apoptosis in FHM cells. These results not only provided new insight

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CRD1			
SGIV-VP96 :MLVVEMLAYLVVYVESI CSDSDHTYTHTDATPVASQGACGSPGFKVASHGSW-SAPTVCVFGIV-TNFR :MLVVGMLAYLVSVESI CSDSDHTYTHTDATGVVSQGACGSPGFKVASHGSW-SAPTVCVF	]:	6	60
GIV-TNFR :MLVVGMLLAYLVSVESI CSDSDHTYTHTDATGVVSQCACCSPCFKWASHCSW-SAPTVCVF	:	6	60
LCDV-C :MIKIKILLLLYWFPVYQCLTYERAVVFPNGTKIILTCPACKSGEKLDSYCNI-THTTACLT	1:	6	60
M-T2 :MFRLTLLLAYVACVYGQGAPYGADRGKCRGNDYEKDGLCCTSCPPGSYASRLCGP-GSDTVCSF			33
Danio Fas :TYQHERNTCCLCPACFKVSTHCTN-TDKTECKC			51
Danio TNFR1:MTVVWLLAEGKIPPPYRPEKEQCNNTTSEYYMKQLGLCCSRCKPGTRLSVQCST-ASDTVCEF			52
rainbow :LHDASGVKRCCERCRKCQYVRTDCGK-STKTECET			15
Atlantic : MDVLRGKWKEKCILNVCALLVLCWSVDPYLLAPPPEGSQCPDGSHYHNANGTCORKCHEGFKLKEHCTKDGENSQCVFHomo :MGLSTVPDLLLPLVLLELLVGIYPSGVIQLVPHLGDREKRDSVCPQGKYIHPQNNSICOTKCHKGTYLYNDOPGPGQDTDGRE			78
Homo :MGLSTVPDLLLPLVLLEL VGIYPSGVIQ LVPHLGDREKRDSVCPQGKYIHPQNNSIC TKCHKCTY YND PGPGQD D GREEN * * * * * * * * * * * * * * * * * *	]:	٥	33
CRD2			
SGIV-VP96 : CGNE-SYMNACTSSKNOVICHTHCAHDELIK-CAGTTDRVCC	:	10	
GIV-TNFR : GGNE-SYMNVYTSSKNGYICHTHCAHDELIK-GAGTADRYCG	:	10	)0
LCDV-C : CPKN-QYTPYDNYGPNCMSC-TKCKHPKVELSP-CTPATNRQCGCKNGYYENNNNCIKCSICYLGEGVEEPCSSNSNT	:	13	35
M-T2 : CKNE-TETASTNHAPACVSCRGRCTGHLSESQS-ODKTRDRVCDCSAGNYCLLKGQEGCRICAPKTKCPAGYGVSGHT			
Danio Fas : CEDG-YYLNNNNENQCRPCKICDANAKMKEIEKCSKSSNTVCCCEEGGFCDKDK		10	
Danio TNFR1: CPDG-MYSENMNHYPNGFKCPTCREEKGLMYGRNGSADTKAVCYCKPGMYCSKYGFSSACEECKKHKTCKPGEGAQRKGTPTGVV rainbow : CQHE-YYTAELNFLKQCLPCRVCYSSSNQKVLREGEASS RQCYCKTGYYCTDDGCEHCLPVTLCPLGSGVVNQANPQNDT	:	14	ΣΕ ΕΦ
rainbow : CQHE-YYTAELNFLKQCLPCRVCYSSSNQKVLRECEASSDRQCYCKTGYYCTDDGCEHCLPVTLCPLGSGVVNQANPQNDT Atlantic : CEEGRTYREKSNYVKTCLRCTLCVDNEEEESPCKKSSNTLCRCKKGFYKNRINSETRECLSCKTCGPGERETQPCTQESDT			
Homo : CESG-SFTASENHLRHCLSCSKCRKEMGQVEISSCTVDRDTVCGCRKNQVRHYWS-ENLFQCFNCSLCLNGTVHLSCQEKQNTV			
* * * * * * *	•	10	,,,
<u>_</u>			
SGIV-VP96 :KYGSVRPHCACDNCASCNVG	:	12	20
GIV-TNFR :KYEPVRPHCACDN	:	12	20
LCDV-C : KCKVCLHETFSNVISSEEPCKPYQNCTIGTKSLNFELSWYDKFCLNCTIF	:	18	35
M-T2 : RTGDVLCTKCPR-YTYSDAVSSTETGTSSFNYISVEFNLYPVNDTSCTTT	:	18	38
Danio Fas :GVNCYPCDPQPNGVKE	:	12	22
Danio INFRI: KCAPCPIGIFSD-RSGSEPCRPHIKCEGSAVLRSGNSIDDIVCVVKPLKAIPEIWPMNIISISIVSV	:	21	.2
SGIV-VP96 :		20	1
Homo : CTCHAGFFLRENECVSCSNCKKSLECTKLCLPQIENVKGTEDSGTTVLLPLVIFFGLCLLSLLFIGLMYRYQRWKSKLYSIVCGK		25	74 50
- · · · · · · · · · · · · · · · · · · ·	•	20	10
SGIV-VP96 : MATANAKTVIANVENRSKNKKILFVCDNRTNKICAFTVIANVENRSKNKKILFVCDNRTNKICAF	:	15	56
GIV-TNFR : MATANAKTVIANVENRSKNKKILFVRLSQTNKICAF	:	15	56
LCDV-C : NATVNLNNFTQDFILYNYYTTDQLKKLARITFKKTRDDVEYMPRWNLESMFTYNDQLPNYMQEADLS	:	25	52
${\tt M-T2} \qquad : \ {\tt AGPNEVVKTSEFSVTLNHTDCDPVFHTEYYGTSGSEGAGGFFTGMDRYQNTTKMCTLNIEIRCVEGDAVRTIPRTSDGVGVLSHSCRIPTSCRI$	:	27	73
Danio Fas : QCTETHNTVCHDAKDLNGTIAAAVVVSLILIAVAAFMIFIWKKKKFCFQVRQSTDKVQTEEALPLIDLSPHLPKIADVLCWKTVK	:	20	)7
Danio TNFR1: LSSDVKHSSTVTTNTQEIRSNPPPDYMTITCITGAVVVVLLILVMTVVTCKLRERKGLTKVPITDANTVEQDPSQSSTPDHQHLL	:	29	<del>)</del> 7
rainbow : AFISRCHWILPTSLWAGLVVTSLIIILICIYWRAKRQSYMPANSSSPGIPVEPAPSSFAPAELKFPTECNSHWSLDQKATEPLFI			
Atlantic : AKPEDTGWDVWSPYLLALSVCVCVLLLVVVGIMGVLVVRRKPKGSSSFPSAEITSQGSETSTRRLIQEDPENVLNQSIPSYSPVC			
Homo : STPEKEGELEGTTTKPLAPNPSFSPTPGFTPTLGFSPVPSSTFTSSSTYTPGDCPNFAAPRREVAPPYQGADPILATALASDPIF	:	33	35
SGIV-VP96 :			_
GIV-TNFR :			_
LCDV-C :GTADILIGYYNTIKEVCLSDFYYIEA	:	27	78
M-T2 : ETITVIGGCLSDVNVDIEYSDSNHPEEVDDFVEYHWGTRLRLFPSPKRCRLVS	:	32	26
Danio Fas : EVARRSGMTAKDIEEQELNHPKDAREQTFGLLEAWSQRQGLDKAYRALITTLQDIGEKATADKIQNIVEASSQP			
Danio TNFR1: HVDRTQTEPSMSSSDSQSQPDCGQSHSSSEWLERSSQDECPSVSSPVLNLSITATFNCQLNPAAASCSIPINPSTLTPHPEALVF			
rainbow : NTAVIQVNGYTSDCEVEADGTTITMTTSERFSQSDHSNGMRGHDIRPSRYLSEPQEDEWPGT	:	31	8
$\verb Atlantic  : ESEQEPLSTLPDCVPKEIKISELIYSVLDQVPPRHVKELVRSLGVSDIVIERAENDHLRDTKEAQYQMLRVWAKGNAQGGGEVLARGE                                    $			
HOMO : NPLQKWEDSAHKPQSLDTDDPATLYAVVENVPPLRWKEFVRRLGLSDHEIDRLELQNGRCLREAQYSMLATWRRRTPRREATLEL	:	42	20
SGIV-VP96 : : -			
GIV-TNFR : : -			
LCDV-C : : -			
M-T2 : : -			
Danio Fas : : -			
Danio TNFR1: LSQEEVCTSSCQQEDGKEALQSVQESGPVLY: 413			
rainbow : : -			
Atlantic : RPLLYHLLDKLRDMDLGGTAEELETKYRDQ : 404			
Homo : LGRVLRDMDLLGCLEDIEEALCGPAALPPAPSLLR : 455			

**Fig. 1.** Amino acid sequence alignment of SGIV-VP96 with other TNFR homologs from human, fish and viruses. The conserved cysteines (C) were indicated by asterisks under the alignment. Boxes above the sequences were the putative cysteine-rich domains (CRDs). Accession numbers of the sequences used for the above analysis were listed as follows: SGIV VP96, YP\_164191; Grouper iridovirus (GIV) TNFR, AAV91081; Lymphocystis disease virus-isolate from China (LCDVC) TNFR, YP\_073525; Myxoma virus T2 (M-T2), NP\_051879; Atlantic Salmon TNFR, ACl68577; Rainbow trout TNFR, NP\_001165342; Zebrafish TNFR, ABG91567; Human HVEM, CAX30822.

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