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Origin and evolution of TNF and TNF receptor superfamilies

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ABSTRACT

The tumor necrosis factor superfamily (TNFSF) and the TNF receptor superfamily (TNFRSF) have an ancient evolutionary origin that can be traced back to single copy genes within Arthropods. In humans, 18 TNFSF and 29 TNFRSF genes have been identified. Evolutionary models account for the increase in gene number primarily through multiple whole genome duplication events as well as by lineage and/or species-specific tandem duplication and translocation. The identification and functional analyses of teleost ligands and receptors provide insight into the critical transition between invertebrates and higher vertebrates. Bioinformatic analyses of fish genomes and EST datasets identify 14 distinct ligand groups, some of which are novel to teleosts, while to date, only limited numbers of receptors have been characterized in fish. The most studied ligand is TNF of which teleost species possess between 1 and 3 copies as well as a receptor similar to TNFR1. Functional studies using zebrafish indicate a conserved role of this ligand–receptor system in the regulation of cell survival and resistance to infectious disease. The increasing interest and use of TNFSF and TNFRSF modulators in human and animal medicine underscores the need to understand the evolutionary origins as well as conserved and novel functions of these biologically important molecules.
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1. Introduction

The tumor necrosis factor superfamily (TNFSF) and the TNF receptor superfamily (TNFRSF) are instrumental in a number of cellular signaling pathways involving inflammation, apoptosis, lymphocyte homeostasis, and tissue development (Bodmer et al., 2002; Ware, 2003). TNFSF ligands are type II membrane proteins that have an intracellular N terminus and an extracellular C terminus. The majority of these ligands are membrane bound, and about half of the different ligands encode proteolytic cleavage sites that can generate soluble forms that retain biological activity (Locksley et al., 2001). The TNF homology domain (THD) is located in the C terminus and is weakly conserved (20–30%) between ligand members. The signature THD is composed of 10 β-strands, which ultimately fold to form a compact "jellyroll" topology. Three monomers join to form a stable conical trimeric protein which is then able to initiate signaling through its respective receptor(s) (Bodmer et al., 2002). The *LTA* gene product is unusual as it can either form a homotrimer known as lymphotoxin-α (LTα also referred to as TNFβ) or it can form a heterotrimer with the lymphotoxin-β gene product resulting in either a $\alpha_1\beta_2$ or $\alpha_2\beta_1$ stoichiometry (Orlinick and Chao, 1998). The family wide tri-fold design produces more contacts between ligand and receptor than occurs with dimers which may lead to higher avidity (Locksley et al., 2001). Commonly, the trimeric ligand binds three monomeric receptors, which is essential for the initiation of the signaling pathway (Bossen et al., 2006). Mouse Tnfsf18 (Gitrl), one of the smallest ligands (125 aa) is unusual as it also associates as a homodimer that has reduced biological activity indicating the potential for alternative oligomerization which may modulate biological function of some ligand members (Chattopadhyay et al., 2008; Zhou et al., 2008). Human TNFSF ligand members are found clustered on the four MHC-paralogous chromosomes: Chr 1 (*TNFSF4*, *TNFSF18*, and *FASLG*), Chr 6 (*LTB*, *TNF* and *LTA*), Chr 9 (*TNFSF15* and *TNFSF8*) and Chr 19 (*TNFSF9*, *CD70* and *TNFSF14*). The remaining genes are found on chromosomes X (*EDA* and *CD40LG*), Chr 3 (*TNFSF10*), Chr 13 (*TNFSF13B* and *TNFSF11*) and Chr 17 (*TNFSF13* and *TNFSF12*). A total of 29 receptor genes have been identified in humans that are dispersed across 14 chromosomes. In this review, we utilize standardized HGNC (human), MGI (Mouse) and ZFIN (Zebrafish) gene and protein nomenclature, but also include original annotation often utilized within the primary literature when it differs from the standardized nomenclature. The reader is also referred to a full list of mammalian gene names and alternative naming of TNFSF and TNFRSF members that can be found at (www.genenames.org) and the reader is also referred to a recent review of mammalian TNFSF and TNFRSF and the schematic depiction of ligand–receptor interacting combinations (Tansey and Szymkowski, 2009). Table 1 summarizes the known invertebrate and teleost fish TNFSF and TNFRSF genes.

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Table 1
Characterized invertebrate and teleost TNFSF and TNFRSF genes/mRNAs. Accession numbers beginning with SPU- are found in EnsemblMetazoa (http://metazoa.ensembl.org/index.html).

	Genus and species (common name)	Gene/mRNA name	Alternative name(s)	Accession # (gene or mRNA)	Putative human homolog	Reference
TNFSF ligands						
Invertebrates	*Drosophila melanogaster* (fruit fly)	*eiger*	*ect1*, *regg1*	AF521176	*EDA*	Moreno et al. (2002)
	Marsupenaeus japonicas (kuruma shrimp)	MjTNF		AB491497	*TNF*	Mekata et al. (2010)
	Haliotis discus discus (disk abalone)	AbTNF-α		EU863217	*TNF*	De Zoysa et al. (2009a)
		AbFas ligand		FJ380204	*FASLG*	De Zoysa et al. (2009b)
	Strongylocentrotus purpuratus(purple sea urchin)	Sp-HVEML		SPU-030072gn/XM784840	*TNFSF14* (LIGHT)	Hibino et al. (2006) and Robertson et al. (2006)
		Sp-TL1A		SPU-009528gn	*TNFSF15* (TL1A/VEGI)	Hibino et al. (2006) and Robertson et al. (2006)
		Sp-EDA		SPU-009527gn	*EDA*	Hibino et al. (2006) and Robertson et al. (2006)
		Sp-EDA2		SPU-015654gn	*EDA*	Hibino et al. (2006) and Robertson et al. (2006)
	Ciona savignyi (Pacific sea squirt)	CsTL		EU216599	Unknown	Zhang et al. (2008)
	Ciona intestinalis (European sea squirt)	CiEDA	EDA	ci0100133562	*EDA*	Hibino et al. (2006) and Robertson et al. (2006)
		CiTNFα	p75	ci0100146130/ NM_001128107	*p75*	Hibino et al. (2006), Robertson et al. (2006) and Parrinello et al. (2008)
	Nematostella vectensis (sea anemone)	NvTNF		SB_31825	*EDA*	Hibino et al. (2006) and Robertson et al. (2006)
Teleosts	*Danio rerio* (zebrafish)	*tnfa*	TNF1	NM_212859	*TNF*	Eimon et al. (2006)
		tnfb	TNF2	NM_001024447	*TNF*	Eimon et al. (2006)
		tnfsf13b	TNFSF13b, BAFF	FJ587513	*TNFSF13b* (BAFF)	Glenney and Wiens (2007), Bossen et al. (2008) and Liang et al. (2010)
		lta	TNF-New	NM_001024821	Unknown	(Savan et al., 2005)
		faslg	TNFSF6, Fas	NM_001042701	*FASLG*	Eimon et al. (2006) and Eimon and Ashkenazi (2010)
		tnfsf10l	DL1a, TRAIL-like–v2	NM_131843	*TNFSF10* (TRAIL)	Eimon et al. (2006)
		tnfsf10l3	DL1b, TRAIL-like-v1	NM_001042713	*TNFSF10*	Eimon et al. (2006)
		tnfsf10l2	DL2, TRAIL-like-v3	NM_001002593	*TNFSF10*	Eimon et al. (2006)
		tnfsf10l4	DL3, TRAIL-like-v4	NM_001013283	*TNFSF10*	Eimon et al. (2006)
		Trail-like	TNFSF10	AF250041	*TNFSF10*	Bobe and Goetz (2001)
		CD40L	TNFSF5	ACL77796	*CD40LG*	Glenney and Wiens (2007) and Gong et al. (2009)
		GITRL	zGITRL, TNFSF18	EU099311	*TNFSF18* (GITRL)	Poulton et al. (2010)
		TL1A	TL1A, TNFSF15	NM_001123259	*TNFSF15* (TL1A, VEGI)	Glenney and Wiens (2007)
	Takifugu rubripes (fugu rubripes)	TNFβ	TNFβ, TNF-new	AB183466	Unknown	Savan et al. (2005)
	Ctenopharyngodon idella (grass carp)	GC-TRAIL	TNFSF10, Apo2 ligand	AY697729	*TNFSF10*	Chang et al. (2006)
	Salvelinus fontinalis (brook trout)	TRAIL-like	TNFSF10	AF289087	*TNFSF10*	Bobe and Goetz (2001)
	Gasterosteus aculeatus (Threespine stickleback)	Eda	EDA	AY897589	*EDA*	Colosimo et al. (2005)
		Ga_Balm		AAY27077	Unknown	Glenney and Wiens (2007) and Colosimo et al. (2005)
	Paralychthys olivaceus (Japanese flounder)	Japanese flounder TNF	TNFα	AB040448	*TNF*	Hirono et al. (2000)
	Cyprinus carpio (common carp)	Carp TNF-1α	TNFα	AJ311800	*TNF*	Saeij et al. (2003)
		Carp TNF-2α	TNFα	AJ311801	*TNF*	Saeij et al. (2003)
		Carp TNF-3α	TNFα	AB112424	*TNF*	(Savan and Sakai, 2004)