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TNF Superfamily 2008

Carl F. Ware [Guest Editor]
Division of Molecular Immunology, La Jolla Institute for Allergy and Immunology, 9420 Athena Circle, La Jolla, CA 92037, Ph 858 752 6735, Fax 858 752 6991, Em cware@liai.org, Web www.liai.org

Abstract

This Special Edition of *Cytokines and Growth Factor Reviews* emerged from the most recent **International TNF Conference**, held May 13–16, 2007. The conference, organized by TNF aficionados, Avi Ashkenazi (Genentech, South San Francisco) and Jeffrey Browning (BiogenIDEC, Boston, MA), was held a second time in the serene coastal environs of the rustic Asilomar State Conference Center in Monterey, California. The scientific presentations at the Asilomar meeting kept pace with the previous 10 *pseudo* biennial TNF-related cytokine conferences, each heralding new discoveries about this important family of cytokines. Perhaps as a sign of the family's maturing knowledge base, new results from clinical trials were revealed for members of the family other than TNF, such as TRAIL in cancer and Lymphotoxin-β in rheumatoid arthritis. The next meeting, the **12th International TNF Conference** is scheduled for April 26–29, 2009 in El Escorial, Madrid, Spain, co-chaired by Marc Feldman and David Wallach (www.tnf2009.org).

Cytokines and Growth Factor Reviews Editor John Hiscott requested (in his ever cogent fashion) an update on the TNF Superfamily. The previous *CGFR* TNF Superfamily special edition in 2003 reflected the meeting held in 2002 in San Diego in which I also served as guest editor [1]. With passage of just five years, we thought the burning questions of the time were addressed, however the 2007 Conference revealed unanticipated features of the TNF Superfamily in all aspects of physiology and development.

The knowledge-base of the TNF Superfamily in 2008 is huge, so large that an attempt to comprehensively cover all aspects of the TNF Superfamily in print risks accelerating global warming. The popularity of TNF is unmatched by any other cytokine. Pubmed various cytokines, TNFα comes up as the big hit at 8×10^4 citations, next in line is IL-2 (4.6×10^4), IL-1 (4.3×10^4), IFNα (2.7×10^4) and CD40 drops in at 8×10^3 citations. In an attempt to cover the breadth of new advances in the field, this special edition of *CGFR* represents an eclectic ensemble of lectures presented at the meeting. I offered the authors the freedom to expand their lectures to include review the their recent work. Due to the limited format, my deep apologies to the many deserving scientists that I was unable to incorporate into this edition.

The portrait of all the ligands and receptors in the TNF Superfamily is large and complicated (Table 1)(see also [2] for binding interactions), yet accessing the structure and genetic features has never been easier due to so many excellent databases, including the official genome nomenclature site (www.genenames.org), which introduced the TNFSF and TNFRSF numbering system.

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The deep penetrance of the TNF Superfamily into many physiological processes [3] brings the realization that pigeonholing any one ligand-receptor pair to a discrete physiologic compartment denies the reality of the functional diversity each 'system". Hence, I loosely organized this volume into four themes: *i*. Regulating differentiation and survival, *ii*. Organogenesis and regeneration, *iii*. CoSignaling in homeostasis and Immune responses, and *iv*. Mechanisms of inflammation and apoptosis.

i. Regulating differentiation and survival

All of the cellular TNF receptors (aside from the decoy receptors) retain the conserved function of activating the family of nuclear factors of κB. NFκB controls many genes that regulate cellular differentiation, survival and death (for an updated list go to: www.nf-kb.org), which determine much of the core functions of the TNFR signaling systems. **Soumen Basak and Alex Hoffmann** (UCSD) discuss the intrinsic and extrinsic dynamics of the family of κB transcription factors, revealing common and unique steps in κB activation by TNFR and LTβR. The TNF receptor associated factors (TRAF) are cytoplasmic adaptors that provide the crucial intracellular link between ligated receptors and activation of NFκB and other intracellular signaling pathways. **Gail Bishop** and colleagues (University of Iowa) review the TRAF family with a focus their role in B cells. **David Wallach** and associates (Weizmann Institute of Science) focus on Caspase 8 in its well known role as death mediator, but as a lesson for aspiring prophets, reveals the unexpected non-cell autonomous impact of caspase 8 inhibition.

ii. Organogenesis and regeneration

Gene mutations in humans and mice often have profound impact on development programs required for nervous system, skin and lymphoid tissues. One of the most dramatic and observable phenotypes in mice impacts the ectoderm. The developmental blueprint of the ectoderm as controlled by the Ectodysplasin (EDA) system is reviewed by **Marja Mikkola** (University of Helsinki), revealing new insights into this model developmental program. Surprisingly, other members of the TNF superfamily such as Rank ligand, lymphotoxins, and TNF impact specific aspects of skin appendage biology, including branching of the mammary gland, hair shaft formation, and hair follicle cycling. **Sergei Nedospasov** and team of geneticists (Engelhardt Institute of Molecular Biology and German Rheumatism Research Centre) review the extraordinary studies aimed at understanding the molecular physiologic functions of TNF using transgenic and knockout models. No less than 20 distinct gene variants constructed to analyze TNF expression, regulation and pathogenesis, reveal the incredible depth of understanding we now have for a mechanism of action of this cytokine. **Sha Mi** (BiogenIDEC) discusses the exciting discovery that the orphan TNF receptor, known as TROY (or Taj) is critical for axon growth and regeneration. Indeed, TROY is more specifically expressed in postnatal and adult neurons than nerve growth factor receptor p75. TROY associates with Nogo receptor 1, functionally replacing in the p75/NgR1/LINGO-1 complex. A new look for a founding member of this receptor superfamily.

iii. CoSignaling in homeostasis and Immune responses

A large cluster of TNFR in human reside on Chr 1p36, and their TNF ligands are clustered in regions of the genome paralogous to the MHC on Chr 6 with TNF, LTα, and LTβ [4]. The TNFR homologs, TNFR2, HVEM, Ox40, 41BB, CD30, GITR and DR3 share cosignaling activity in directing the complex differentiation of T cells. **Michael Croft** and colleagues (La Jolla Institute for Allergy and Immunology) describe their work on OX40 (CD134) and 4-1BB (CD137) as costimulatory receptors for both CD4 and CD8 T cell proliferation, survival, and cytokine production. Croft proposes a role of these costimulatory TNFR in the function of regulatory T cells to explain unexpected properties of Ox40 and 41BB. What T cells have, B

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lymphocytes more than make up for it in the complicated biology associated with BAFF (B cell activating factor of the TNF Family). With three distinct receptors and shared ligands the BAFF APRIL family rivals TNF and LT. **Fabienne Mackay** (The Garvan Institute of Medical Research) and **Pascal Schneider** (University of Lausanne) look closely at the BAFF receptor, TACI. TACI$^{-/-}$ mice revealed two sides to this receptor, a positive one driving T cell-independent immune responses, and a negative side, down-regulating B cell activation and expansion. Two sides to a TNFR is an emerging theme. The herpesvirus entry mediator (HVEM) binds two ligands on opposite sides of the molecule [5]. HVEM binds LIGHT, a ligand related to LTβ, and BTLA, (B and T lymphocyte attenuator), an Immunoglobulin family member with inhibitory signaling properties [6,7]. My associate, **Carl De Trez** (Université Libre de Bruxelles), discusses results revealing the HVEM-BTLA pathway provides inhibitory signaling to dendritic cells, which counter acts the trophic action of LTβR signaling necessary for the local proliferation of DC in lymphoid tissues [8]. **Yang-Xin Fu** and colleagues (University of Chicago) highLIGHT the anti-tumor properties of Lymphotoxin-related ligand, LIGHT. LIGHT conditions the tumor microenvironment in a sufficiently robust fashion to drive CD8 T cell differentiation into cytotoxic effectors that can eradicate metastases. The work implicates LIGHT as promising candidate for an effective cancer immunotherapy.

iv. Mechanisms of inflammation and apoptosis

In what was one of the most illuminating lectures **Shigekazu Nagata** revealed a molecular pathway linking apoptosis, DNA degradation with IFN and TNF production to a autoimmune like syndrome, chronic polyarthritis. Basic research on apoptotic pathways revealed a defect in lysosomal DNA degradation activates macrophages to produce cytokines such as IFNβ and TNF in a Toll-like receptor (TLR)-independent manner. IFNβ expressed in the fetal mouse induces apoptosis of erythroid and lymphoid precursor cells, with fatal results. However, loss of DNAse II after birth leads to chronic TNF production causing chronic polyarthritis that resembles human rheumatoid arthritis. **Sun-Mi Park and Marcus Peter** explore micro RNAs, discovering a new mechanism of regulating apoptosis through Fas/CD95 signaling pathway involving miRNAs as regulators of death receptor signaling. Many conventional therapies for cancer fail because mutational inactivation of the *p53* tumor-suppressor gene, which regulates apoptosis via the cell-intrinsic pathway, reduces sensitivity to chemotherapy. **Avi Askenazi** (Genentech) reports on exploiting the cell extrinsic apoptotic pathway using two agonists of the death receptors for TRAIL. In contrast to TNF, the initial data on recombinant TRAIL and an agonist monoclonal antibody to TRAIL death receptors, Apomab, in safety trials confirm that these agents are suitable for further clinical investigation as cancer therapeutics. TNFR signaling rapidly activates cellular death and survival pathways within minutes, and the regulatory brakes must parallel this speed. Ubiquitination delivers a rapid posttranslational mechanism covalently modifying proteins and for controlling protein abundance. The first ubiquitinylated derivative identified in the signaling cascade was Inhibitor of NF-κB. **Ingrid E. Wertz and Vishva M. Dixit** (Genentech) show that nearly every step of TNFR1 signaling is regulated by ubiquitination.

This issue of CGFR provides a close examination of several individual members of the TNF Superfamily and as a collective volume the hope is to provide the reader with a cross section of the TNF superfamily revealing the integrated nature of these cellular communication systems common to the entire family.

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Table 1

Table 1a	TNF SuperFamily-chromosomal locations				
	chromosomal location		mRNA accession numbers		
gene name/alias	human	mouse	human	mouse	Ligand symbol
TNF	6p21.3	ch17 (19.06 cm)	NM_000594	NM_013693	TNFSF1A
LTα	6p21.3	ch17 (19.06 cm)	NM_000595	NM_010735	TNFSF1B
LTβ	6p21.3	ch17 (19.06 cm)	NM_002341	NM_008518	TNFSF3
OX40-L	1q25	ch1 (84.90 cM)	NM_003326	NM_009452	TNFSF4
CD40-L, CD154	Xq26	chX (18.0 cM)	NM_000074	NM_011616	TNFSF5
Fas-L	1q23	ch1 (85.0 cM)	NM_000639	NM_010177	TNFSF6
CD27-L, CD70	19p13	ch17 (20.0 cM)	NM_001252	NM_011617	TNFSF7
CD30-L, CD153	9q33	ch4 (32.20 cM)	NM_001244	NM_009403	TNFSF8
4-1BB-L	19p13	ch17 (20.0 cM)	NM_003811	NM_009404	TNFSF9
TRAIL	3q26	ch3	NM_003810	NM_009425	TNFSF10
RANK-L, TRANCE	13q14	ch14 (45.0 cM)	NM_003701	NM_011613	TNFSF11
TWEAK	17p13	ch11	NM_003809	AF030100	TNFSF12
APRIL/TALL2	17P13.1	ch13	NM_003808	NM_023517	TNFSF13
BAFF, BLYS, TALL1	13q32–q34	ch8 (3cM)	NM_006573	NM_033622	TNFSF13B
LIGHT	19p13.3	ch17 (D-E1)	NM_003807	NM_019418	TNFSF14
TL1A	9q33	ch4 (31.80cM)	NM_005118	AF520786	TNFSF15
GITRL, AITRL	1q23	unknown	NM_005092	unknown	TNFSF18
EDA1	Xq12–q13.1	chX (37.0 cM)	NM_001399	NM_010099	
EDA2	Xq12–q13.1	chX (37.0 cM)	AF061189	AJ243657	

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Table 1b **TNF Receptor SuperFamily**

	chromosomal location		mRNA accession numbers		
Gene name/aliases	**human**	**mouse**	**human**	**mouse**	**Gene Symbol**
TNFR-1, p55–60	12p13.2	ch6 (60.55cM)	NM_001065	NM_011609	TNFRSF1A
TNFR2, p75–80	1p36.3-36.2	ch4 (75.5cM)	NM_001066	NM_011610	TNFRSF1B
LTβR	12p13	ch6 (60.4cM)	NM_002342	NM_010736	TNFRSF3
OX40	1p36	ch4 (79.4cM)	NM_003327	NM_011659	TNFRSF4
CD40	20q12–q13.2	ch2 (97.0cM)	NM_001250	NM_011611	TNFRSF5
FAS, CD95	10q24.1	ch19 (23.0cM)	NM_000043	NM_007987	TNFRSF6
DcR3	20q13	unknown	NM_003823	unknown	TNFRSF6B
CD27	12p13	ch6 (60.35)	NM_001242	L24495	TNFRSF7
CD30	1p36	ch4 (75.5cM)	NM_001243	NM_009401	TNFRSF8
4-1BB	1p36	ch4 (75.5cM)	NM_001561	NM_011612	TNFRSF9
TRAILR-1, DR4	8p21	unknown	NM_003844	unknown	TNFRSF10A
TRAIL-R2, DR5	8p22-p21	ch14 (D1)	NM_003842	NM_020275	TNFRSF10B
TRAILR3, DcR1	8p22-p21	ch7 (69.6cM)	NM_003841	NM_024290	TNFRSF10C
TRAILR4, DcR2	8p21	ch7 (69.6cM)	NM_003840	NM_023680	TNFRSF10D
RANK, TRANCE-R	18q22.1	ch1	NM_003839	NM_009399	TNFRSF11A
OPG, TR1	8q24	ch15	NM_002546	NM_008764	TNFRSF11B
FN14	16p13.3	ch17	NM_016639	NM_013749	TNFRSF12A
TRAMP, DR3, LARD	1p36.3	ch4 (E1)	NM_003790	NM_033042	TNFRSF25
TACI	17p11.2	ch11	NM_012452	NM_021349	TNFRSF13B
BAFFR	22q13.1–q13.31	ch15	NM_052945	NM_028075	TNFRSF13C
HVEM, HveA, ATAR	1p36.3–p36.2	ch4	NM_003820	NM_178931.2	TNFRSF14
p75NTR, NGFR	17q12–q22	ch11 (55.6cM)	NM_002507	NM_033217	TNFRSF16
BCMA	16p13.1	ch16 (B3)	NM_001192	NM_011608	TNFRSF17
AITR, GITR	1p36.3	ch4 (E)	NM_004195	NM_009400	TNFRSF18
RELT	11q13.2	unknown	NM_152222	unknown	TNFRSF19L
TROY, TAJ	13q12.11–q12.3	ch14	NM_018647	NM_013869	TNFRSF19
EDAR	2q11–q13	ch10	NM_022336	NM_010100	
DR6	6P12.2–21.1	ch17	NM_014452	NM_052975	TNFRSF21

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Table 1b **TNF Receptor SuperFamily**

	chromosomal location		mRNA accession numbers		
Gene name/aliases	**human**	**mouse**	**human**	**mouse**	**Gene Symbol**
EDA2R	Xq11.1	unknown	NM_021783	unknown	
mTNFRH3	unknown	ch7(69.9cM)	unknown	NM_175649	