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X-ray crystal structure of TNF ligand family member TL1A at 2.1 Å

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Abstract

The TNF family has been one of the most intensively studied protein families in the past two decades and it has rapidly expanded through the era of genomics and bioinformatics. However, the structural basis of the functional and interactional similarities and differences of this family is poorly understood. TL1A is a recently identified TNF family member that has received increasing attention. Here, the crystal structure of human TL1A is reported. TL1A forms a homotrimer with each monomer assuming a jellyroll β-sandwich fold. The CD loop in TL1A is the longest among the TNF ligand members with known structure and the AA′ loop in TL1A is the second longest after that in TRAIL, where part of it is disordered. Both these loops are known to participate in receptor binding in TNFβ/LTα. The AA′ loop may be very different in other TL1A variants if the overall fold is to be preserved.

Keywords: X-ray crystallography; Angiogenesis; Apoptosis; Inflammation; TL1; VEGI; TNFSF15; DR3; DcR3

The tumor necrosis factor (TNF) superfamily of cytokines and their receptors regulate diverse biological functions, including cell proliferation, immune regulation, inflammation, cell death, and cell differentiation (for review, see [1]). Tumor necrosis factor alpha (TNFα, named for its anti-tumor properties) was isolated more than 30 years ago [2] and the TNF family have been implicated in a large number of diseases, including cancer, Alzheimer's disease, type II diabetes, and inflammatory disorders. To date, at least 19 TNF family ligands and 29 TNF receptor family members have been identified (for review, see [3]). The extracellular domain of a TNF ligand family protein contains a TNF homology domain (THD) which is generally a globular homotrimer with each monomer assuming a jellyroll β-sandwich fold. In contrast to the globular ligands, the extracellular domains of TNF receptor superfamily members are elongated molecules composed of cysteine-rich pseudo-repeats typically forming structural modules termed cysteine-rich domains [4].

Many TNF family ligands bind to multiple receptors and many of the receptors have more than one ligand [1,3]. Interaction of the TNF family of ligands with their cognate receptors can lead to cell growth, differentiation, survival, or death, depending on the cellular context and the nature of the ligand and receptor interaction [5]. To date, the basis of the specificity of the TNF family ligand–receptor association is still poorly understood. Thus, structural characterization of TNF ligand family members is required.

Tumor necrosis factor ligand superfamily member 15, TNFSF15 (also known as TL1, VEGI, and TL1A) is believed to be one of the evolutionarily earliest members of the TNF superfamily [6]. Full length TL1A is a 251-amino acid protein. It contains a predicted hydrophobic transmembrane region near the N-terminus and an extracellular carboxyl domain (containing 180 amino acids) that can be cleaved off from the cell membrane by an unidentified protease(s) and can exist in a soluble form [7].

Functionally, association of TL1A with its receptor, death receptor 3 (DR3), recruits intracellular death receptor associated proteins which in turn activates caspases [8] and induces apoptosis. DR3 activation can also result

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in the activation of NF-κB, a central transcription factor that controls expression of numerous genes in the immune system. Recombinant soluble TL1A can induce NF-κB activation in DR3-expressing cells and increased ectopic expression of the TL1A cDNA in human endothelial cells was shown to induce apoptosis via DR3 [9]. However, in TF-1 cells, TL1A significantly increased the production of the NF-κB dependent anti-apoptotic protein c-IAP2 [10]. Thus, depending on the cellular context, the activity of TL1A may regulate the balance between pro-survival and pro-death molecules. TL1A was also demonstrated to bind to soluble decoy receptor 3 (DcR3), a TNFR family member which is also known to bind to FasL and LIGHT [11]. Recombinant DcR3 has been shown to induce angiogenesis in endothelial cells by inhibiting TL1A action in the cells [12], indicating that TL1A might also have therapeutic value to target angiogenesis in tumor growth. TL1A may also play a role in the pathogenesis of inflammatory bowel diseases (IBD) as a Th1 polarizing cytokine [13].

The short form TL1/VEGI was also believed to have a transmembrane peptide. Its C-terminus (being the C-terminal 151 amino acid of all known forms of TL1A) can also be expressed in a soluble form which inhibited the growth of colon carcinomas in mice [14] and induced apoptosis of endothelial cells [15]. Towards understanding how the N-terminal of the different forms of soluble TL1A dictates its functions and understanding the structural basis of the interaction between TL1A and its receptors, we determined the X-ray crystal structure of one form of the soluble TL1A.

Materials and methods

Expression of recombinant soluble human TL1A, its purification and crystallization, as well as X-ray data collection, data processing, and initial phasing by molecular replacement have been described [16]. Briefly, human soluble TL1A was expressed in *Escherichia coli* and purified with Ni^{2+} affinity, hydrophobic interaction, anion exchange, and size exclusion chromatography. Since then, a new X-ray diffraction data set at 2.1 Å resolution has been collected at the Southeast Regional Collaborative Access Team (SER-CAT) 22ID beamline at the Advanced Photon Source (APS), Argonne National Laboratory. The initial molecular replacement solution indicated three TL1A molecules in the asymmetric unit. The model was then completed with semi-automated model building using the programs XtalView [17] and Coot [18]. Final rounds of refinement were accomplished using CNS [19] and Refmac [20] alternated with manual model adjustments using XtalView and Coot. Atomic coordinates and structure factors for TL1A, 2O0O for the old data set and 2RE9 for the new data set, have been deposited in the Protein Data Bank. Figures were prepared using the programs XtalView and PyMol (DeLano Scientific LLC). Multiple structure alignment was carried out with the program MUSTANG [21].

Results and discussion

We wished to determine the structure of TL1A in order to understand the structural basis of the association between TL1A and its receptors and to provide information for understanding the structural basis of the ligand–receptor specificities of the TNF family. The final model of the TL1A structure determined at 2.1 Å includes 492 amino acids, a magnesium ion, two glycerol molecules, and 500 water molecules. The final refined model gave R/R_{free} values of 19.8%/25.33% for all data to 2.1 Å (Table 1 and Fig. 1). The RMSD from idea empirical values are 0.0058 Å for bond lengths and 1.35° for bond angles. On the Ramachandran plot, 83.9%, 15.4%, and 0.7% residues are in the most favored, additionally allowed, and generously allowed regions, respectively.

There are three TL1A monomers in the asymmetric unit and they are related by a 3-fold non-crystallographic symmetry (NCS). However, inclusion of the NCS did not improve the data fitting and it was not used in the refinement. For each monomer, 16 residues from the N-terminus were disordered and not included in the model. For the side chain of F39 in protomer B, only the C_β was located in the electron density map and included in the model.

Overall, the three TL1A monomers in the asymmetric unit form a trimer that resembles the trimer structure of other TNFL family members. Each of the three protomers assumes a jellyroll β-sandwich fold containing two β-sheets (Fig. 1B). Strands A′, A, H, C, and F form the inner sheet and contribute most of the interfaces among the monomers within the homotrimer. The trimer interfaces at the 3-fold axis of the NCS buries 7736 $Å^2$ solvent-accessible surface (SAS). In comparison, the SAS buried by other TNF members calculated using the coordinates with the highest resolution for each of the TNF members are: TRAIL_1DG6 [22], 7354; TNFβ_1TNR [23], 6828; CD40L_1ALY [24],

Table 1
X-ray crystallographic statistics and refinement

Data collection	
Wavelength (Å)	1.0
Temperature (K)	110
Space group	$P4_12_12$
$a = b$, c (Å)	114.911, 119.346
Resolution limits (Å)[a]	47.19–2.10 (2.18–2.10)
Number of observed reflections	370693
Number of unique reflections[a]	46993 (4595)
Completeness (%)[a]	99.8 (99.6)
Mean $I/I(\sigma)$[a]	13.1 (1.9)
$R_{sym}(5\%)$[a,b]	13.1 (96)
Refinement	
Resolution range (Å)	47.19–2.10
Number of reflections	
Working set	41764
Test set[c]	2194
Number of atoms	
Protein	3945
Water	500
Ligands and ion	13
R/R_{free} (%)	19.80/25.33
RMSD from ideal geometry	
Bond lengths (Å)	0.0058
Bond angles (deg)	1.349

[a] Numbers in parentheses are in the outer shell.
[b] $R_{sym} = (\sum|I - <I>|)/\sum I$.
[c] 5% of the reflections from thin shells in the center of each reflection bin.

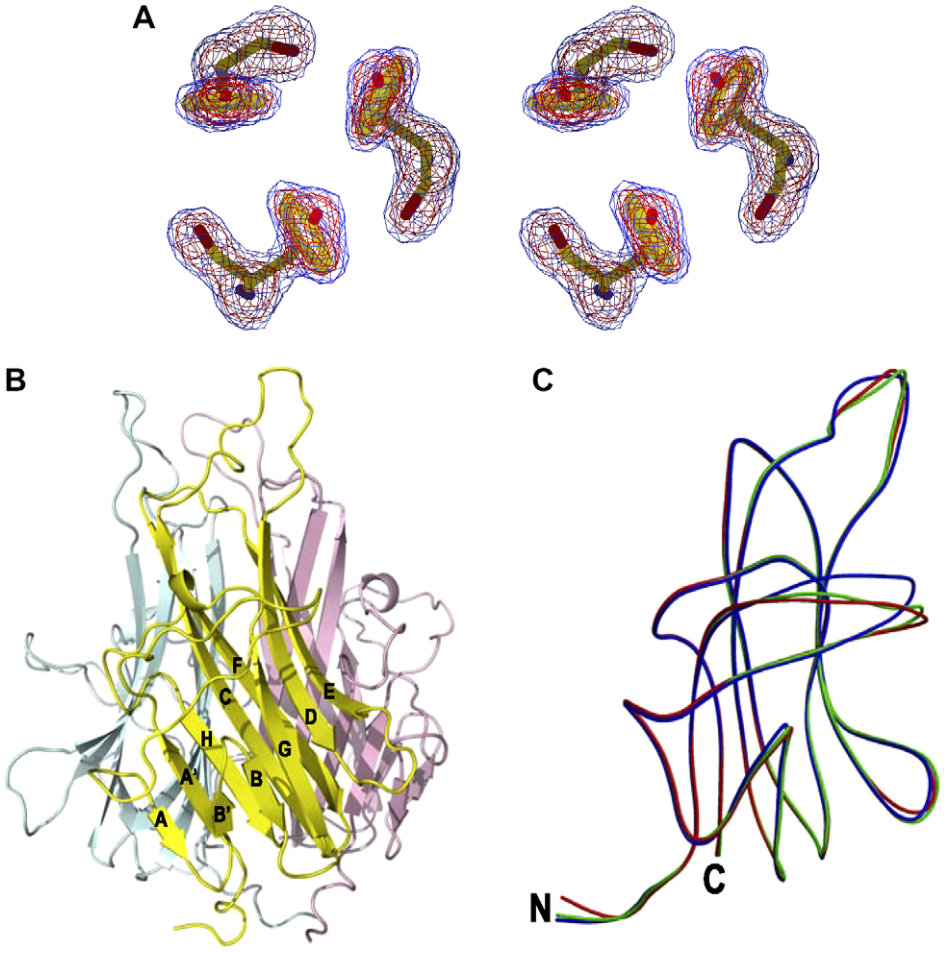

Fig. 1. Structure of the soluble form of human TL1A. (A) A stereoview of an $F_o - F_c$ simulated anneal omit map to 2.1 Å resolution calculated by CNS with Y142 in all three protomers omitted. The starting temperature was raised to 5000 K to eliminate model bias. The map was contoured at 5σ (blue) and 7σ (red). A stick representation of the omitted residues in the final TL1A trimer model is shown in the density. (B) A ribbon diagram of the TL1A trimer. Protomers A, B, and C are colored in yellow, cyan, and pink, respectively. Strands are labeled in strand order in protomer A. (C), the three protomers are superimposed with chain A, B, and C colored in red, green, and blue, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

6125; TNFα_4TSV [26], 5842; EDA_1RJ8 [25], 5791; BAFF_1KXG [27], 5569; and OX40_2HEV [28], 2390. The relatively large SAS buried by TL1A trimerization may indicate slightly stronger monomer–monomer association.

Strands B′, B, G, D, and E constitute the outer sheet which is more exposed to solvent. Soluble TL1A contains two cysteine residues (C91 and C131) and they form an intra-chain disulfide bond between the CD loop and the EF loop. The AA′ loop is the longest loop and it is involved in crystal packing in two of the protomers. While a large portion of this loop is not affected by the differences in crystal packing for protomer C and for protomers A and B, superposition of the three TL1A protomers shows that part of the AA′ loop has the most conformational variation (Fig. 1C).

As shown in Fig. 2A, protomer A and protomer B are involved in interacting with other trimers, but protomer C is not tightly packed against another trimer. The interaction between adjacent trimers is mostly a monomer–monomer interaction, between protomer A from one trimer and protomer B from the other. The outer sheets of the two monomers almost constitute a continuous β-sheet at first glance. However, the two B′ strands are perpendicular and there is no hydrogen bond interaction between those two strands. The inner sheets from the two monomers reside on the opposite sides of the ''extended sheet''. A total of 1114 $Å^2$ of SAS is buried between the trimers, or the interacting monomers. This is less than the buried surface expected for a typical homodimer, which has been estimated to be 1685 $Å^2$ [29]. Thus this trimer–trimer interaction might be a result of crystal packing especially in light of the protein being purified as trimers based on the size exclusion chromatographic data. There is a metal ion at the interface of the interacting protomers from two adjacent trimers that can be clearly identified in the electron density map (Fig. 2B). X-ray fluorescence scan indicated that there was no Ni^{2+} in the crystal (data not shown) that could have been possibly retained by the protein during the IMAC purification. This metal ligand is most likely a magnesium

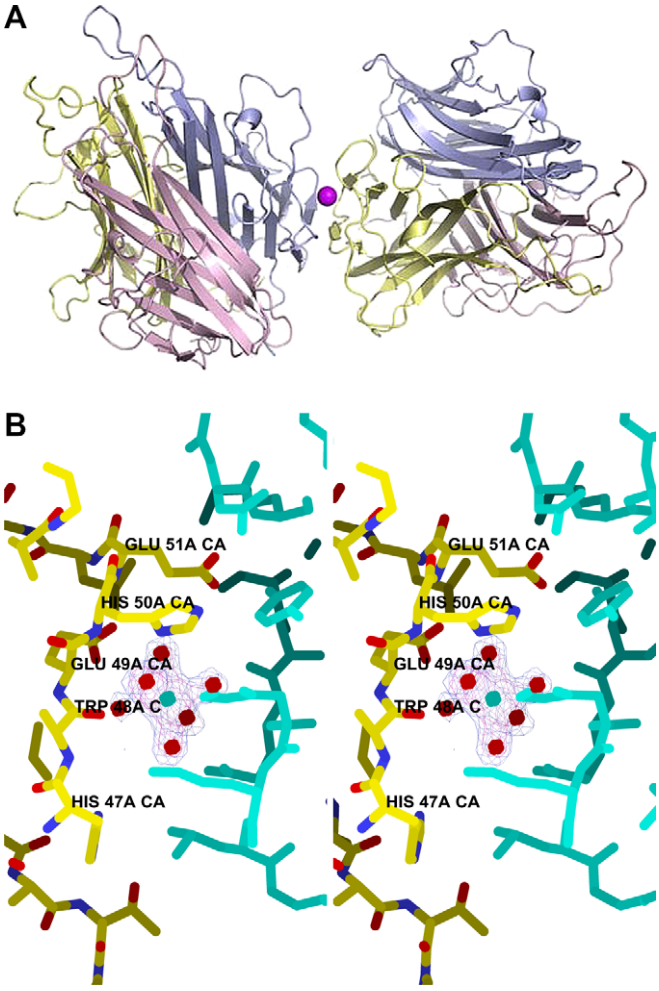

Fig. 2. TL1A crystal packing/trimer–trimer interaction. (A) A ribbon diagram representation showing TL1A trimer–trimer interaction in the crystal. Chains A, B, and C in each trimer are colored yellow, cyan, and pink, respectively. (B) A stereoview diagram showing the location of the metal ion at the TL1A trimer–trimer interface. Chain A of a TL1A trimer is shown in stick presentation with CPK coloring. Chain B of the interacting trimer is presented as sticks and colored cyan. A $F_o - F_c$ simulated anneal omit map to 2.1 Å resolution calculated by CNS [19] with the Mg^{2+} and its coordinating water molecules omitted is contoured at 4σ (blue) and 6σ (magenta). The Mg^{2+} and the waters are colored cyan and red, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

ion since the mother solution contained 0.2 M magnesium formate. Therefore, an Mg^{2+} was included in the structural model. No protein atom is directly coordinating the metal ion. Rather, they interact with the metal ion through water molecules (Fig. 2B). The presence of this metal binding site might be the reason why an Ni^{2+} column can be used for TL1A purification since no other metal binding configuration can be found in the structure.

The angle between the 3-fold trimer axes of two interacting trimers is 90°. The extension of the trimer–trimer association forms a right handed helix with four trimers per turn. The displacement along the helix axis is 119.346 Å per turn and this helical arrangement forms the 4_1 screw axis of the crystal. The C protomers of the trimers face the outside of the helix. Because TL1A is purified as a homotrimer, it is unlikely that this trimer–trimer interaction will normally result in stable higher order oligomerization of TL1A. However, although this interaction may be merely an effect of crystal packing, the large SAS it buries makes whether this interaction affects TL1A's binding with its receptors and hence its function an open question. Interestingly, cross-linking of the extracellular domain of FasL and TRAIL increases their proapoptotic activity up to 1000 times [30] and the oligomeric form of EDA-A1 is reported to be required for its in vivo function [31]. Whether TL1A has a higher affinity to other metals and whether metal binding affects the specificity of TL1A's binding with different receptors (e.g. DR3 and DcR3) also need to be further studied.

Comparison with other TNFL family members

The conservation level of amino acid among TNF members is low. Information on the three-dimensional structures of many of the TNF members is not yet available and the specificity among the ligands and receptors is not well understood. Nonetheless, the resemblance between TL1A and other TNF members is greater than would be suggested by sequence homology. As shown by Fig. 3, multiple-structure-alignment (based on Cα–Cα distance after superimposition) of TL1A and all other human TNF family members with known structure indicates that most strands in all the structures are very similar in length and the overall structures superimpose well with one another. The loop between the first two strands varies the most, ranging from 3 amino acids (in OX40L) to 36 residues (in TRAIL), but 12 amino acids in this loop are missing in the structure of TRAIL. TL1A has the second longest AA′ loop with 26 amino acids in it and the metal coordinating residues reside in this loop. As indicated by the alignment, the metal ion coordinating residues (E49 and H50, and to a lesser extent H47 which is bridged with the Mg^{2+} through two H_2O molecules) are only present in TL1A in the aligned positions. Consistent with this, no metal ion binding to the AA′ loop was found in other TNF ligand family members. Another TNF family member, BAFF, forms a virus-like structure [32,33] and whether the 60-mer virus-like structure is the physiologically functional unit of BAFF is under debate [34]. The BAFF trimer–trimer interaction involved mostly the DE loop referred as a flap and there are metal ions positioned at the BAFF trimer–trimer interface [27]. Interestingly, Fig. 3 also shows that a number of the residues in TNFβ that are involved in receptor recognition [23] reside in the AA′ loop. The metal coordinating residues in TL1A are also in the AA′ loop and partially aligned with the receptor binding residues in TNFβ. The CD loop in TNFβ is also involved in receptor binding and the CD loop in TL1A is the longest among the members aligned in Fig. 3. Thus, metal coordinating residues in TL1A and other residues in the AA′ and CD loops may deserve special consideration

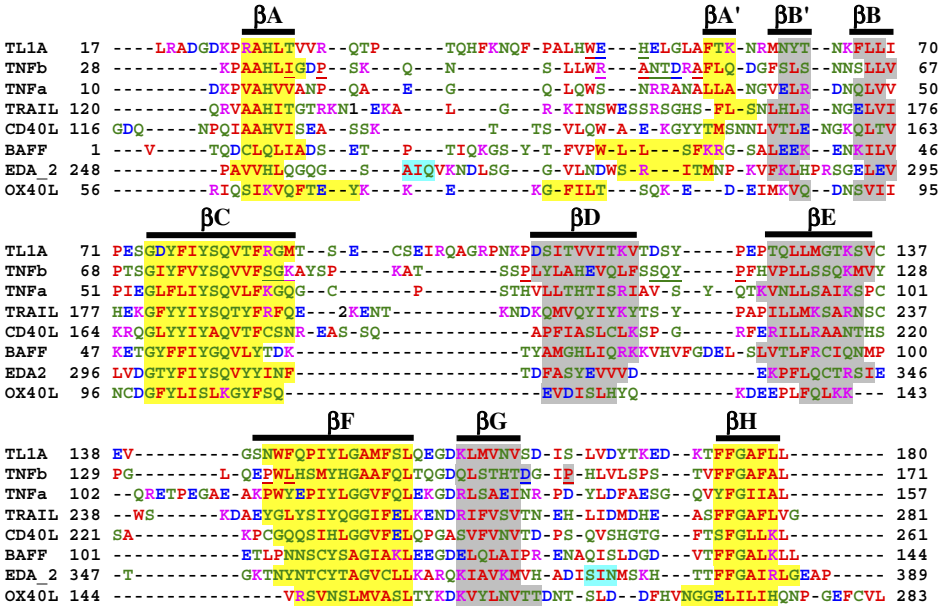

Fig. 3. Structure-based alignment of human TNF family cytokines with TL1A. The sequences of the extracellular core domains of the human TNF family cytokines TL1A (this study, PDB code 2RE9), TNFβ/LTα(1TNR), TNFα(4TSV), TRAIL(1DG6), CD40L(1ALY), BAFF(1KXG), EDA2(1RJ8), and OX40L(2HEV) are aligned using the program MUSTANG [21] with minimal manual adjustment. A number in a sequence denotes missing residues (1 = 12 missing residues; 2 = 2 missing residues). Color letter indicates the chemical nature of the amino acid: red, aromatic and small hydrophobic residues (AFILMPVW), blue, acidic (DE), magenta, basic (KR), and green, amino acids with hydroxyl groups and/or amine groups (CGHNQSTY). Residue numbers are those in the PDB files. Secondary structure assignments are depicted above the sequences. Strands in the inner sheet of each protein are highlighted in yellow and those in the outer sheet are highlighted in gray. Extra strands in EDA are highlighted in skylight. Secondary structure assignments are taken from the PDB files. Underlined residues in TL1A are those in the vicinity of the metal ion in protomers A and B. Underlined residues in TNFβ denote TNFR contact sites on TNFβ. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

in designing TL1A mutations that may differentially affect/regulate its binding with individual receptors, and hence have therapeutic values. Further supporting this notion is the structural characterization of ligand–receptor complex reported for TRAIL [35,36], where the AA′ loop of the ligand is also important for receptor binding.

Figs. 1 and 3 also show that if the soluble form of TL1A that resulted from the short version of TL1/VEGI is to preserve the TNF fold, it will have a very different AA′ loop since this short soluble form of TL1A starts after strand A′. Whether part of the AA′ loop takes the position of strand A′ in this short TL1A awaits future investigation.

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