Zinc finger proteins: insights into the transcriptional and post transcriptional regulation of immune response

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Abstract
Background Zinc finger proteins encompass one of the unique and large families of proteins with diversified biological functions in the human body. These proteins are primarily considered to be DNA binding transcription factors; however, owing to the diverse array of zinc-finger domains, they are able to interact with molecules other than DNA like RNA, proteins, lipids and PAR (poly-ADP-ribose). Evidences from recent scientific studies have provided an insight into the potential functions of zinc finger proteins in immune system regulation both at the transcriptional and post transcriptional level. However, the mechanism and importance of zinc finger proteins in the regulation of immune response is not very well defined and understood. This review highlights in detail the importance of zinc finger proteins in the regulation of immune system at transcriptional and post transcriptional level.

Conclusion Different types of zinc finger proteins are involved in immune system regulation and their mechanism of regulation is discussed herewith.

Keywords Interleukins · Macrophages · mRNA degradation · Transcription factors · Tumor Necrosis factor (TNF) · Zinc finger proteins

Abbreviations

ZFPs Zinc finger proteins
Blimp1 B lymphocyte-induced maturation protein 1
BCL1 B cell lymphoma-1
EBF Early B-cell factors
ZNF521 Zinc finger protein 521
LRF Leukemia/lymphoma-related factor
Zbtb1 Zinc finger and BTB domain containing 1
CLP Common lymphoid progenitor
KRAB-ZFPs Kruppel-associated box domain Zinc finger proteins
KSHV Kaposi’s sarcoma-associated herpes virus
MCPIP1 Monocyte chemotactic protein-induced protein 1
ARE AU rich elements
TNF Tumor Necrosis factor
TTP Tristetraprolin
DP Constitutive Decay Element
PRRs Pattern recognition receptors
LPS Lipopolysachharide

Background

Zinc plays an important role in different aspects of human health (clinical as well as epidemiological) in public health practices. Zinc is an essential nutrient which serves as a cofactor to many enzymes involved in the metabolism of various biomolecules including proteins, carbohydrates, nucleic acids and lipids. It is known to play a key role in the immune system, affecting both cellular and humoral immunity [1]. The essentiality of Zn was first of all established in the mid-nineteenth century by the French physiologist, Raulin when it was observed that this element was mandatory for the growth of bread mould (Aspergillus niger).

The Zn chemistry principally is centered in its involvement in the function of a diverse set of proteins which includes different metalloenzymes/metalloproteins in
addition to nuclear transcription factors. One of the important classes of zinc proteins is zinc finger proteins (ZFPs), which were first discovered in the cell nucleus of a frog, Xenopus laevis [2]. Zinc ions complexed with cysteine and histidine amino acid residues forms Cys2His2 zinc finger motifs, thereby conferring a native tertiary configuration to the protein, hence the name. Later on, it was found that several negatively charged amino acids combining in various ways (e.g. Cys2His2, Cys4, Cys6, etc.) were also found in zinc finger proteins [3]. The different types of zinc finger proteins are listed in Table 1.

The in-depth characterization of Zinc finger proteins has implicated them in several functions. Zinc finger proteins are basically thought of as transcription factors meant primarily to bind DNA. However, some of the zinc finger proteins and related zinc binding motifs are also known to bind to RNA [4], lipids [5] and some of the other proteins [6]. These proteins serve diverse biological functions in human body, such as in development and differentiation processes, metabolism, transcriptional as well as post transcriptional regulation and activation, protein degradation and signal transduction etc. In fact, the diverse combinations and functions of these zinc finger proteins have made these proteins versatile in biological system.

### Involvement of zinc finger proteins in immune system

The immune response is regulated at both the transcriptional as well as the post transcriptional level. Zinc finger proteins have important role to play in the control and

| Type of Zinc finger protein | Structure | Examples |
|----------------------------|-----------|----------|
| 1. Zinc fingers C2H2-type(ZNF) | C-x-C-x-H-x-H | KLF4, KLF5, EGR3, ZFP637, SLUG, ZNF750, ZNF281, ZBP89, GLIS1, GLIS3 |
| 2. LIM domain containing | C-x-C-x-H-x-C-x-C-x-C-x-C-x-H-x-(C,H,D) | ZNF185, LIMK1, PXN |
| 3. PHD finger proteins(PHF) | C-x-C-x-C-x-C-x-H-x-H-x-C-x-C-x-C | KDM2A, PHF1, ING1 |
| 4. Ring finger proteins(RNF) | C-x-C-x-C-x-H-x-H-x-C-x-C-x-C | MDM2, BRCA1, ZNF179 |
| 5. Nuclear hormone receptors(NR) | C-x-C-x-C-x-C-x-H-x-H-x-C-x-C-x-C | ZNF41, ESR1, NR4A1 |
| 6. Zinc fingers CCCH-type(ZC3H) | C-x-C-x-C-x-H | RC3H1, HELZ, MBNL1, ZFP36, ZFP36L1 |
| 7. Zinc fingers CCHC-type(ZCHC) | C-x-C-x-H-x-C | CNBP, SF1, LIN28A |
| 8. Zinc fingers FYVE-type(ZFYVE) | C-x-C-x-C-x-C-x-C-x-C-x-C-x-C | EE1A, HGS, PIKfyVE |
| 9. Zinc fingers DHHC-type(ZDHHC) | C-x-C-x-H-x-C-x-C-x-C-x-C-x-C-x-C | ZDHHC2, ZDHHC8, ZDHHC9 |
| 10. Zinc fingers MYND-type(ZMYND) | C-x-C-x-C-x-C-x-C-x-C-x-C-x-C-x-C | PDCD2, RUNX1T1, SMYD2, SMYD1 |
| 11. Zinc fingers RANBP2-type(ZRANB) | C-x-C-x-C-x-C | YAF2, SHARPIN, EWSR1 |
| 12. Zinc fingers ZZ-type(ZZZ) | C-x-C-x-C-x-C | HERC2, NBR1, CREBBP |
| 13. Zinc fingers C2HC-type(ZC2HC) | C-x-C-x-H-x-C | IKBKGA, 3MBTL1, ZNF746 |
| 14. GATA zinc-finger-domain containing (GATAD) | C-x-C-x-C-x-C | GATA4, GATA6, MTA1 |
| 15. ZF class homeoboxes and pseudogenes | C-x-C-x-H-x-H | 10ADNP, ZEB1, ZHX1 |
| 16. THAP domain containing(THAP) | C-x-C-x-C-x-C | THAP1, THAP4, THAP11 |
| 17. Zinc fingers CXXC-type(CXXC) | C-x-C-x-C-x-C-x-C-x-C-x-C-x-C-x-C | CXXC1, CXXC5, MBD1, DNM1T |
| 18. Zinc fingers SWIM-type(ZSWIM) | C-x-C-x-C-x-C-x-C-x-C-x-C-x-C-x-C | MAP3K1, ZSWIM5, ZSWIM6 |
| 19. Zinc fingers AN1-type(ZFAND) | C-x-C-x-C-x-C-x-C-x-C-x-C-x-C-x-C | ZFAND3, ZFAND6, IGHMBP2 |
| 20. Zinc fingers 3CxxC-type(Z3CXXC) | C-x-C-x-C-x-C-x-C-x-C-x-C-x-C | ZAR1, RTP1, RTP4 |
| 21. Zinc fingers CW-type(ZCW) | C-x-C-x-C-x-C | MORC1, ZCWPW1, KDM1B |
| 22. Zinc fingers GRF-type(ZGRF) | C-x-C-x-C-x-C | TTF2, NEIL3, TOP3A |
| 23. Zinc fingers MIZ-type(ZMIZ) | C-x-C-x-C-x-C | PIAS1, PIAS3, PIAS4 |
| 24. Zinc fingers BED-type(ZBED) | C-x-C-x-C-x-C | ZBED1, ZBED4, ZBED6 |
| 25. Zinc fingers HHT-type(ZNHT) | C-x-C-x-C-x-C-x-C-x-C-x-C-x-C-x-C | ZNHT3, DDX39, INO80B |
| 26. Zinc fingers C2H2C-type | C-x-C-x-C-x-C-x-C-x-C-x-C-x-C-x-C | MYT1, MYT1L, ST18 |
| 27. Zinc fingers DBF-type(ZDBF) | C-x-C-x-C-x-C-x-C-x-C-x-C-x-C-x-C | DBF4, DBF4B, ZDBF2 |
| 28. Zinc fingers MYM-type(ZMYM) | C-x-C-x-C-x-C | ZMYM2, ZMYM3, ZMYM4 |
| 29. Zinc fingers matrin-type(ZMAT) | C-x-C-x-C-x-C | ZNF638, ZMAT1, ZMAT3, ZMAT5 |
| 30. Zinc fingers PARP-type | C-x-C-x-C-x-C | PARP1 |
coordinated immune responses both at the level of transcript as well as post transcriptional level.

**Zinc finger proteins: transcriptional regulation of immune response**

Many of the known zinc finger proteins have an important transcriptional role to play in the regulation of immune response.

**B lymphocyte-induced maturation protein 1 (Blimp-1)**

Although the differentiation of B cell into immunoglobulin secreting cell is one of the important process in biology yet the complete understanding of overall changes in gene expression is relatively poor. One of the zinc finger protein named B lymphocyte-induced maturation protein 1 (Blimp-1) is involved in regulating the terminal differentiation of B lymphocytic cells to antibody secreting plasma cells [7]. It is basically a DNA binding zinc finger protein having a C2H2 type zinc finger consensus. Blimp-1 was first of all cloned from the B cell lymphoma-1 (BCL1) cells from murine upon differentiation to plasma cell state [8] and its enforced expression in mouse spleenocytes or (BCL1) cells helps to convert the B cells to antibody producing plasma B cell primarily by quenching gene expression in mature B cell and by termination of cell cycle in mature B cells. Blimp-1 represses many important genes encoding transcription factors, like the two recently discovered targets (Id3 and Spi-B) involved in regulating signaling by B cell receptor) and PAX5, c-myc, PAX5. Further, Blimp-1 down regulates several transcription factor genes (like E2A, EBF etc.) essential for development and function of B cell. Primarily, Blimp-1 functions as a transcriptional repressor causing differentiation of B cells into plasma cells typified by secretion of antibody M, termination of cell division and syndecan-1(a proteoglycan) expression on the cell surface [9, 10]. The mechanism of action of Blimp-1 is outlined in Fig. 1.

**Early B-cell factors (EBF)** Another protein with its role in B lymphopoiesis and mature B cell function termed as the early B-cell factors (EBF) is a member of an evolutionary conserved transcription factors having an atypical helix-loop-helix motif and zinc finger. The EBF1 protein is characterised by the presence of an N-terminal atypical zinc finger motif (known as “zinc knuckle” with DNA-binding activity important for transcriptional activation of some of the important target genes [11–13]. This transcription factor EBF1 is important in early B cell development primarily for lineage specification. It controls important functions like the development of progenitor-B cell followed by its commitment, and then finally its transformation to the pre-B cell stage. Once activated, EBF1 acts upon its wide range of targets which expresses to form various signaling molecules like Igβ, Igα, VpreB1/2 and surrogate light chains λ5, and all are needed in B-cell development [14]. Infact, the role of this zinc finger protein in B lymphocyte generation is intertwined with other important zinc finger proteins Blimp-1 and zinc finger protein 521 (ZNF521). EBF1 regulates the
activity of Blimp-1 functioning as a transcriptional repressor for primary effector of immune response and maturation of lymphocyte lineage. ZNF521 plays a role in B cell development by inhibiting EBF1 and therefore influences expression of B cell maturation [15]. The involvement of EBF-1 in B-lymphocyte development is outlined in Fig. 2.

Leukemia/lymphoma-related factor (LRF) Another finger protein named as leukemia/lymphoma-related factor (LRF), which forms dimer in the B lymphocyte nucleus is known to regulate humoral immune response and fate of mature B cell [16].

Zbtb1 (zinc finger and BTB domain containing 1), also known as BTB-ZF The transcriptional regulators involved in development of lymphocytes are of special interest in the field of biology and research with many of them playing a vital role in lymphoid tumorigenesis [17, 18] and some of them involved in directing reprogramming of cell fate [19]. One of the most important transcriptional regulator Zbtb1 (zinc finger and BTB domain containing 1), also known as BTB-ZF (Broad complex, Tramtrack, and Bric à brac–zinc finger) influences different processes in immune system like the development of lymphocytes from common lymphoid progenitor (CLP) [20], T lymphocyte versus B lymphocyte development [21], T-helper cell versus Tcytotoxic cell selection [22] and also the development of Natural killer T cell lineage [23]. There are around 49 Zbtb gene family members in mammals containing multiple C2H2 zinc finger domains, with two Cys and two His residues in a C-2-C-12-H-3-H sequence in canonical form. Zn atom stabilizes 12 central residues in the Zbtb forming a projection which interacts with the major groove in a double stranded helix [24]. Examples of proteins belonging to Zbtb family include Th-POK/ZFP67, PLZF, BCL6/ZNF51 and PLZF/Zbtb16 etc. ZBTB1, like many of the other proteins belonging to Zbtb family act as potential transcriptional repressor, function as switches at branch points in different developmental pathways of human immune system [25, 26] analyzed the transcriptional activity of truncated Zbtb1 proteins containing either a BTB or ZNF functional domain, and concluded that the ZNF domain exhibited strongest repressive activity.

Kruppel-associated box domain (KRAB-ZFPs) One of the important Zinc finger protein Kruppel-associated box domain (KRAB-ZFPs) is a member of one of the largest transcriptional regulators family. These proteins are characterized by the presence of KRAB domain localized at the amino terminus and an array of zinc fingers present at the carboxyl terminus which binds DNA. KAP1 (also known as TRIM28) is a co-factor which helps these proteins in regulating different processes at transcriptional level. One of the important role played by these zinc finger proteins (KRAB-ZFPs) is in adaptive immune system where they are involved in the control of viral replication. Both KAP1 and KRAB-ZFP are associated with the repression of Kaposi’s sarcoma-associated herpes virus (KSHV). The best characterized example of zinc finger protein is ZNF426 (K-RBP) known to repress transcription of the KSHV transactivator RTA gene known to induce lytic phase from its latent stage and KAP1 which binds and repress several KSHV genes involved in lytic phase [27, 28].

Human immunodeficiency virus (HIV) is also known to be regulated at transcriptional level by zinc finger proteins and two KRAB-ZFPs. HIV infection in macrophages leads to the upregulation of ZNF175 (OTK18) gene which has shown promising results in the regulation of HIV transcription [29, 30]. Other Zinc finger protein ZBRK1 in combination with KAP1 binds and control expression of HIV promoter [31].

Also another important role played by KRAB-KAP1 complex is in the regulation of c-Rel/NFkB transcription factors which are implicated in the control of interleukins and lineage specific transcription factors. The zinc finger complex negative regulates NFkB transcriptional activity by inhibiting acetylation (through interaction with acetyltransferase p300/CREB) of NFkB present at the interleukin-6 (IL-6) gene [32]. It is important to mention the role of signal transducers and activators of transcription 3 (STAT 3) which is one of the main activators of cytokine genes for T lymphocytes and help in driving B cell differentiation. KAP1 primarily exerts its role as transcriptional regulator of NFkB through its interaction with STAT3 [33].

Zinc finger proteins: post transcriptional regulation of immune response

Though the transcriptional control of immune response is well defined, yet the importance of post transcriptional
regulation of the immune responses combating infectious microbes is still a matter of enigma. There are various steps of RNA metabolism like capping at 5′ end, splicing of introns, addition of poly A tail at 3′ end and degradation where the post transcriptional control can occur. Although, zinc finger proteins are basically the transcription factors which bind DNA, sixty CCCH zinc finger proteins so far identified in mice and humans function as RNA binding proteins and are implicated in the regulation of RNA metabolism [34]. CCCH zinc finger proteins as the name suggests consist of three cysteines and a histidine residue with one or more characteristic CCCH zinc finger domain. The functional importance of these Zinc finger proteins (Zfps) has not been extensively elucidated. However, few definitive studies have suggested the role of these in a diverse array of biological immune responses like the production of cytokines, activation of B and T cells of immune system, antiviral responses and immune homeostasis to name a few [35, 36].

**Three Main CCCH protein families**

There are three CCCH zinc protein families which are evolutionarily closely related- tristetraprolin(TTP), roquin 1 and roquin 2, and monocyte chemotactic protein-induced protein 1 (MCPIP1) or regnase 1, which targets mRNA for degradation and modulate various signalling pathways to control the activation of both adaptive and innate immune responses [34].

**TTP**

It belongs to Zfp36 gene family and was discovered when fibroblasts were stimulated with mitogens and growth factors [37, 38]. This protein is known to associate with the AU rich elements(AREs) in mRNA and this increases the likelihood of mRNA degradation by causing the removal of polyadenylated tail (deadenylation) [39]. Besides containing the unique CCCH zinc finger domains, this protein also contains three proline rich domains, a conserved NOT1 binding domain present at the C terminus which binds the NOT1 scaffolding protein and nuclear export sequence localized at the amino terminus.

**Physiological roles of TTP**

**Tumor Necrosis Factor (TNF) production regulation**

The mRNAs encoding cytokine TNF (a mediator of immune and inflammatory responses) are normally subjected to degradation involving the AREs in the 3′UTR. The TTP is a sine quano element in this regard because of its direct binding to AREs in the 3′-UTR and moreover it also recruits two key complexes (CCR4-CAF1-NOT1 deadenylase and 4EHP-GYF2 cap binding complex) for the destabilization of mRNA by deletion of AREs from the transcript which thereby results in the TNF hypersecretion [40]. The experimental evidence for the role of TTP in this aspect came from the studies in which it was shown that the mice lacking TTP developed several pathological conditions like inflammatory arthritis, dermatitis, autoantibodies generation, cachexia and myeloid hyperplasia [41]. Moreover, when such deficient mice were treated with either antibody specific for TNF or crossed with mice deficient in TNF receptor 1, the occurrence of above pathological states could be mitigated.

**Interleukin 6 (IL-6, Aproinflammatory cytokine) production regulation**

The IL-6 transcript is unique because of the presence of five ARE in the 3′-UTR and can promote the destabilization of mRNA by binding to ARE2, ARE3 and ARE4. A study conducted by [42] showed that the mice deficient in TTP and injected with IL-1β depicted marked elevation in IL-6 production which therefore opines that TTP is involved in the direct regulation of IL-6.

**Interleukin 10 (IL-10) production regulation**

It acts as an inhibitor of inflammation through the suppression of pro-inflammatory cytokine production by macrophages. As with other cytokines, TTP was known to mediate mRNA degradation by direct binding to ARE in the 3′-UTR [43]. Moreover, IL-10 induced TTP expression in macrophages through activation of STAT3 (activator and signal transducer of transcription) which therefore conjures the negative feedback loop controlling IL-10 cytokine production [44].

**Roquin**

It was discovered as a product of the mutation taking place in the Roquin gene locus [45]. This is unique because it is known to have ROQ domain (~ 300 amino acids) through which it recognizes the stem loop motifs present in the 3′-UTR of its target mRNA. It promotes the degradation of mRNA by interacting with an additional enhancer protein like EDC4 (decapping protein) and RCK(helicase protein) [46, 47].

**Physiological roles of roquin 1**

**TNF production regulation**

This protein mediates TNF mRNA degradation by binding to the Constitutive Decay Element(CDE) present downstream to the ARE in the 3′-UTR through its ROQ domain and also
recruits RCK (a helicase) and EDC4 (decapping enzyme) [48]. It is noteworthy here that both TTP and Roquin CCCH zinc finger proteins are involved in the TNF production regulation as is evident from an in vivo study in which Roquin 1san/san mice developed pathological conditions of inflammation and arthritis just like mice deficient in TTP [49]. As reports are coming from across the global scientific community that insurmountable levels of TNF are associated with development of an inflammatory response in the lungs of patients affected with COVID-19 [50], the complex TTP and Roquin pathways might be the novel drug targets for the treatment of coronavirus pandemic along with other inflammatory diseases.

**MCPIP1, MCPIP2, MCPIP3 and MCPIP4**

These contain RNase domain rich in Serine residues at the carboxyl terminus, an ubiquitin associated domain at the amino terminus besides containing the CCCH zinc finger domain [51]. These are known to mediate the decay of mRNA by the binding of RNase domain to the target mRNA where it depicts an intrinsic ribonuclease action.

**Physiological roles of MCPIP1**

**IL-6 production regulation**

It is a key regulator for the production of IL-6 by macrophages and mediates this action by binding and cleaving a conserved stem loop element present in the transcript of IL-6 at the 3′-UTR through its endonuclease activity aided by a helicase (UPF1) [51, 52]. This finding was supported by the fact that the mice lacking MCPIP1 depicted higher IL-6 levels as compared to normal mice since its mRNA was found to be more stable in MCPIP1 deficient macrophages compared with the normal wild type macrophages [51]. MCPIP1 and Roquin CCCH Zinc finger proteins are known to cause degradation of mRNAs at different phases of immune response, with MCPIP1 controlling the early phase and degrading active mRNA whereas Roquin 1 controlled the later phase of inflammation by degradation of an inactive mRNA. These findings corroborate the fact that the three CCCH zinc finger proteins (TTP, MCPIP1 and Roquin 1) involve a complex interplay to coordinate the pro-inflammatory and anti-inflammatory cytokine expression in order to generate an efficient and timely immune response.

Apart from the physiological roles of Roquin, TTP and MCPIP1 discussed above, the CCCH zinc finger proteins have a role in macrophage activation, T cell activation etc.

**Role of CCCH zinc finger proteins in macrophage activation**

The CCCH zinc finger proteins are known to control macrophage activation at the level of post transcription by causing the degradation of the inflammatory cytokines (TNF, IL-6, IL-10 etc.) mRNA or causing attenuation of the RNA synthesis through inhibition of the various signal transduction pathways that activate their expression. Basically, macrophages are known to express pattern recognition receptors (PRRs) which are important for the activation of various transcription factors like AP-1 and NF-κB and therefore this leads to the cytokine expression involved in the immune activation [34]. TLR ligands like Lipopolysaccharide (LPS) and various pro-inflammatory cytokines like IL-1β, TNF induces the expression of MCPIP1 mRNA which in turn negatively regulate the activation of macrophages through various mechanisms. To exemplify, this involves the ribonuclease activity of MCPIP1 in order to induce the degradation of pro-inflammatory cytokines (IL-12, IL-6, IL-1β) mRNA [53]. In addition to this, MCPIP1 might act as an adapter molecule involved in the formation of a complex with other proteins like USP10 and TANK to inhibit transcription factors like NF-κB and JNK (mitogen activated protein kinase) by promoting the deubiquitylation of TNF receptor associated factor 3 and factor 6 [54–56]. TTP was shown to negatively regulate the NF-κB signalling by functioning as a co-repressor or by interfering with the translocation of p65 in the nucleus [57–59]. The experimental evidence for the TTP and MCPIP1 mediating their effects through the same pathway came from the mice models lacking TTP and MCPIP1 which were shown to be highly sensitive to LPS induced septic shock due to elevated TNF levels [60, 61]. Although Regnase and TTP was shown to negatively regulate NF-κB signalling, Roquin was known to promote the activity of the NF-κB kinase inhibitor (IKK). This is accomplished by causing degradation of an Ubiquitin editing enzyme (A20) mRNA through its CCCH zinc finger and ROQ domains which interact with a stem loop structure present downstream to the ARE in the 3′-UTR [62].

**Role of CCCH zinc finger proteins in T cell activation**

In the T cells, the CCCH zinc finger proteins are highly expressed [51]. MCPIP1 is of paramount importance in preventing the autoantibodies generation in a process known as autoimmunity. The negative regulation of T cell activation involves the degradation of mRNA expressing various immunoregulatory molecules like REL which is normally associated with the TH1 cell activation for the generation of autoimmune disorders [63]. The functional validation for this role was confirmed by studies in mouse models deficient in MCPIP1, where the loss of REL inhibited the generation
of the auto-immunity which thereby authenticates that the increased REL expression because of defect in mRNA decay contributes to T cell activation [64].

Besides the destabilization of mRNA, splicing of mRNA to remove introns is also vital to negatively regulate T cell activation. CD45 (a tyrosine phosphatase) removes inhibitory phosphate from various kinases like LCK and SRC and is involved in the T cell activation [65]. The CCCH zinc finger protein U2AF26 cooperates with GF11 to cause CD45 splicing which results in the formation of CD45RO isoform that is transcriptionally less active [66].

That being said, these studies reiterate the fact that post transcriptional events especially mRNA decay is vital to suppress the aberrant activation of both the adaptive and innate immune responses.

Conclusion

It is reasonable to conclude that zinc finger proteins have an important role to play in the regulation of immune responses at transcriptional and post transcriptional levels. Insights into these pathway and mechanism of regulation by zinc finger proteins might provide clues for targets implicated in the treatment of various inflammatory and autoimmune diseases.

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Declarations

Conflict of interest The authors do not have any financial or non-financial conflict of interest.

Informed consent All the authors declare their consent for publication.

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