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# Role of tristetrapolin protein in muscle regeneration: an *Insilico* analysis

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**Abstract**
Skeletal muscle has a highly complex structure and shaving a numerous roles animal body. A set of inhouse satellite has an interal role in the regeneration pathway forming new myofibers post tissue damage due to injury or a degeneration. On getting a signal of from necrosis in muscle fibres, satellite cells get activated, have an asymmetric division to self-generate, and form activated myoblasts capable of proliferating and reaching the site of damage, and bind to the already present myofibers or create newer ones. It is known that Tristetraprolin, an RNA-binding protein involved in the regulation of cytokine expression has a function of muscle regeneration. Tristetraprolin is present in humans, mice and rats. It is encoded by the Zinc Ring Finger Protein 36 gene. In this study, we have elucidated the role of Tristetraprolin in muscle regeneration by using *insilico* approaches.

**Keywords:** Muscle, regeneration, transcripts, RNA-binding protein

## 1. Introduction
Messenger RNA decay is a important way to regulate the expression of numerous inflammation- and cancer-related genes [1]. These transcripts are tagged for quick breakdown via AU-rich element (ARE) motifs present in the mRNA 3'untranslated region (3'UTR) [2]. Tristetraprolin (TTP), also termed as zinc finger protein 36 homolog ZFP36, is present in humans, mice and rats and encoded by the ZFP36 gene [3].

TTP, an RNA-binding protein performs a pivotal function of regulating the expression of ARE-encompassing mRNAs. Owing to its potential of attaching to AREs it tags the corresponding mRNA for quick breakdown, TTP can decrease the expression of numerous important genes generally overexpressed during inflammation and cancer. Mice deficit in TTP have a complicated syndrome of inflammatory diseases [4]. Regulation of TTP is at many strata via cellular signaling pathways to regulate transcription, mRNA turnover, phosphorylation status, cellular localization, binding to other proteins, and proteosomal degradation, all affecting TTP's potential to enhance ARE-promoted mRNA desaggregation and decay-independent role of TTP.

Regeneration of damaged muscle is a complicated pathway encompassing numerous cell types and the mediation of a many growth factors, cytokines, chemokines, extracellular matrix components and signaling molecules [5]. Skeletal muscle development, repair and function rely on highly regulated expression of many genes. Myogenic precursor cells called satellite cells exist in adult skeletal muscle. Satellite cells refer to adult myogenic stem cells that regenerate damaged muscle. The capability for muscle regeneration needs effective satellite cell expansion post injury, their differentiation to form myoblasts that can reform damaged fibres and their self-renewal to regenerate the muscle stem cell pool for further cycles of injury and recovery. Dormant satellite cells are activated via signals coming from damaged muscle. Sachidanandan *et al.* have shown the quick activation of two genes post to muscle injury; these transcripts encode LPS-inducible CXC chemokine (LIX), a neutrophil chemoattractant, and Tristetraprolin (TTP), an RNA-binding protein involved in the regulation of cytokine expression [5]. LIX and TTP mRNAs have a short life span and are quickly upregulated in reply to muscle damage *in vivo* [5]. Along with generating new cells for repair, induced satellite cells might be a reservoir of signaling molecules implicated in tissue remodeling during regeneration [5]. Tristetraproline (TTP) binds RNAs that has AU-rich parts and binds enzymes that degrade RNA. The activity of TTP is controlled by phosphorylation. MK2 phosphorylates TTP that further binds 14-3-3.

The binding to 14-3-3 restricts phosphorylated TTP from having assess to stress granules and stabilizes mRNA flanked by phosphorylated TTP [6].

This studies suggest that TTP is playing an important role in muscle regeneration. In this paper *insilico* approaches have been used to study the interactions of TTP with other proteins through which it could be playing a role in muscle regeneration.

## 2. Material and Methods

**String –** The interactions network of the TTP protein with other protein was found out using the STRING database (http://string-db.org) [7]. The sequence used as a query was the human TTP protein Accession no. AAA61240 retrieved from NCBI database. (http://www.ncbi.nlm.nih.gov/protein) [8].

**Bio grid –**The interactions of TTP protein were also studied using BIOGRID database (https://thebiogrid.org/) [9].

## 3. Results and Discussion

TTP is an RNA-binding protein that plays a role in regulating the expression of ARE-containing mRNAs. It has the ability to bind AREs and target the bound mRNA for rapid degradation. It has been cited in literature that TTP expression increases after muscle injury [5]. In the present study we have used *insilico* approaches to find the role of TTP protein in muscle regeneration after injury. The results of the protein interaction databases STRING (Fig 1 and Table 1) and BIOGRID (Fig 2 and Table 2) showed that TTP interacts with various proteins like chemokines, proteins involved in cytoskeleton organization, phosphorylation etc.

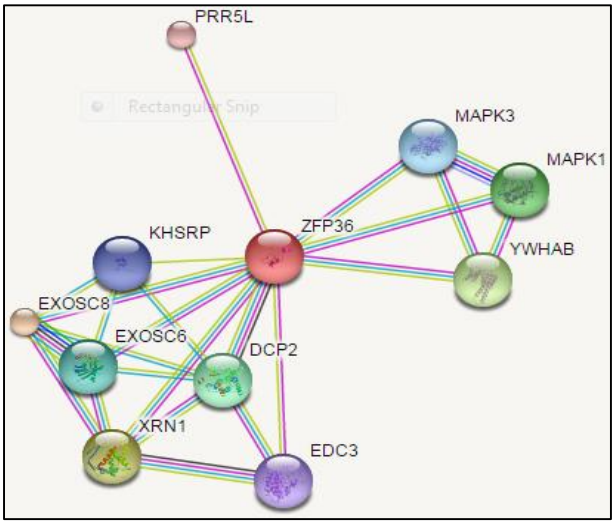


**Fig 1:** Showing the protein interactions of Human TTP protein using the STRING database

**Table 1:** TTP interacting proteins using string database

| S. No. | TTP Interacting Protein | Functions |
|---|---|---|
| 1 | EXOSX8 | 3'-5' exoribonuclease activity and participates in degrading events. It help in the elimination of mRNA with processing defects |
| 2 | EXOSX6 | Play role in replication dependent histone mRNA degradation, major 5'-3' exoribonuclease |
| 3 | EDC3 | Enchance mRNA decapping |
| 4 | KHSRP | Degrade unstable mRNA by recruiting degrading machinery |
| 5 | PRR5L | Modulate phosphorylation of PKCA and regulate actin cyto-skeleton organization |
| 6 | MAPK3 | Extracellular signal regulated kinase important role in MAPK/ERK cascade this signaling pathway mediate cell growth and differentiation through regulating transcription |
| 7 | YWHAB | Adaptor protein implicated in the regulation of specialized signaling pathway |
| 8 | RGS16 | Regulator of G protein signaling family. Inhibition of G protein subunit by GTP ase. |

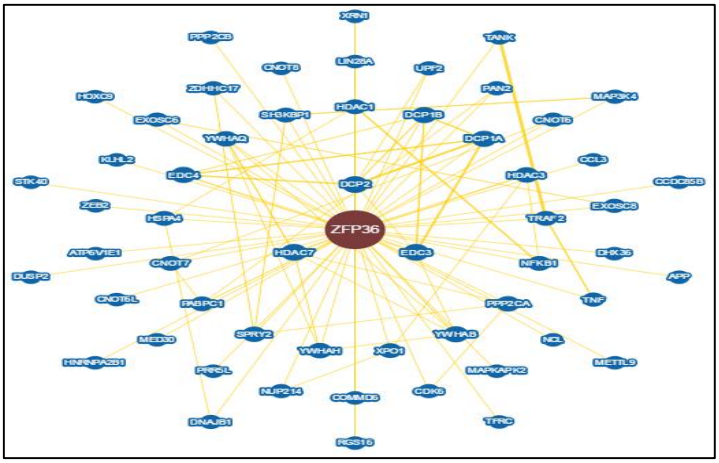


**Fig 2:** Showing the protein interactions of Human TTP protein using the BIOGRID database

**Table 2:** TTP interacting proteins using bio grid

| S. No | TTP Interacting Proteins | Functions |
|---|---|---|
| 1 | APP | Activate a widespread caspases dependent self destruction program |
| 2 | ATP6V1E1 | Hydrogen exchange ATPase helps in phosphorylation |
| 3 | CCDC85B | Hydrogen exchange ATPase helps in phosphorylation |
| 4 | CCl3 | It is a chemokine which increases rapidly during muscle injury and returns to control levels during muscle regeneration by stimulating myoblast proliferation |
| 5 | CNOT6L | involved in deadenylation dependent degradation of CDKMIB mRNA mediates peroliferation and cell survival and prevent cellular senescence |
| 6 | CNOT6 | Function as poly A nuclease |
| 7 | CNOT7,CNOT8 | 3'-5' exoribonuclease activity forms complex with CCR4-NOT for bulk mRNA decay |
| 8 | COMMD6 | Negative regulation of NF kappa B transcription factor activity |
| 9 | DCP1A,DCP1B | Main activatiom of DCP2 |
| 10 | DCP2 | Forms complex with DCP main decoupling enzyme |
| 11 | DHX36 | RNA helicases associated with AU rich element |
| 12 | DNAJB1 | Heat shock protein |
| 13 | DUSP2 | Dual phosphatase, terminate MAPK activity and helps in dephosphorylation |
| 14 | EDC3 | Enchancer of mRNA decapping |
| 15 | EDC4 | Involved in deadenylation dependent decay |
| 16 | EX0SC6 | Required for rapid degradation of ARA containing RNA but not for poly A shortening |
| 17 | EXOSC8 | Shows 3'-5' exoribonuclease activity and participates in degrading events eliminating mRNA with processing defects |
| 18 | HDAC1 | Global repressor but regulate specific genes by repressing and activation at specific parts |
| 19 | HDAC3 | Effective co repressor acts as binding site for myocyte enhancer factor 2 |
| 20 | HDAC7 | Involves in maturation by repressing of myocyte enhancer factor(MEF-1) |
| 21 | HNRNPA2B1 | Helps in poly A RNA binding |
| 22 | HSPA4 | it is co enzyme and enzyme regulator which Binds with ATP, selectively and non covalently |
| 23 | KLHL2 | Helps the factor binds to RNA |
| 24 | MAP3K4 | Activates by mytogenic stimulation due to environment |
| 25 | MAPKAPK2 | Medicates phosphoryl of TTP which regulates myo- D by mRNA decay leads in the activation of satellite cell regulation |
| 26 | MED30 | Facilitates gene expression by various transcription activation |
| 27 | METTL9 | Function to help in Protein binding |
| 28 | NCL | Abundantly expressed acidic phosphoprotein in growing cell |
| 29 | NFKB1 | Involved in negative regulation of transcription helps in binding to regulatory region |
| 30 | NUP214 | Mediates nucleocytoplasmic transport |

Analyzing the protein interactions from these two databases we have shortlisted a list of proteins like PRR5L, MAPK3, CCl3, HDACs etc. having a probable role in muscle regeneration as listed in Table 3.

**Table 3:** TTP interactions playing a role in Muscle regeneration.

| S. No. | TTP Interacting Protein | Functions |
|---|---|---|
| 1 | PRR5L | Modulate phosphorylation of PKCA and regulate actin cyto -skeleton organization |
| 2 | MAPK3 | Extracellular signal regulated kinase important role in MAPK/ERK cascade this signaling pathway mediate cell growth and differentiation through regulating transcription |
| 3 | YWHAB | Adaptor protein implicated in the regulation of specialized signaling pathway |
| 4 | RGS16 | Regulator of G protein signaling family. Inhibition of G protein subunit by GTPase. |
| 5 | PRR5L | Modulate phosphorylation of PKCA and regulate actin cyto -skeleton organization |
| 6 | CCl3 | It is a chemokine which increases rapidly during muscle injury and returns to control levels during muscle regeneration by stimulating myoblast proliferation |
| 7 | HDAC1 | Global repressor but regulate specific genes by repressing and activation at specific parts |
| 8 | HDAC3 | Effective co repressor acts as binding site for myocyte enhancer factor 2 |
| 9 | HDAC7 | Involves in maturation by repressing of myocyte enhancer factor(MEF-1) |

It can be seen that TTP binds either to ARE-containg mRNAs, or to MAP kinases (Table 1). MAP kinases have a role of phosphorylating TTP at the $Ser^{52}$ and $Ser^{178}$ positions, so prevents its interface with and employment of explicit deadenylases to the target mRNAs [6]. TTP interactions with YWHAB stops its nuclear translocation [10].

## 4. Conclusions

There are reports in literature citing the role of TTP in muscle cell regeneration. In this study, we have used the protein interaction databases to explain the role of TTP in muscle regeneration. It was seen that it does so by interacting with a number of proteins involved in cytoskeleton rearrangement, chemokine secretion, cell growth and signaling pathways (Table 3). This study shows that *insilico* approaches can be used for elucidating protein function. In this study protein interactions have been used to characterize the function of TTP in muscle regeneration. These may be further corroborated by using *invitro* approaches.

## 5. Acknowledgments

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