

ACTIVATION OF TELOMERE SIGNALING AND MAINTENANCE PATHWAYS IN IDIOPATHIC INFERTILE MEN TREATED WITH ANTIOXIDANTS: AN IN-SILICO ANALYSIS OF SPERM PROTEOME

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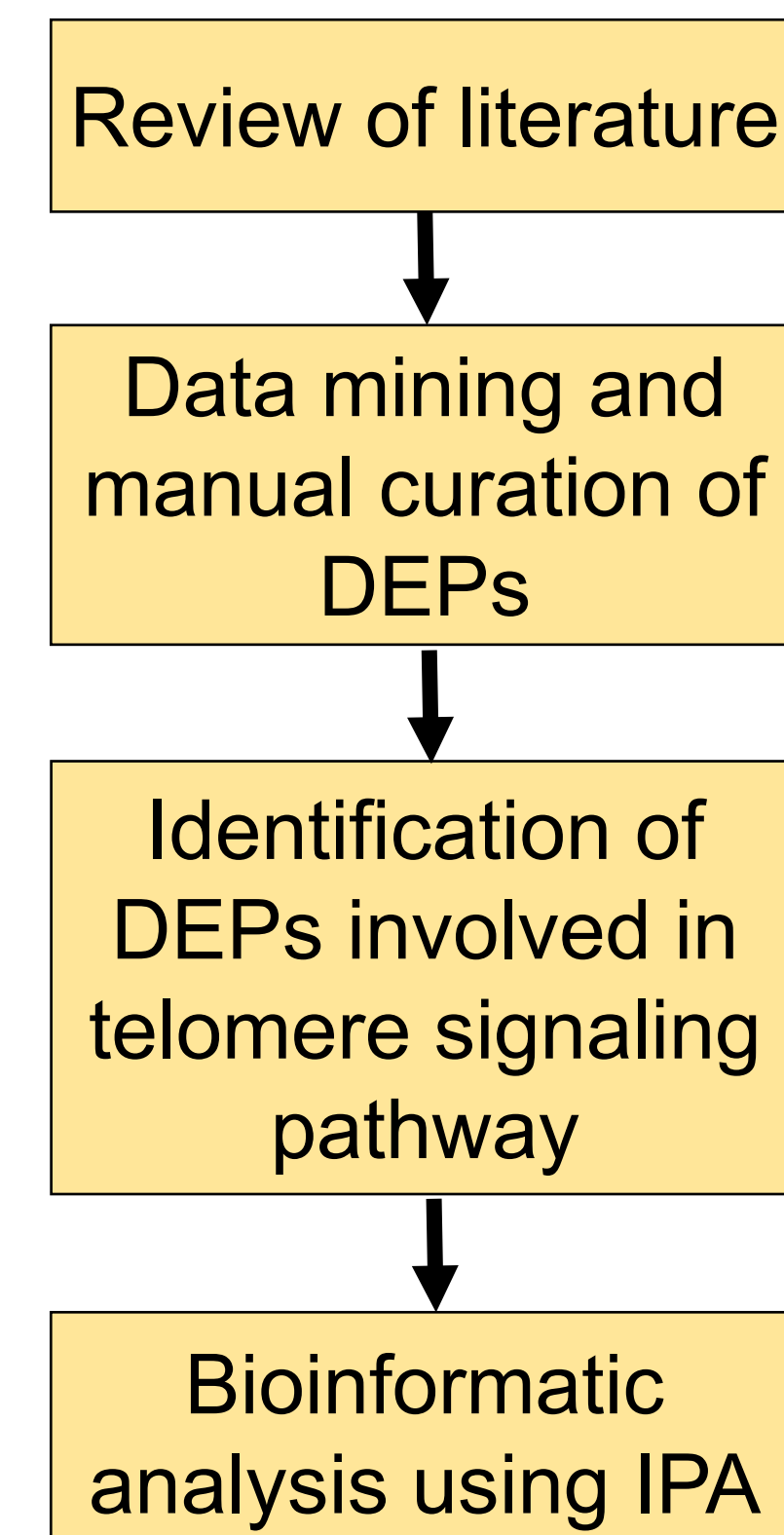
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INTRODUCTION

- ❖ Telomere protects the chromosomal DNA from damage and is considered as a marker of cellular senescence. Oxidative stress (OS) linked to male infertility can trigger or accelerate telomere shortening.
- ❖ Antioxidant (AOX) therapy is widely used in the management of OS-mediated male infertility. However, the role of antioxidants in modulating sperm telomere signaling and maintenance is unknown.
- ❖ The main objective is to conduct *in silico* analysis of sperm proteome of patients subjected to AOX treatment to understand the effect of AOX on pathways involved in regulating sperm telomere length in infertile men.

METHODS

- ❖ A comprehensive literature search was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
- ❖ Annotated and curated proteins were subjected to downstream analysis using ingenuity pathway analysis (IPA) software.
- ❖ Molecular Interaction Search Tool (MIST) was used to display interaction between the transcription factors and kinases associated with telomere signaling and maintenance pathway.



RESULTS

- ❖ A total of 73 upstream regulators and 338 master regulators were found to be either activated (Z-score ≥ 2) or inhibited (Z-score ≤ -2) in sperm after antioxidant treatment.
- ❖ In-depth analysis revealed activation of two kinases (EGFR and MAPK3) and 4 transcription factors (CCNE1, H2AX, MYC, RB1 and TP53) associated with telomere function (Table 1). MIST analysis displayed the interaction type (protein-protein or genetic) between these molecules and their abundance in the testis (Fig 1).

Molecule	Category	Z-score	Telomere associated function(s)
MYC	Transcription regulator	4.67	Telomere signaling, maintenance of telomere length
CCNE1		3.04	Clustering of telomere
MAPK3	Kinase	2.75	Modification of telomere length
TP53	Transcription regulator	2.53	Telomere signaling, maintenance of telomere length
RB1		2.35	Telomere signaling, maintenance of telomere length
H2AX		2.09	Modification of telomere length
EGFR	Kinase	2.06	Telomere signaling

Table 1: Transcription regulators activated in sperm after antioxidant therapy

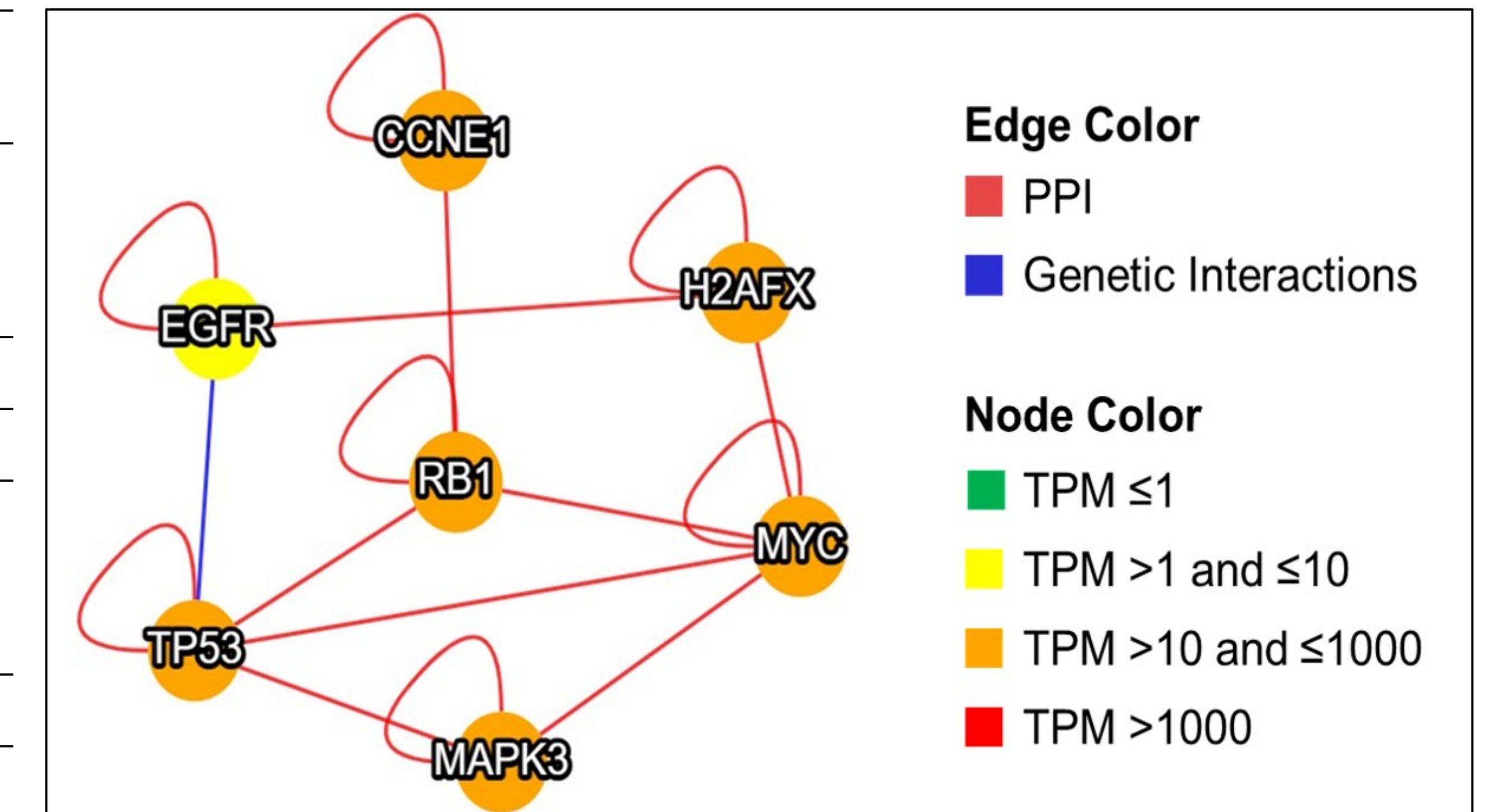


Figure 1: Interaction between transcription regulators and kinases involved in telomere signaling and maintenance pathway in sperm after antioxidant treatment

CONCLUSIONS

- ❖ Using bioinformatic approach, our results demonstrate that antioxidant therapy has positive effect on transcription factors and kinases associated with telomere function in sperm. This is a unique finding.
- ❖ Altered expression of EGFR, MAPK3, CCNE1, H2AX, MYC, RB1, and TP53 can serve as biomarkers for telomere dysfunction in sperm of infertile men, and opens new approaches to target improved therapies.