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Research Article

Co-expression of P53 and P60-katanin shapes transcriptome dynamics

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Abstract: Microtubules (MT), essential elements of the cytoskeleton have important roles in the cell such as intracellular cargo transport, cell motility and cell division. They provide support, growth and maintenance of the axonal and dendritic processes in neurons. Microtubule severing proteins such as katanin and spastin have roles in microtubule reconfiguration. Katanin is one of the best characterized severing proteins and is composed of catalytic subunit p60-katanin and regulatory subunit p80-katanin. The microtubule severing mechanism of p60-katanin has been depicted in detail, but how p60-katanin itself is regulated is still little-known. p53 is an important protein between proliferation and differentiation. It regulates different cellular mechanisms such as cell cycle arrest, senescence, differentiation, and apoptosis. p53 controls proliferation in dividing cells and is related to differentiation by means of affecting neuronal process length in non-dividing neurons. Both p53 and p60-katanin have critical roles in proliferation and differentiation separately. Moreover, these proteins were shown to physically interact, but their combined effect remains unclear. To this aim, the current study reveals the effects of p53 – p60-katanin co-expression on transcriptome of the fibroblast cells. Data indicated that the transcriptome of many different pathways such as actin regulation, neuroactive ligand-receptor interaction, and serotonergic synapses pathways were altered under p53 – p60-katanin co-expression conditions. Exploring combined effect of p53 and p60-katanin will help in design of new studies to better understand not only microtubule regulation but also neurodegenerative diseases that are linked to the reactivation of cell cycle and neuronal damage where two of these players take place.

Özet: Mikrotübüller (MT), hücre iskeletinin temel elemanları olup hücre içi kargo taşınması, hücre hareketliliği ve hücre bölünmesi gibi hücrede önemli rollere sahiptir. Ayrıca sinir hücreleri olan nöronlarda, aksonal ve dendritik yapıların desteklenmesi ve uzaması için önemli görevlere sahiptirler. Katanin ve spastin gibi mikrotübül kesici proteinler, mikrotübüllerin yeniden yapılandırılmasında rol oynar. Katanin, en iyi karakterize edilmiş MT kesici proteinlerden olup, katalitik alt birim p60-katanin ve düzenleyici alt birim p80-katanin'den oluşur. p60-katanin'in mikrotübül kesme mekanizması oldukça iyi bilinmektedir, ancak p60-katanin'in kendisinin nasıl düzenlendiği halen az bilinen bir konudur. p53, proliferasyon ve farklılaşma arasında kritik bir proteindir. Hücre döngüsünü, yaşlanma, farklılaşma ve apoptoz gibi farklı hücresel mekanizmaları düzenler. p53'ün bölünen hücrelerde proliferasyonu kontrol ettiği, bölünmeyen nöronlarda ise farklılaşma ile ilişkili olduğu ortaya konmuştur. Hem p60-katanin hem de p53, ayrı ayrı proliferasyon ve farklılaşmada kritik rollere sahiptir. Ayrıca, bu proteinlerin fiziksel olarak etkileşimde bulunduğu da gösterilmiştir, ancak bu proteinlerin birleşik etkisi belirsizliğini korumaktadır. Bu amaçla, mevcut çalışma, p53 ve p60-katanin'in birlikte eksprese edilmesinin fibroblast hücrelerinin transkriptomu üzerindeki etkilerini ortaya koymaktadır. Veriler, aktin düzenlenmesi, nöroaktif ligand-reseptör etkileşimi, serotonerjik sinaps yolları gibi birçok farklı yolakların transkriptomlarının p53 – p60-katanin'in birlikte ekprese edildiğinde değiştiğini göstermiştir. p53 ve p60-katanin'in birleşik etkisinin araştırılması, sadece mikrotübül düzenlemesini daha iyi anlamak için değil, aynı zamanda bu iki proteinin rol oynadığı hücre bölünmesinin yeniden aktifleşmesi ve nöronal hasarla ilişkili nörodejeneratif hastalıkları daha iyi anlamak için yeni çalışmaların tasarlanmasına da öncülük edecektir.

Introduction

The tumor suppressor protein p53 and the microtubule-severing enzyme p60-katanin play essential roles in various cellular processes such as cell cycle control, DNA damage response, neuronal differentiation

and cytoskeletal organization (Lane 1992, McNally & Vale 1993, Vousden & Prives 2009). p53 acts as a key guardian of genomic integrity by managing the cells' reactions to stress, guiding processes like cell cycle arrest, DNA repair, or apoptosis to ensure genomic stability (Lane 1992, Vousden & Prives 2009). On the other hand, p60-katanin influences microtubule dynamics, which affects cell division, intracellular transport, and overall cell shape (McNally & Vale 1993, McNally 2013). p53 and p60-katanin have roles both in dividing and in non-dividing cells, specifically in the differentiation process of neurons. The role of p60-katanin in neuronal processes is extensively studied. Similarly, p53 was shown to affect neuronal process lengths in non-dividing neurons (Ferreira & Kosik 1996, Hudson *et al.* 2005, Kim *et al.* 2011, Di Giovanni *et al.* 2006).

Although each of these proteins has been studied extensively on its own, their interactions and combined effects on cells' transcriptome are not yet fully understood (Baas 1997, Hayashi & Karl Seder 2013). Available findings suggest that they might affect shared signaling pathways or transcriptional networks, thereby altering how cells respond to different stimuli (Hayashi & Karl Seder 2013). A recent study showed for the first time that p53 and p60-katanin interact physically at protein level via p53's DNA binding domain and p60-katanin's C-terminal (Korulu & Yildiz 2020). However, the exact mechanisms behind this interaction and the full extent of their impact on gene expression are still not clear and need more comprehensive investigation.

This novel finding prompted us to explore the molecular changes that occur when p60-katanin and p53 are co-expressed in the cell. Investigating how p53 and p60-katanin co-expression affects transcriptome of the cell is a crucial step for understanding their complex roles in cellular regulation and disease development (Dai & Lu 2004, Duan *et al.* 2006). These preliminary findings also offer a reliable starting point for upcoming research in the field. Abnormalities in p53 and p60-katanin are linked to various human diseases, including cancer, neurodegenerative conditions, and developmental disorders (Vousden & Prives 2009, McNally 2013). Unraveling the details of their combined effect could provide new insights into disease mechanisms and potentially lead to innovative therapeutic approaches.

Materials and Methods

Construction of the plasmids

Constructs were obtained by cloning p53 (AB082923) and p60-katanin (NM_007044) into 3XFLAG-CMV™-10 and pcDNA3.1/myc-His vectors respectively.

Cell transfection

Rat RFL-6 cells were gifted by Prof. Dr. Arzu Karabay Korkmaz (Istanbul Technical University) and were cultivated in F12K (Lonza, Switzerland) medium containing 20% FBS (Thermo Fisher, USA), NEAA (Lonza) and L-Glutamine (Thermo Fisher). One day prior to transfection, cells were seeded in 6 well-plates, as 500,000/well. The following day, cells were transfected by using Lipofectamine 3000 (Thermo Fisher Scientific, USA). Cells were transfected with either p60-katanin-pcDNA3.1/myc-His and p53-3XFLAG-CMV™-10 (p60-katanin and p53 co-overexpressed) or pcDNA3.1/myc-His and 3XFLAG-CMV™-10 vectors (control cells). RNA extraction was performed 48 hours post transfection by using High Pure RNA Isolation Kit (Roche, Switzerland).

Sample labeling and purification

The Agilent One-Color Microarray-Based Gene Expression Analysis protocol was used for RNA labeling/hybridization. Briefly, total RNA was labeled with Cy3-dCTP during amplification. The labeled cRNAs were purified with the help of RNAeasy Mini Kit (Qiagen, Switzerland) and quantified with the NanoDrop ND-1000 spectrophotometer.

Hybridization and Scan

Labeled cRNA were fragmented to an average size of approximately 50±100 nucleotides by heating with the help of blocking agent and fragmentation buffer. Fragmented cRNA was hybridized and analyzed with the Agilent SurePrint G3 Human GE 8X60K, V3 Microarrays (Agilent®).

Statistical analysis

Gene-enrichment and functional annotation analyses were performed using Gene Ontology (www.geneontology.org) and KEGG (http://kegg.jp).

Results

The transcriptome analysis of RFL-6 cells where p60-katanin and p53 genes were overexpressed revealed significant changes in the mRNA levels of several genes. These changes were relative to control cells where cells were transfected with mock plasmids only and did not contain excessive expression of the proteins. For the current study, briefly, the genes that have over 3-fold up- or down-regulation have been summarized (Fig. 1). FOXO4, PLK5, and LPIN3 showed increased expression, suggesting activation of cellular pathways involved in stress response, cell cycle regulation, and lipid metabolism, respectively. Conversely, EMC10, BTBD8, and HOXC-AS1 exhibited decreased expression, indicating potential disruptions in ER function, transcriptional regulation, and chromatin remodeling (Table 1).

KEGG enrichment pathway analysis was also performed to elucidate the biological significance of the differentially expressed genes/proteins identified. This analysis revealed several enriched pathways associated with various cellular processes summarized in Fig. 2. These findings provide important insights into the possible functional effects of the observed changes in gene expression and shed light on the molecular mechanisms involved in the co-overexpression of p60-katanin and p53.

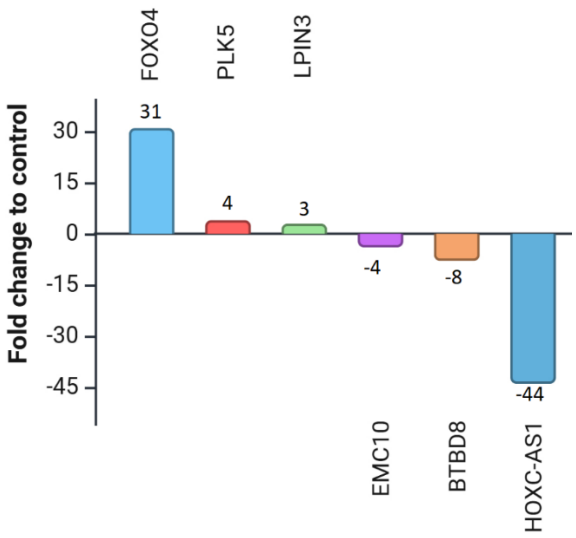

Fig. 1. Genes found to have increased and decreased expression change over 3-fold.

Table 1. Putative biological functions of the differentially expressed genes.

Putative Biological Function	Gene
Transcription factor promoting cell cycle arrest and apoptosis.	FOXO4
Kinase involved in cell cycle progression.	PLK5
Protein involved in lipid phosphate signaling and cytoskeletal remodeling.	LPIN3
Component of the ER exit sites complex, potentially regulating protein trafficking.	EMC10
Protein involved in clathrin-mediated endocytosis and neuronal development.	BTBD8
Antisense RNA potentially regulating HOXC cluster genes important for development.	HOXC-AS1

For instance, transcriptional misregulation in cancer, proteoglycans in cancer, and pathways in cancer were significantly enriched, suggesting a strong link between p60-katanin and p53 co-overexpression and tumor-related processes

Pathways like MAPK signaling, PI3K-Akt signaling, Wnt signaling, and p53 signaling showed notable enrichment. These are crucial pathways regulating cell survival, apoptosis, and growth, further indicating the potential role of p60-katanin and p53 in cell fate decisions. Additionally, pathways like regulation of actin cytoskeleton and cell cycle were also enriched, highlighting changes in cytoskeletal dynamics and cell division, consistent with p60-katanin's role in microtubule severing. Moreover, neuroactive ligand-receptor interaction, serotonergic synapse, and synaptic vesicle cycle pathways were implicated, suggesting that the co-overexpression might also affect neuronal function and differentiation.

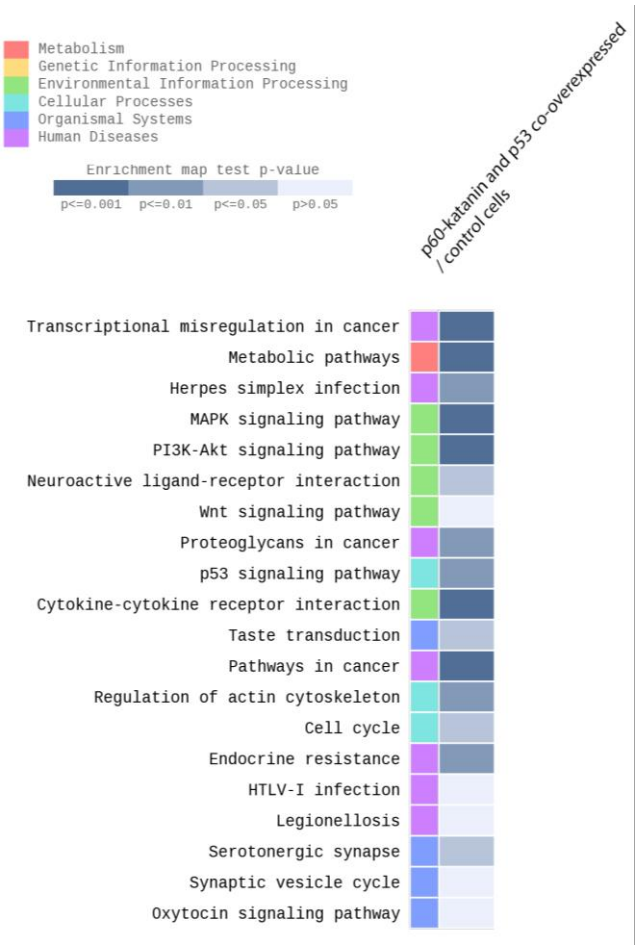

Fig. 2. KEGG enrichment pathway analysis.

Discussion

When comparing transcription changes in cells co-overexpressing p60-katanin and p53, the gene expression profile reveals significant alterations in the expression of key genes involved in various cellular processes. For instance, FOXO4, known to interact with p53 in regulating senescence and apoptosis, may play a critical role in how the co-overexpression of p60-katanin and p53 affects the transcriptional misregulation observed in cancer-related pathways. (Zhang *et al.* 2023). FOXO4's role in inhibiting p53-mediated apoptosis aligns with the observed enrichment in pathways like the p53 signaling pathway and transcriptional misregulation in cancer (Fig. 1). This indicates that FOXO4 could modulate p53's effects under co-overexpression, either by enhancing or shadowing p53-driven pathways (Zhang *et al.* 2023). On the other hand, PLK5 and LPIN3 suggest a coordinated cellular response to environmental stimuli or metabolic needs (de Cárcer *et al.* 2011). The modest rise in PLK5, a cell cycle regulator, may signal an active cell division phase or a reaction to DNA damage, aiding in cellular proliferation and repair. The enrichment in pathways like MAPK signaling and PI3K-Akt signaling, both of which are crucial for cellular growth and survival (de Cárcer *et al.* 2011) points towards a potential regulatory role for PLK5 in these pathways. PLK5 may interact with these

signaling cascades, particularly in neuronal cells, where p60-katanin is involved in cytoskeletal dynamics. Since PLK5 is also involved in the DNA damage response (de Cárcer *et al.* 2011), it could synergize with p53 to enhance cellular responses to stress, including regulation of actin cytoskeleton and neuronal differentiation processes. On the other hand, the human PLK5 gene is significantly silenced in astrocytoma and glioblastoma by promoter hypermethylation, suggesting a tumor suppressor function for this gene (de Cárcer *et al.* 2011). Additionally, the upregulation of LPIN3, a lipid metabolism regulator (Su *et al.* 2023), points to increased lipid biosynthesis or metabolic adjustments to fulfill cellular energy requirements. PLK5, the least studied member of the PLK family, is involved in neurodevelopment and tumor suppression (Su *et al.* 2023). Finally, LPIN3's role in maintaining lipid homeostasis could influence cellular membrane dynamics, which may affect processes like synaptic vesicle cycling, an enriched pathway in this analysis. This suggests that LPIN3 could be influencing neuronal structure and signaling indirectly through its regulation of lipid metabolism, which may further connect with p60-katanin's known role in regulating microtubule dynamics.

In contrast, the decreased expression of EMC10, BTBD8, and HOXC-AS1 highlights potential disruptions in cellular balance or regulatory pathways.

In response to cellular stress, p53 triggers apoptosis. However, when overexpressed, it can disrupt protein synthesis and cause ER stress, affecting the levels of essential proteins like EMC10. On the other hand, since p53 regulates promoter of p60-katanin (Kırımtay *et al.* 2020), overexpression of both proteins could probably result with excessive activity of p60-katanin, hence severing and disruption of microtubules, thus disruption of railways required for protein delivery. Reduced levels of EMC10, which is involved in ER protein translocation and quality control, may impair protein folding or ER function, leading to cellular stress as well. Moreover, EMC10 was shown to be a strong candidate that plays a key role in developmental milestones, with the potential to cause neurodevelopmental disorders in humans (Umair *et al.* 2020).

BTBD8, also known as AP2-Interacting Protein, silencing in neurons was associated with severe impairment of maturation at early developmental stages, reduced synaptic vesicle density, enlarged endosome-like structures, and defects in synaptic transmission, consistent with an impaired clathrin/AP2-mediated synaptic vesicle recycling (Piccini *et al.* 2017). Since BTBD8 is involved in clathrin-mediated endocytosis and synaptic vesicle recycling, the disruption of microtubule dynamics caused by p60 overexpression can impair these processes, leading to reduced synaptic vesicle density and defects in synaptic transmission. This suggests that BTBD8's function is closely tied to the stability and organization of the microtubule network.

The significant downregulation of HOXC-AS1 (A long non-coding RNA HOXC cluster antisense RNA 1), suggests significant changes in chromatin remodeling and developmental processes. p53 can epigenetically suppress the expression of non-coding RNAs like HOXC-AS1 (Parfenyev *et al.* 2021). On the other hand, the effects of p60-katanin on the cytoskeleton can lead to disruptions in chromatin structure and the organization of genetic material (Lombino *et al.* 2019). Both p53 and p60-katanin can directly or indirectly suppress HOXC-AS1 transcription. In addition, HOXC-AS1 was shown to have cancer-promoting effect (Yang *et al.* 2023). Overexpression of p53 enhances its ability to induce cell cycle arrest and apoptosis, preventing the proliferation of damaged cells. Simultaneously, downregulation of HOXC-AS1 reduces oncogenic signals, supporting p53's tumor-suppressing functions. Together, these mechanisms maintain cellular homeostasis.

Overall, these gene expression changes reflect the dynamic responses of cells to internal and external signals, underscoring the complex interplay of cellular pathways and gene regulation in maintaining homeostasis and adapting to environmental challenges.

As a result, it is thought that p53 and p60-katanin proteins may play a role in the regulation of molecules such as Foxo4, PLK5, LPIN3, EMC10, BTBD8 and HOXC-AS1 by working together. This suggests that critical cellular processes such as cell cycle, apoptosis, intracellular protein traffic, and endocytosis can be coordinated under the joint influence of these two proteins and a wide range of cellular functions can be managed. This cooperation of p53 and p60-katanin may play an important role in maintaining cellular homeostasis by affecting many vital processes from cell cycle control to gene expression regulation.

Additional experimental validation, by means of i.e. qRT-PCR, functional assays, and network analysis, may provide further depth to the findings, and these additional experiments may be pursued in future work when resources allow. Despite these limitations, the current data offer valuable insights for the research in this area.

Ethics Committee Approval: Since the article does not contain any studies with human or animal subject, its approval to the ethics committee was not required.

Data Sharing Statement: All data are available within the study.

Conflict of Interest: The author has no conflicts of interest to declare.

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