New roles in mitochondria are revealed by the NEK10 interactome and depletion.

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Abstract

Different facets of the cell cycle are controlled by members of the NEK protein kinase family (also known as NIMA-related kinases). According to reports, NEK10 participated in the upkeep of the G2/M checkpoint after being exposed to ultraviolet radiation. On the other hand, the functions of the NEK1, NEK5, NEK2, and NEK4 proteins have been connected to mitochondria. HEK293T cells were transfected with FLAG-NEK10 or FLAG-empty vector before being given Zeocin or not. Trypsin digestion of the proteins co-precipitated with FLAG constructs was followed by LC-MS/MS proteomic analysis. Following the retrieval of proteomic data, the Integrated Interactome System was used to analyse it, and Cytoscape was used to assemble differentially expressed proteins into protein networks and assign them to Gene Ontology biological processes. Two durable Nek10 silenced HeLa cell clones were produced for functional, cellular, and molecular studies.

Keywords: Mitochondria, NEK Protein, HEK293T Cells, Cytoscape.

Introduction

The inhibition of mitochondrial respiration, specifically the ATP-linked oxygen consumption rate and spare capacity, was the final effect of NEK10 knockdown. Additional effects included changes in the levels of reactive oxygen species (ROS) in the mitochondria and decreased citrate synthase activity. Due to possible DNA damage, NEK10 depletion also reduced the ratio of mtDNA amplification. The total amount of mtDNA rose, nevertheless, indicating that NEK10 might be involved in the regulation of mtDNA content [1].

In breast and lung cancer, where variations in the BRCA1/2 (breast cancer type 1/2 susceptibility protein) gene were discovered, NEK10 mutations have been documented. Following ultraviolet (UV) exposure, Moniz and Stambolic discovered that the NEK10 protein was involved in the maintenance of the G2/M checkpoint. After UV exposure, the NEK10 protein forms a complex with RAF1 and MEK1 and functions as a positive regulator of ERK1/2 (Extracellular signal-regulated protein kinases 1 and 2). A recent study revealed the significance of NEK10 for ciliogenesis. NEK10 functions in a cAMP-dependent pathway and interacts with PKA and PCM1 to help generate cilia. Cytosolic organelles with double membranes and unique genomes are mitochondria. They contribute to the ageing process, cell death, chronic inflammation, and Ca2+ homeostasis in addition to energy production. Cardiomyopathies, cancer, neurodegeneration, and metabolic diseases are all impacted by alterations in mitochondrial homeostasis [2].

We recognised mitochondrial proteins as NEK10 interactors by Mass Spectrometry (MS) analysis of immunoprecipitated (IP) materials. Glutamate dehydrogenase (GLUD1) and Citrate Synthase were two of them (CS). As a result, we looked into how NEK10 affects the structure and function of mitochondria as well as the production of ROS, citrate synthase, mtDNA integrity, and mtDNA copy numbers. Our data suggest that the NEKs are kinases that control the functional interaction between mitochondria and cell cycle checkpoints by adding NEK10 as another member of the NEK family that is involved in mitochondrial functions [3].

The mitochondrial outer membrane translocase complex, or TOM20, is a crucial import receptor that can identify the mitochondrial sequence. It is a component of the TOM complex. TFAM is involved in various processes, including mtDNA transcription, replication, maintenance, and repair. The outer mitochondrial membrane (OMM) contains the voltage-dependent anion channel (VDAC), which contributes to the permeabilization of the mitochondria. Sucinate dehydrogenase and succinate:ubiquinone oxidoreductase are other names for mitochondrial complex II (CII) (SDH). The nuclear genome encodes the four CII subunits, which are involved in generating energy. In order to assess NEK10's contribution to cellular bioenergetics, we examined the oxygen consumption of mitochondria in whole cells. Our findings demonstrate that mitochondrial respiration was hampered by NEK10 deficiency [4].

When NEK10 was depleted, cells displayed lower non-mitochondrial oxygen consumption than control cells. Despite

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the fact that non-mitochondrial oxygenases can be activated by cells like neutrophils, mitochondria still account for the majority of cellular respiration. The main source of cellular oxygen consumption in macrophages may be the action of non-mitochondrial NADPH oxidases. An inhibitor of the mitochondrial electron transport chain, such as rotenone, can be used to gauge non-mitochondrial oxygen consumption. 10% of the oxygen consumption in non-mitochondrial cells is carried out by desaturation and detoxifying enzymes [5].

Conclusion

In conclusion, we described the NEK10 protein interactome here and showed its novel functions in mitochondrial homeostasis. When NEK10 expression is silenced, the morphology of the mitochondria changes, mtDNA damage and content rise, cell death is accelerated, ROS levels rise, and citrate synthase and respiration in the mitochondria are blocked. With regard to the underlying mechanisms in mitochondrial homeostasis, such as respiration, and associated diseases, such as cancer, our research offers up new research directions for the investigation of NEK10 activities.

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