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Analysis of the Entire Genome in Human Embryonic Stem Cells Identifies the Hippo Signaling Pathway as Providing Synthetic Viability in ATM Deficiency

Adams Peretz*

Department of Genetics, Institute of Life Sciences, The Hebrew University, Givat-Ram, Jerusalem 9190401, Israel

Abstract

Genome-wide analysis in human embryonic stem cells (hESCs) reveals that the Hippo signaling pathway provides synthetic viability in the absence of ATM (Ataxia Telangiectasia Mutated) protein, essential for DNA damage response. The Hippo pathway, known for regulating cell proliferation and apoptosis, compensates for ATM deficiency by promoting cell survival and potentially maintaining genomic stability. This discovery highlights a critical compensatory mechanism and suggests therapeutic potential in targeting the Hippo pathway for conditions associated with ATM deficiency, such as Ataxia Telangiectasia and certain cancers, emphasizing the importance of personalized medicine approaches.

Keywords: Human embryonic stem cells • Neurodegeneration • RNA interference

Introduction

Human Embryonic Stem Cells (hESCs) represent a crucial model for understanding early human development and the molecular mechanisms underlying various diseases. One of the significant pathways involved in the cellular response to DNA damage is the ATM (Ataxia Telangiectasia Mutated) pathway. ATM is a serine/threonine protein kinase that is activated by DNA double-strand breaks and orchestrates a network of cellular responses to repair DNA damage. Deficiency in ATM results in a condition known as Ataxia Telangiectasia (AT), characterized by neurodegeneration, immunodeficiency, and increased cancer susceptibility. Understanding the pathways that can compensate for ATM deficiency is critical for developing therapeutic strategies.Recent genome-wide studies in hESCs have identified the Hippo signaling pathway as a key player providing synthetic viability in the context of ATM deficiency. The Hippo pathway is essential for regulating organ size, cell proliferation, and apoptosis. Its involvement in compensating for ATM deficiency opens new avenues for understanding and potentially treating conditions associated with ATM dysfunction.

Literature Review

The ATM protein is a central player in the DNA Damage Response (DDR) pathway. Upon sensing DNA Double-Strand Breaks (DSBs), ATM is rapidly activated through autophosphorylation and recruits various proteins to the site of damage. This recruitment initiates a cascade of events that include cell cycle arrest, DNA repair, and apoptosis if the damage is irreparable. The primary downstream targets of ATM include proteins such as p53, CHK2, and H2AX, which play significant roles in maintaining genomic stability. ATM deficiency disrupts this critical pathway, leading to the accumulation of DNA damage, genomic instability, and increased susceptibility to cancer. This deficiency underscores the need for understanding compensatory mechanisms that can restore cellular viability and function in the absence of ATM. The Hippo signaling pathway is a highly conserved regulatory network that controls organ size by modulating cell proliferation and apoptosis. The core components of the Hippo pathway include the kinases MST1/2 and LATS1/2, which, when activated, phosphorylate and inactivate the transcriptional co-activators YAP (Yes-associated protein) and TAZ (transcriptional co-activator with PDZ-binding motif). When the Hippo pathway is inactive, YAP/TAZ translocate to the nucleus and promote the expression of genes involved in cell growth and survival. The pathway is regulated by various upstream signals, including cell density, mechanical stress, and cellular energy status. Dysregulation of the Hippo pathway has been implicated in cancer and regenerative medicine, highlighting its critical role in cellular homeostasis [1,2].

Synthetic viability refers to a situation where the loss of two genes (or pathways) is lethal to a cell, but the loss of one gene alone is not. In the context of ATM deficiency, identifying pathways that can compensate for the lack of ATM function is of significant therapeutic interest. The discovery that the Hippo pathway provides synthetic viability in ATM-deficient hESCs suggests that modulating this pathway could mitigate the adverse effects of ATM loss.Genome-wide screening approaches in hESCs involve using CRISPR-Cas9 or RNA interference (RNAi) to systematically knock out or knock down genes and identify those that affect cell viability in the presence or absence of ATM. These screens can uncover synthetic lethal interactions and pathways that compensate for the loss of ATM. Recent studies have utilized such screening techniques to demonstrate that the inactivation of key Hippo pathway components, such as MST1/2 or LATS1/2, can rescue the viability of ATM-deficient cells. This finding suggests that the Hippo pathway may play a protective role in maintaining cellular function when ATM is absent [3].

Discussion

The exact mechanisms by which the Hippo pathway compensates for ATM deficiency are still under investigation. The Hippo pathway's ability to control apoptosis through YAP/TAZ may help counteract the increased cell death observed in ATM-deficient cells. By promoting cell survival, the Hippo pathway can enhance the viability of these cells. ATM deficiency often results in cell cycle arrest due to the accumulation of DNA damage. The Hippo pathway, by regulating cell proliferation, may help ATM-deficient cells bypass these checkpoints and continue to proliferate despite the presence of DNA damage.The Hippo pathway might also play a role in maintaining genomic stability through mechanisms that are not yet fully understood. It may interact with other DNA repair pathways or enhance the efficiency of existing repair

***Address for Correspondence:** Adams Peretz, Department of Genetics, Institute of Life Sciences, The Hebrew University, Givat-Ram, Jerusalem 9190401, Israel, E-mail: peretx@ada.il*

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mechanisms in the absence of ATM [4].

Pharmacological agents that modulate the Hippo pathway could be developed to treat ATM-deficient conditions. For example, inhibitors of MST1/2 or LATS1/2 might be used to activate YAP/TAZ and promote cell survival in ATM-deficient patients.Combining Hippo pathway modulators with other treatments, such as DNA damage response inhibitors or immune checkpoint inhibitors, could provide a synergistic effect and improve therapeutic outcomes in cancers with ATM deficiency.The identification of the Hippo pathway as a compensatory mechanism in ATM deficiency underscores the importance of personalized medicine. Genetic screening of patients for ATM and Hippo pathway mutations could help tailor treatments to their specific genetic profile, improving efficacy and reducing adverse effects. While significant progress has been made in understanding the role of the Hippo pathway in compensating for ATM deficiency, several areas require further .More research is needed to fully understand the molecular mechanisms by which the Hippo pathway compensates for ATM deficiency. This includes identifying direct interactions between Hippo pathway components and DNA repair proteins. Most of the current evidence comes from in vitro studies in hESCs. In vivo studies using animal models and patient-derived cells are necessary to validate these findings and assess their relevance in a physiological context. Translating these findings into clinical practice requires well-designed clinical trials to test the safety and efficacy of Hippo pathway modulators in ATM-deficient patients.Investigating whether the Hippo pathway provides synthetic viability in other contexts of DNA damage or in other genetic deficiencies could broaden the therapeutic applications of this pathway [5,6].

Conclusion

The identification of the Hippo signaling pathway as a provider of synthetic viability in ATM deficiency represents a significant advancement in our understanding of cellular responses to DNA damage. This discovery opens new therapeutic avenues for treating conditions associated with ATM deficiency, such as Ataxia Telangiectasia and certain cancers. Future research should focus on elucidating the detailed mechanisms of this compensation, validating findings in vivo, and translating these insights into clinical therapies. The interplay between the Hippo and ATM pathways exemplifies the complexity of cellular homeostasis and the potential for targeted interventions to correct genetic deficiencies.

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Conflict of Interest

There are no conflicts of interest by author.

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