Brief Report
Volume 13:04, 2024

Molecular Biology: Open Access

ISSN: 2168-9547 Open Access

BAG2 Disrupts the Ubiquitination of HSP72 Mediated by CHIP

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Introduction

The cellular proteostasis network is vital for maintaining protein homeostasis within the cell, allowing it to adapt to stress and modulate various physiological functions. Among the key players in this network are Heat Shock Proteins (HSPs), particularly HSP72, which act as molecular chaperones. HSP72 assists in the correct folding of nascent proteins and the refolding of misfolded proteins, thereby preventing aggregation and facilitating degradation of irreparably damaged proteins. The regulation of HSP72 is complex, involving various mechanisms, including ubiquitination, a process that tags proteins for degradation via the proteasome. Ubiquitination is mediated by a cascade of enzymes, including E_1 (ubiquitin-activating enzymes), E_2 (ubiquitin-conjugating enzymes) and E_3 (ubiquitin ligases). The E_3 ligase CHIP (C-terminus of HSP70-interacting protein) is particularly significant in regulating the fate of HSP72. CHIP interacts with HSP72 and promotes its ubiquitination, leading to its degradation under certain conditions, such as cellular stress or in the presence of misfolded proteins. This function highlights CHIP's role as a critical regulator of proteostasis and cellular response to stress [1].

In recent studies, BAG2 (Bcl-2 associated athanogene 2) has emerged as a novel regulator of HSP72 and its associated pathways. BAG2 is known to modulate various chaperone activities, interacting with different HSPs and influencing their functions. Importantly, BAG2 has been shown to disrupt the ubiquitination of HSP72 mediated by CHIP, thereby potentially altering the degradation and functional availability of this crucial chaperone. This interaction raises intriguing questions about the mechanisms through which BAG2 influences cellular stress responses and protein quality control [2].

Description

The interaction between BAG2 and CHIP introduces a new layer of complexity to our understanding of how HSP72 is regulated. By interfering with the ubiquitination process, BAG2 may stabilize HSP72, allowing it to exert its chaperone functions more effectively under stress conditions. This stabilization could be critical in various physiological contexts, including neurodegenerative diseases, cancer and other conditions characterized by proteotoxic stress. The mechanistic details of how BAG2 disrupts CHIP-mediated ubiquitination of HSP72 are still being elucidated. It is hypothesized that BAG2 competes with CHIP for binding sites on HSP72, thereby preventing CHIP from facilitating ubiquitin transfer. Alternatively, BAG2 may alter the conformational dynamics of HSP72, rendering it less accessible to CHIP-mediated ubiquitination. This interaction suggests a finely-tuned balance between chaperone activity and proteasomal degradation, with implications for how cells respond to stress and manage protein quality [3].

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Received: 01 August, 2024, Manuscript No. MBL-24-148609; **Editor Assigned:** 03 August, 2024, PreQC No. P-148609; **Reviewed:** 15 August, 2024, QC No. Q-148609; **Revised:** 20 August, 2024, Manuscript No. R-148609; **Published:** 27 August 2024, DOI: 10.37421/2168-9547.2024.13.445

The consequences of BAG2's interference with HSP72 ubiquitination are far-reaching. In conditions of elevated stress, where protein misfolding and aggregation are prevalent, the ability of HSP72 to remain functional could dictate cellular outcomes. For instance, in neurodegenerative diseases like Alzheimer's and Parkinson's, where protein aggregates are characteristic, the stabilization of HSP72 by BAG2 could enhance the cell's capacity to manage misfolded proteins, potentially slowing disease progression. Conversely, in cancer, where HSP72 can promote cell survival, the modulation of its degradation might impact tumor growth and response to therapies. BAG2 is part of a larger family of BAG proteins that interact with HSP70 family members, influencing their activity and interactions. This family of proteins serves diverse functions, primarily in regulating the cellular stress response and protein degradation pathways. BAG2, in particular, has been shown to interact not only with HSP72 but also with other chaperones, effectively coordinating a network that maintains protein homeostasis.

Through its binding to HSP72, BAG2 modulates the chaperone's activity, potentially enhancing its ability to assist in protein folding and refolding. This is crucial in maintaining cellular integrity under stress conditions, such as heat shock or oxidative stress. By preventing the degradation of HSP72, BAG2 ensures that the cell has a ready supply of this essential chaperone, which is necessary for counteracting the adverse effects of protein misfolding. The disruption of HSP72 ubiquitination by BAG2 carries significant implications for several diseases. In neurodegenerative disorders, the accumulation of misfolded proteins is a hallmark. The ability of BAG2 to stabilize HSP72 may enhance cellular resilience to these stresses, promoting the clearance of toxic aggregates. For example, in Alzheimer's disease, where tau and amyloid-beta aggregates are prevalent, enhanced HSP72 activity facilitated by BAG2 could mitigate neuronal damage [4].

Conversely, in cancer, HSP72 can play a dual role. While it protects cancer cells from stress-induced apoptosis, it can also promote the survival of cells under therapeutic treatment. The regulation of HSP72 levels through BAG2's inhibition of CHIP-mediated degradation could therefore influence tumor progression and resistance to therapies. Targeting BAG2 or manipulating its interaction with HSP72 and CHIP may provide novel therapeutic strategies to either enhance or inhibit HSP72 activity, depending on the disease context. The relationship between BAG2, CHIP and HSP72 is part of a broader network involving multiple ubiquitin ligases and Deubiquitinating Enzymes (DUBs). These enzymes collectively dictate the fate of HSP72 within the cell. For instance, other E_3 ligases might compete with CHIP for HSP72 and their activity could be influenced by BAG2. Understanding how BAG2 fits into this complex interplay can yield insights into how cells prioritize different degradation pathways based on stress levels and protein misfolding scenarios. Moreover, BAG2 itself may undergo post-translational modifications that affect its binding affinity for HSP72 or CHIP. Phosphorylation, for example, could enhance or inhibit its activity, creating another layer of regulation in the chaperone network.

The integration of these signals could allow the cell to finely tune its response to stress, enhancing resilience when needed or promoting degradation when necessary. Given the pivotal role of BAG2 in regulating HSP72 levels and activity, it represents a promising therapeutic target. Strategies could include small molecules designed to enhance BAG2's protective effects on HSP72, thereby promoting cell survival in neurodegenerative diseases. Conversely, in cancers where HSP72 supports tumor growth, inhibiting BAG2 or enhancing CHIP activity could facilitate the degradation of HSP72, potentially sensitizing cancer cells to treatments. In addition to pharmacological approaches, gene therapy or CRISPR-based strategies could be employed to modulate BAG2

expression levels. By understanding the precise mechanisms through which BAG2 regulates HSP72 ubiquitination, more targeted interventions can be developed, potentially leading to breakthroughs in the treatment of diseases characterized by protein misfolding [5].

Conclusion

In conclusion, the interplay between BAG2, HSP72 and CHIP represents a critical nexus in the cellular management of protein homeostasis. By disrupting the ubiquitination of HSP72 mediated by CHIP, BAG2 not only stabilizes HSP72 but also reshapes the landscape of cellular stress responses. Understanding this interaction opens new avenues for research, particularly in the context of diseases characterized by protein misfolding and aggregation. Future studies aimed at elucidating the precise mechanisms and broader implications of BAG2's action will be crucial for developing targeted therapeutic strategies that leverage the proteostasis network to mitigate disease processes. The potential of modulating BAG2 activity or enhancing HSP72 stability presents an exciting frontier in biomedical research, offering hope for innovative interventions in diverse pathological conditions.

Acknowledgement

None.

Conflict of Interest

None.

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How to cite this article: Liang, Wei. "BAG2 Disrupts the Ubiquitination of HSP72 Mediated by CHIP." *Mol Biol* 13 (2024): 445.