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Commentary

Uncovering Crosstalk Between mTOR and Hippo Pathways in Cancer Metastasis: A New Frontier in Targeted Therapy

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DESCRIPTION

Cancer metastasis remains the leading cause of cancer-related deaths globally, particularly in high-income countries where extended life expectancy and lifestyle factors contribute to high cancer prevalence. As research moves beyond the genetic origins of cancer to explore signaling networks and cellular communication, two pathways mTOR (mechanistic target of rapamycin) and Hippo have emerged as central players. Although their independent roles in tumor growth and progression have been widely studied, recent insights suggest a complex interplay between them, with significant implications for metastasis and therapy resistance. The mTOR pathway is a key regulator of cell growth, metabolism and survival. It integrates signals from growth factors, nutrients and cellular energy status to promote protein synthesis and inhibit autophagy. On the other hand, the Hippo pathway is crucial for controlling organ size, cell proliferation, and apoptosis. Its downstream effectors, YAP (Yes-associated protein) and TAZ, are transcriptional coactivators that promote gene expression programs favoring cell proliferation and stemness. Dysregulation of either pathway can drive oncogenesis, but mounting evidence shows that their interaction is particularly important in the context of metastatic behavior.

One critical point of intersection between the two pathways involves the regulation of YAP/TAZ by components of the mTOR complex. Specifically, mTORC2 activity has been shown to enhance YAP stability and nuclear localization through phosphorylation events. This boosts the transcription of genes that promote Epithelial-Mesenchymal Transition (EMT), cellular migration and invasion key steps in the metastatic cascade. Conversely, the active Hippo pathway, through its core kinases MST1/2 and LATS1/2, can suppress mTOR signaling by indirectly downregulating PI3K/Akt signaling, highlighting a bidirectional regulatory mechanism. What makes this crosstalk particularly significant in metastatic tumors is the influence of the tumor microenvironment. Hypoxia, nutrient limitation and extracellular matrix stiffness conditions common in metastatic niches can simultaneously activate mTOR and inhibit Hippo signaling. This dual effect leads to the upregulation of YAP/TAZ activity and mTOR-driven anabolic processes, creating a cellular state primed for dissemination and colonization of distant tissues.

Additional complexity arises from integrin and G-protein coupled receptor (GPCR) signaling, both of which feed into and modulate the mTOR and Hippo pathways. These signals contribute to the mechanical and biochemical cues that tumor cells interpret as they adapt to new environments during metastasis. Thus, the crosstalk between mTOR and Hippo is not a simple linear interaction but part of a larger signaling network that integrates intrinsic cellular status with extrinsic environmental factors. Therapeutically, this insight offers new possibilities. While mTOR inhibitors such as rapalogs have shown clinical utility, their efficacy is often limited by feedback activation of survival pathways or the development of resistance. Similarly, agents that inhibit YAP/TAZ activity are still in early development stages. Combining inhibitors that target both mTOR and Hippo signaling may yield synergistic effects, blocking compensatory pathways and more effectively suppressing metastatic potential. This dual-targeting approach could be especially beneficial in tumors with high YAP activity and mTOR pathway upregulation, such as pancreatic ductal adenocarcinoma or triple-negative breast cancer.

However, these pathways also play essential roles in normal tissue maintenance, posing a risk of toxicity with systemic inhibition. To address this, researchers are exploring tumor-targeted delivery systems, such as nanoparticles and context-specific inhibition strategies that exploit differences in pathway regulation between cancer and normal cells. In addition, there is growing interest in how this crosstalk influences the tumor immune microenvironment. Both pathways have been implicated in immune evasion, suggesting that targeting them could also enhance responses to checkpoint inhibitors and other forms of immunotherapy. As we gain deeper insights into the mTOR-Hippo interface, new biomarkers are being identified to stratify patients who may benefit most from these combined therapies. This precision medicine approach aligns with the broader movement in oncology to tailor treatments based on tumor biology rather than tissue origin alone.

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CONCLUSION

The emerging crosstalk between mTOR and Hippo signaling pathways represents a significant paradigm shift in our understanding of cancer metastasis. Far from operating in isolation, these pathways form an interconnected network that governs critical aspects of tumor cell behavior, including proliferation, migration and survival under stress. Disrupting this network holds promise for halting the metastatic spread and improving outcomes in aggressive cancers. Future research must focus on elucidating the precise molecular mechanisms underpinning this crosstalk and translating this knowledge into effective, safe therapeutic strategies. With advances in genomic profiling, targeted drug development and delivery technologies, the potential to exploit this interaction therapeutically is within reach. By targeting the dynamic relationship between mTOR and Hippo pathways, we may be able to significantly improve our ability to manage and ultimately overcome metastatic cancer.