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Rational Targeting of Protein Translation in Cancer Cells

Summary

Deregulation of protein translation is associated with a growing number of human diseases, including tumorigenesis. The mammalian mTOR pathway has garnered considerable interest as a major target for new anti-cancer therapies due to its key role in regulating cell growth. However, clinical applications have been limited due to the role of this pathway in normal cell growth as well as downstream compensatory mechanisms that reduce the effects of mTOR inhibitors. A UMB researcher has identified the heterogenous ribonucleoprotein (hnRNP A18) as a specific inhibitor of protein translation in cancer cells. hnRNP A18 is upregulated in 40-60% of prostate, breast, colon, and melanoma tumors compared to normal adjacent tissue, with its expression highest in early stages of carcinogenesis. Transcripts targeted by hnRNP A18 are associated with tumor progression and can confer growth advantages to tumor cells. Downregulation of hnRNP A18 expression shows oncolysis and decreased proliferation, invasion, and migration in cancer cells, making it a viable anti-cancer target.

Key Investigator

France Carrier

Field

Therapeutics

Technology

hnRNP A18-targeting compounds for the treatment of cancer

Advantages

Protein translation is inhibited preferentially in cancer cells

Status

Available for licensing
Available for sponsored research

Patent Status

Pending, published on 10/6/2016
(US 2016/ 0289311)

UMB Docket Reference

FC-2015-047

External References

Chang ET et al. (2016) *Oncotarget*. 7(9):10578-93.

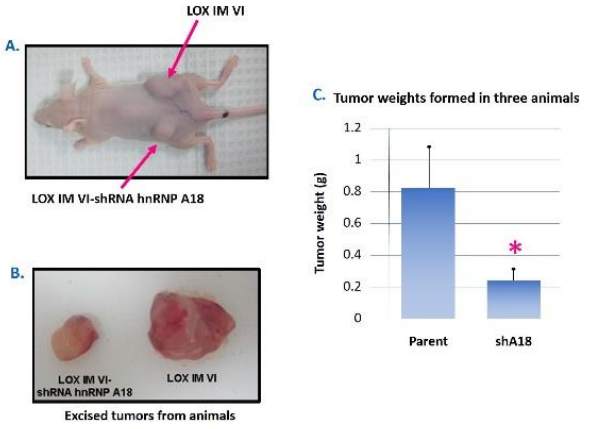
Market

There are currently no FDA-approved cancer therapies that specifically target protein translation in cancer cells. Two drugs targeting mTOR are FDA-approved for the treatment of cancer. Temsirolimus (Pfizer) was approved in 2007 for the treatment of advanced renal cell carcinoma. Everolimus (Novartis) was approved in 2009 for the treatment of kidney cancer, with subsequent approvals for neuroendocrine tumors, renal cell carcinoma, and a subset of tuberous sclerosis-assocciated and breast cancer tumors. Novartis reported $749 million in sales of Everolimus in 2013 and is estimated to make $3.5 billion by 2018.

Additional derivatives have shown antiproliferative activity against a diverse range of cancer types in preclinical studies and are undergoing clinical development for the treatment of mantle cell lymphoma, renal cell carcinoma, and tuberous sclerosis complex-related tumors. Early clinical trials have also shown promising initial efficacy but, due to the compensatory nature of the pathway, have had limited success. Targeting hnRNP, either alone or in combination, is a novel approach that could compete with established mTOR inhibitors.

Technology

Genetic downregulation of hnRNP A18 via shRNA significantly decreases tumor volume and weight, by approximately 70%, in mouse xenograft models of melanoma and breast cancer (see figure). The same strategy inhibited proliferation, invasion, and migration in a melanoma cell line.



Down regulation of hnRNP A18 reduced by more than 80% melanoma tumor growth mouse xenografts. A) Mouse no 1, 10 days after inoculation with 3 x 10^6 LOX IM VI cells in the right flank and 3 X 10^6 LOX IM VI cells stably transfected with shRNA for hnRNP A18 on the left flank. **B)** Tumors excised from mouse no 1. **C)** Bar graph of tumor weight excised from three xenograft mice.

Technology Status

The functional effect of hnRNP A18 inhibition has been tested in proof of concept experiments using shRNA in mouse xenograft models of melanoma and breast cancer.

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