Washington University in St. Louis
Office of Technology Management

LONG NON-CODING RNA AS CANCER BIOMARKER AND DRUG TARGET

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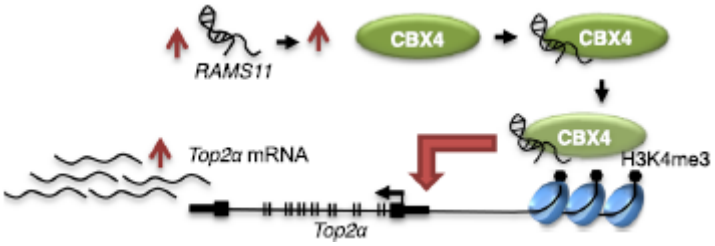
T-018788

Technology Description

Researchers in Prof. Christopher Maher's research program (in conjunction with collaborator Ryan Fields) discovered that RAMS11 (RNA Associated with Metastasis 11), a novel long non-coding RNA, (i) promotes metastatic disease, (ii) confers resistance to topoisomerase inhibitors and common chemotherapeutics, (iii) is expressed in aggressive subtypes of colon cancer and (iv) associates with poor patient outcomes in colorectal cancer. These findings highlight the potential use of RAMS11 as a prognostic marker to stratify patients based on risk of disease recurrence and to predict disease severity or response to treatment. It may also represent a novel target for therapeutics. Notably, these findings may impact a much broader patient population (beyond CRC) since additional studies indicate that RAMS11 is altered across multiple cancers types.

Currently, there are no reliable biomarkers to predict which patients with colorectal cancer will respond to treatment. In addition, metastatic colorectal cancer is nearly universally fatal due to development of resistance to systemic therapy. This is, in part, due to our limited understanding of the underlying biological mechanisms. To address these issues, the inventors identified RAMS11 through transcriptome sequencing that compared long non-coding RNAs in normal, primary tumors and distant metastatic tissue in patients with colon cancer. RAMS11 was associated with poor disease-free survival; it promoted aggressive phenotypes in vitro and in vivo; and it was revealed to have a mechanistic role in resistance to certain cancer drugs (chemotherapeutics and topoisomerase inhibitors). Additional studies suggest that RAMS11 could also play a role in other types of solid tumors (e.g., breast, prostate, pancreas). These findings indicate that RAMS11 could potentially be used as a biomarker to stratify high-risk patients and is also a promising target for developing therapies to treat aggressive, metastatic disease.



RAMS11 binds to CBX4 to promote invasive phenotype by up-regulating expression of Topoisomerase II alpha

Stage of Research

The inventors discovered that RAMS11 was associated with aggressive metastatic colorectal cancer and poor disease-free survival. Importantly, it is not expressed in normal colon tissue. However, RAMS11 is expressed in primary tumors of patients that do metastasize and is highly expressed in metastatic lesions. Collectively, this makes RAMS11 a strong candidate maker of advanced disease. This was further validated through studies that demonstrated RAMS11 promoted oncogenic phenotypes in vitro and in vivo in several cancer types. Through a drug screen, RAMS11 was found to specifically

regulate Topoisomerase II alpha and increased resistance to more than half the topoisomerase inhibitors screened. Subsequent mechanistic experiments demonstrated RAMS11-dependent CBX4 transcriptional regulation of Top2a. The drug screen also revealed that elevated RAMS11 promotes resistance to commonly used chemotherapies in CRC. Subsequent *in vivo* experiments confirm that elevated RAMS11 promotes metastasis *in vivo* and do not respond to chemotherapy.

Publications: Silva-Fisher, J. M., Dang, H. X., White, N. M., Strand, M. S., Krasnick, B. A., Rozycki, E. B., ... & Cabanski, C. R. (2020). Long non-coding RNA RAMS11 promotes metastatic colorectal cancer progression. *Nature communications*, 11(1), 1-13.

Applications

- **Diagnostic/prognostic biomarker**: RAMS levels in primary tumors could be used to evaluate disease severity and predict response to treatment in high-risk patients
- **Patient stratification in clinical trials** for new cancer therapeutics: identify potential drug resistance, particularly to topoisomerase inhibitors
- **Drug target:** RAMS11 could serve as a therapeutic target, particularly for metastatic and high risk cancer using RNA-based agents or small molecules.

Key Advantages

- **Metastatic biomarker:** potential indicator of disease severity and progression, unlike previous biomarkers that were discovered through studies of primary tumors
- **Potential for improved patient outcomes**:
    - personalized treatment plans based on predicted response to certain therapies could improve disease-free survival rates
    - exploiting RAMS11 as a target in regulating Topoisomerase II alpha is likely to have less non-specific target toxicity than current anthracyline therapies

Patents: Application pending

Related Web Links: Maher Profile, Maher Lab