The central dogma of molecular biology posits that genes are transcribed into messenger RNA (mRNA), which is then translated into proteins, which, in turn, are ultimately responsible for all cellular functions. Yet recent research has revealed that RNAs that do not encode proteins — known as noncoding RNAs — play important roles in normal physiological processes and can contribute to human diseases such as cancer. In fact, only approximately 1.5% of the roughly 3 billion base pairs of DNA in the human genome represent protein-coding sequence, whereas a large majority of human DNA is detectably transcribed into RNA under some conditions. These findings have raised the possibility that noncoding RNAs represent an untapped reservoir of potential therapeutic targets for diverse diseases. Nevertheless, few definitive studies involving animals that robustly model human disease have shown therapeutically beneficial results from pharmacologic inhibition of a noncoding RNA. Results recently described by Arun and colleagues, however, provide an exciting example of the potential of noncoding RNAs as therapeutic targets in the treatment of breast cancer. Moreover, the experimental strategy that they used could be broadly applicable to the treatment of many human diseases.

A heterogeneous class of noncoding RNAs known as long noncoding RNAs (lncRNAs) — defined simply by having a length exceeding 200 nucleotides — has been the subject of recent and intensive study. One of the first human lncRNAs to be discovered was identified because of its high expression in metastatic lung cancer cells, as compared with nonmetastatic lung cancer cells. Named metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), its elevated expression has subsequently been associated with metastasis and reduced survival in patients with multiple tumor types. In human cancer cells grown in the laboratory, MALAT1 inhibition results in reductions in cell proliferation, survival, migration, and invasive capacity, as well as in reduced metastasis when the cells are implanted into immunocompromised mice. Surprisingly, however, mice harboring a complete deletion of Malat1 develop normally and have a normal life span, which indicates that this IncRNA is dispensable outside the context of cancer. These findings raise the possibility that inhibition of MALAT1 might impair cancer-cell growth, metastasis, or both, with minimal side effects.

Through genetic and pharmacologic inhibition of Malat1 in a well-characterized mouse model of luminal B breast cancer, Arun and colleagues have now provided compelling evidence that targeting this IncRNA could represent a safe and effective treatment for this type of cancer. These investigators documented that breast cancers in humans often have elevated levels of MALAT1 in metastatic lesions. To test whether Malat1 promotes metastasis, Malat1-knockout mice were bred with mice expressing a strong oncogene in mammary tissue (MMTV-PyMT mice). In Malat1-deficient mice produced in this cross, cystic tumors with poor metastatic potential developed. In contrast, in mice with normal levels of Malat1 expression, there was development of poorly differentiated, aggressive mammary carcinomas that were prone to metastasizing to the lung. Next, to more closely model a clinical scenario, the authors used antisense oligonucleotides (ASOs) to inhibit Malat1 expression in mice with established mammary tumors (Fig. 1). Subcutaneous injection of anti-Malat1 ASOs strongly reduced expression of this IncRNA in tumors. Strikingly, the tumors in ASO-treated animals had a cystic, poorly metastatic phenotype that closely mimicked those that arose in animals with genetic deletion of Malat1. These findings provide strong support for the further clinical investigation of MALAT1 inhibitors for
Despite the remarkable effects of Malat1 depletion in the MMTV-PyMT mouse model, the underlying mechanism through which this lncRNA influences breast cancer behavior remains unclear. Although MALAT1 was one of the first lncRNAs to be discovered, its function is still poorly understood. The nucleotide sequence of MALAT1 has been highly conserved through evolution, which strongly suggests that it has an important cellular function. In addition, MALAT1 associates with thousands of protein-coding genes while they are being transcribed into mRNA and may broadly influence mRNA abundance and splicing.5 But how these general effects on cellular gene expression can profoundly influence the behavior of cancer cells without having an identifiable effect on the behavior of normal cells is highly mysterious. Further investigation of the molecular function of MALAT1 will be a critical component of efforts to bring anti-MALAT1 therapies to the clinic.

It is tempting to speculate that, as a candidate therapeutic target, MALAT1 lncRNA represents the tip of the iceberg. The human genome encodes many thousands of lncRNAs whose functions in normal physiological processes and in disease remain to be characterized. It is likely that aberrant expression of additional lncRNAs contributes to other pathologic states. If so, their inhibition (should it be possible to target lncRNAs in the relevant target tissue) might be beneficial for patients. Moreover, the strategy of targeting lncRNAs such as MALAT1 represents an exciting opportunity to develop new therapeutic approaches for the treatment of breast cancer and possibly other cancers.
involving ASOs used by Arun et al. to inhibit MALAT1 can be adapted to target virtually any lncRNA sequence. Therefore, further exploration of the molecular, physiological, and pathophysiological functions of noncoding RNAs has the potential to expand the clinical armamentarium for the treatment of many diseases.

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