Editorial



# What's up with MALAT1?

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Long noncoding RNAs (lncRNAs) comprise transcripts longer than 200 nucleotides which do not code for proteins. lncRNAs have engendered considerable interest with regard to their potential role(s) in metastasis and cancer progression, with particular interest focused on the lncRNA metastasis-associated lung adenocarcinoma transcript 1 [MALAT1; see (1,2) for recent reviews]. While nearly all reports on MALAT1 have described it as promoting cancer metastasis/progression, a recent report in *Nature Genetics* by Kim *et al.* (3) clearly and thoroughly describes a suppression of metastasis in human breast cancer cells and a variety of mouse models (transgenic, xenograft, and syngeneic). In their molecular studies, these authors found that MALAT1 interferes with the pro-metastatic transcription factor TEAD, preventing it from interacting with its co-activator YAP, and thus interfering with activity at target gene promoters (there were also a number of other MALAT1 interacting factors identified, although these consisted of a bewildering array of other proteins containing cytosolic proteins, neurofilaments, etc.). Kim *et al.* (3) point out that other reports in general "have never been validated to be MALAT1 specific through rescue experiments": While this is true, it is not tantamount to declaring that all pro-metastatic results are wrong. There are several examples of particular genes acting as tumor suppressor in one setting vs. oncogene in another (e.g., the lncRNA XIST, etc.). In fact, there may be several reasons to question whether any particular molecular pathway(s) underpin the global effects of MALAT1 (and for that matter other lncRNAs) in cancers in general.

Perhaps more importantly than specific molecular mechanisms are the clinical ramifications of MALAT1 expression. Whereas the molecular pathway was clearly defined, the clinical results described by Kim *et al.* are at odds with nearly all the existing literature: They found that "lower MALAT1 levels correlated with shorter distant metastasis-free survival in total breast cancers and in luminal A and basal subtypes", although these results are unfortunately relegated to supplementary materials. Diametrically opposed to this, there are a large number of studies which have clearly (and uniformly) documented just the opposite, with MALAT1 expression levels directly related to poor clinical outcomes, which creates a real problem for interpretation. Furthermore, it should be noted that the clinical correlations are essentially independent of any putative molecular mechanisms observed in companion studies. Several large studies have correlated MALAT1 expression levels with poor clinical outcomes in many cancers [including overall survival, disease free survival, lymph node metastases, distant metastases, etc.; see (4-6) for recent meta-analyses; these included 87 studies encompassing 11,066 patients], and the literature also prominently includes correlations between MALAT1 expression and poor clinical outcomes in breast cancer [(7-10); these included 2,320 patients]. In addition, there are even genetic variants of MALAT1 which appear to impact breast cancer susceptibility and even expression levels (11).

It is noteworthy that these meta-analyses extracted data directly from publications meeting generally strict inclusion criteria, or generated their own data in general. While the analyses presented by Kim *et al.* (3) appear to be standard approaches, it should be noted that they often

included relatively small numbers of samples, and/or they relied on TCGA data, which are known to suffer from various problems, which seem to be increasingly recognized (12-14). Wang *et al.* (13) actually identified MALAT1 as being badly under covered in large numbers of "exome" samples across multiple cohorts within the TCGA data. In fact, they determined that the commonly used VCRome exome capture kit does not even contain probes for the loci containing MALAT1 (and for that matter XIST). How this may relate to a potential misinterpretation of MALAT1 expression levels is not clear, although it seems quite likely that RNASeq (transcriptome) data may not be optimized for amplifications of lncRNAs.

To further complicate matters significantly, expression levels of several other lncRNAs also correlate with poor clinical outcomes in cancer patients in essentially the same manner as MALAT1 does. Specific examples where expression levels of lncRNAs have been directly correlated with poor clinical outcomes include NEAT1 (15), HOTAIR (16), LINC00152 (17), XIST (18,19), AFAP1-AS1 (20), HULC (21), CCAT2 (22), HOTTIP (23), and HOXA11-AS (24), as well as several lncRNAs considered together (25). This would seem to suggest that lncRNAs may be acting in a more global manner (26), perhaps involving complex competing endogenous RNA networks (27), and not necessarily through singular specific molecular pathways. This may well involve unique structural features of MALAT1 (28,29) and potentially the other lncRNAs as well [for example, HOTAIR appears to function as a scaffold (30)]. In fact, this seems to suggest some sort of "functional substitution" is possible between lncRNAs.

Finally, the other feature of MALAT1 expression which isn't explained at all is the very high expression levels which are generally observed. The sheer magnitude of the high expression would not seem to be necessary to overwhelm particular transcription factors or other singular molecular targets. So, what's really going on with MALAT1 and other lncRNAs?

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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