Editorial Commentary

NEAT1 isoform expression in breast cancer

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Numerous studies have shown that the *NEAT1* (nuclear enriched abundant transcript 1) lncRNA plays a key role in cancer biology. *NEAT1* is overexpressed in many solid cancers including but not limited to colorectal, ovarian, gastric, non-small cell lung and breast cancer (1-5). Conversely, *NEAT1* expression is reportedly lower in haematological malignancies including chronic myeloid leukemia and acute promyelocytic leukemia (6,7). Although several studies have shown that *NEAT1* is implicated in multiple cancers, the majority of studies do not delineate between *NEAT1* isoforms. *NEAT1* is transcribed as two major isoforms which are both initiated from the same promoter, but are vastly different in length. The long isoform, *NEAT1_2* (~23 kb), is essential for the formation of paraspeckles, ribonucleoprotein bodies found in mammalian cells, which regulate gene expression through the sequestration of RNA and proteins (8). The short isoform, *NEAT1_1* (~3.7 kb), is more abundant in paraspeckles (8) but has also been found in non-paraspeckle foci in the nucleus implicating *NEAT1_1* in paraspeckle-independent functions (9).

A recent study by Knutsen *et al.*, has assessed the expression of *NEAT1* isoforms in breast cancer (10). Using RNA-FISH and RNA-seq expression analyses they show that *NEAT1* isoforms display different expression patterns across human breast cancer subtypes. *NEAT1_2* is highly expressed in human epidermal growth factor receptor 2 positive (HER2+) breast cancers whereas *NEAT1_1* is more highly expressed in estrogen receptor positive (ER+) subtypes. Both isoforms are driven from the same promoter, therefore *NEAT1* isoform expression is controlled post-transcriptionally. Indeed, previous studies have shown the paraspeckle protein, hnRNPK, increases the production of *NEAT1_2* by negatively regulating the polyadenylation signal of the shorter *NEAT1_1* isoform (8). In breast cell lines, hnRNPK is induced by growth factors, but blocked by treatment with anti-HER2 antibodies suggesting hnRNPK may play an important role in HER2 signalling (11). However, whether the increased expression of *NEAT1_2* in HER2+ breast cancers is driven by hnRNPK will require additional research.

NEAT1 overexpression has been reported to be associated with poor survival in multiple cancers types (1,4,12,13). However, many of these studies are based on small samples sizes and larger cohorts are required to confirm these observations. Furthermore, a previous study showed that *NEAT1_2* but not *NEAT1_1* is associated with poor progression free survival in ovarian cancer patients treated with platinum-based chemotherapy (14). Notably, Kaplan Meier-plotter analysis (15), indicates that low levels of total *NEAT1* (as opposed to high levels in other cancer types) is associated with relapse free breast cancer survival (logrank $P=1\times10^{16}$; n=1,764), however there is no association with survival when the cohort is stratified into ER+ (logrank P=0.067; n=762) and ER- breast tumors (logrank P=0.058; n=347). Therefore, it is likely that the association of total *NEAT1* with improved survival, reflects that *NEAT1_1* is more abundant and is expressed higher in ER+ breast cancers, which have a significantly better prognosis. The studies performed by Knutsen *et al*, showing that *NEAT1_2* is associated with more aggressive breast cancers, highlights the importance of determining whether *NEAT1_2* is associated with outcome in different breast cancer subtypes. Unfortunately, this is not possible with polyA enriched RNAseq data, such as the breast TCGA

cohort, as *NEAT1_2* is not polyadenylated and therefore will not be annotated in these datasets. Additional total RNAseq from cohorts with survival data will be required to conduct these studies.

Paraspeckle formation is often observed in different cell types under stress conditions. For example *NEAT1* is induced under hypoxia (16), heat shock (17), mitochondrial stress (18) and viral infection (19). The upregulation of *NEAT1* in malignant tissues is therefore not surprising. In summary, the study by Knutsen *et al*., highlights the need to perform isoform-specific studies when assessing the function of *NEAT1* and the expression in normal and disease conditions. Clearly, *NEAT1* plays an important role in cancer and other disease states and further research is required to identify whether specific *NEAT1* isoforms will be useful cancer biomarkers or therapeutic targets.

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Footnote

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