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Commentary Article

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Dynamic Regulation of MALAT1 in Leader Cell Formation and Collective Cancer Invasion

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Abstract

The primary mechanism in cancer metastasis, collective invasion is becoming more widely recognized. Leader cells are specially trained cancer cells that invading the tumors. They are crucial in establishing invasion pathways, organizing follower cells, and facilitating the survival of cancer cells throughout the metastatic cascade. To aid group invasion, these leader cells activate a variety of mechanical, genomic, and metabolomic pathways. Leader cell development and function are influenced by stromal cells, matrix properties, genetic and epigenetic factors, and more.

Keywords: Leader Cells; Live Single Cell Analysis; Long Noncoding RNAs; MALAT1; FRET nano biosensor.

Commentary

Collective invasion is increasingly becoming recognized as the primary mechanism in cancer spread. Leader cells are cancer cells that have been properly taught to infiltrate tumors. They are critical in building invasion paths, organizing follower cells, and allowing cancer cells to survive throughout the metastatic cascade. These leader cells use a range of mechanical, genetic, and metabolomic routes to aid in group invasion. Stromal cells, matrix characteristics, genetic and epigenetic variables, and other factors all influence leader cell formation and function. The development and metastasis of cancer have been shown to be significantly influenced by long noncoding RNAs (lncRNAs) [1]. Despite not having the ability to code for proteins, lncRNAs can regulate gene expression using a variety of methods. They play a role in post-transcriptional regulation of cytoplasmic RNA and post-translational regulation of chromatin-modifying enzymes, alternative splicing, and epigenetic regulation of chromatin- modifying enzymes. Numerous lncRNAs, such as urothelial cancer-associated 1 (UCA1) [2] and metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) [3], have been found to control the spread of cancer. For instance, through controlling genes linked to metastasis and affecting splicing patterns, MALAT1 encourages metastasis in lung and other malignancies. By deactivating pro-metastatic transcription factors and controlling the epithelial-mesenchymal transition (EMT), MALAT1 has also been discovered to inhibit metastasis in breast and colon cancers. These studies highlight the complex roles that lncRNAs play in cancer and the difficulties in understanding how they work, calling for the development of new technologies to better comprehend how lncRNAs play important roles in cancer [4].

Investigating the function of MALAT1 in leader cell production and cancer invasion is the main goal of this study. The role of lncRNAs must be investigated using live single-cell biosensors with high spatio-temporal

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resolution because leader cells make up a very small portion of cancer cells. Miserably, current methods that lyse or fix samples, including RNA sequencing and RNA fluorescence in situ hybridization (FISH), are unable to shed light on the spatio-temporal dynamics of RNAs in cancer cells during collective cancer invasion. This study introduces a FRET nano-biosensor for dynamic analysis of lncRNAs in live single cells in both two-dimensional (2D) and three-dimensional (3D) invasion models to overcome this constraint. To improve the signal-to-noise ratio, this novel nano-biosensor combines the double-stranded lock nucleic acid (dsLNA) probe, the dual probe design, and FRET-based sensing. Utilising this FRET method, the nano-biosensor reduces background noise brought on by autofluorescence and thermal quencher probe dissociation, making it easier to detect endogenous RNA transcripts in living single cells. Transient knockdown experiments utilizing small interfering RNA (siRNA) and stimulation with transforming growth factor beta 1 (TGF-1) are used to validate the FRET signal of the biosensor. The nano-biosensor is effective in identifying lncRNA expressions in migrating cell monolayers, tumor organoids made from patient samples, and three-dimensional cancer spheroids. The study evaluates the expression of β-actin, MALAT1, and UCA1 transcripts in active bladder cancer cells using the FRET nano-biosensor. Fluorescent puncta in the FRET channel, which stand for one or more RNA transcripts, are used to detect the presence of these RNA transcripts. The distribution of RNA transcripts in live cells is also assessed by the investigation using nuclear and cytoplasmic markers. The co-localization of RNA transcripts with the nuclei is identified using confocal microscopy and a live cell nuclear dye. There were often more β-actin, MALAT1, and UCA1 transcripts in the cytoplasm than there were co-localized with the nucleus. Additionally, TGF-β therapy, a recognized EMT inducer, causes an overall rise in MALAT1 and UCA1 expression in the cells, especially in the nucleus. However, both the cytoplasmic and nuclear areas continue to express β-actin mRNA at the same levels.

The work uses a scratch cell migration assay, generally known as a wound healing assay, to examine the distribution of lncRNAs during collective cancer migration. This assay enables the study of lncRNA dynamics in a population of cancer cells travelling together. The cells in the study migrate coherently and organize into projecting points with a leader-follower structure, which is consistent with another research. After roughly eight hours of scratching, migration tips and leader cells start to form. Cells at the protruding tips were categorized in the study as leader cells, and cells behind them as follower cells. Surprisingly, leader cells were show to have considerably more MALAT1 expression than follower cells. The expressions of UCA1 and β- actin mRNA in leader and follower cells, however, do not alter noticeably.

Further in this study used siRNA therapy to reduced MALAT1 expression in order to investigate MALAT1 roles in collective cancer migration. The findings shows that transiently inhibited MALAT1 prevented the development of migration tips and messes up collective cell movement. The monolayer boundary slightly contracts, lowered the average migration rate. Furthermore, MALAT1 knockdown results in a non-migratory phenotype, cell morphology. In contrast, downregulating UCA1 does not result in a significant alteration of cell shape, and the rate of migration was equivalent to that of cells treated with control siRNA. Additionally, TGF-β treatment of moving monolayers causes the separation of cancer cells and breakdown of cell-cell adhesion. Notably, certain dissociated cells exhibit increased MALAT1 expression.

Through single-molecule tracking, the work explored MALAT1 in leader and follower cells further. It is possible to calculate the mean squared displacement (MSD) of molecules by monitoring the positions of transcripts over time. The cytoplasmic MALAT1 has a diffusivity of about 0.09 $\mu m^2/s$, which is comparable to that of β-actin mRNA. It is interesting to note that the nuclei of leader cells exhibit a decreased diffusivity of MALAT1. MALAT1 in the cytoplasm of leader cells has a higher diffusivity (0.089 ± 0.017 $\mu m^2/s$), but MALAT1 in the cell nuclei has a lower diffusivity (0.050 ± 0.011 $\mu m^2/s$). The MALAT1 diffusivity in follower cells, however, is comparable in the cytoplasm (0.097 ± 0.033 $\mu m^2/s$) and nuclei (0.010 ± 0.043 $\mu m^2/s$). Furthermore, only around 50% of MALAT1 transcripts are mobile (diffusivity 0.005 $\mu m^2/s$), yet this percentage is constant between leader and follower cells. Since leader cells have lesser diffusivity than follower cells, it is possible that MALAT1 in leader cells participated in different molecular complexes and activities. These results revealed that MALAT1 activation in leader cells varies during collective.

Conclusion

The significance of MALAT1 in leader cell formation and mass cancer invasion is highlighted by this study. The study sheds light on the dynamic control of lncRNAs in living single cells using a FRET nano-biosensor. The results showed that during collective cancer migration, MALAT1 expression is increased in leader cells as opposed to follower cells. The development of migration tips is disrupted and collective cell migration was impaired when MALAT1 is knock-down, highlighting the critical function of MALAT1 in orchestrating collective invasion. The study also shown that MALAT1 has a variable distribution and level of activity in leader cells, pointing to its participation in various molecular complexes and functions. Furthermore, MALAT1 expression is heterogeneous in bladder cancer samples and tumor organoids, indicating its relationship with invasive

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characteristics. Overall, this study reveals that the FRET nano-biosensor potential for study lncRNA dynamics and emphasizes the role of MALAT1 in bladder cancer invasion co-ordination. It is necessary to conduct more research to clarify the MALAT1 molecular mechanisms and roles, which could lead to the development of new cancer diagnostic and therapy.

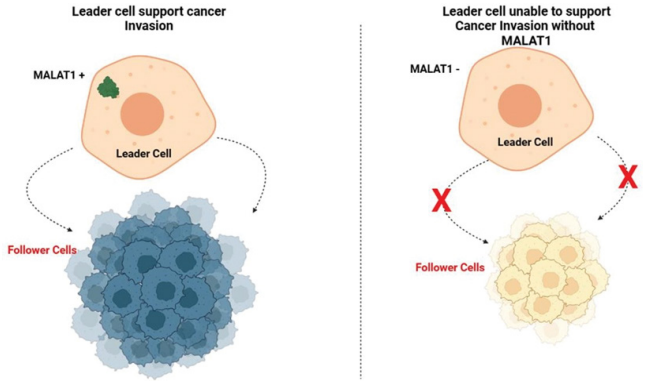

Figure 1: MALAT1 Expression in Leader Cells and its impact on Cancer Invasion.

Conflict of Interest

Authors declared no conflict of interest.

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