CRITICAL RESEARCH PERIODICAL

IS tRNA DRIVING BREAST CANCER PROGRESSION?

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ABSTRACT

This critical research periodical is mainly based on critical review of research article titled 'Modulated Expression of Specific tRNAs Drives Gene Expression and Cancer Progression published in Cell by Goodarzi et al[1]. According to Globocan, 2008 report[2], breast is among the leading site of new cancer cases and deaths (691,300/268,900) in females of developing countries and second leading site in USA (Globocan, 2012)[3]. The extensive research is in progress on different aspects of molecular mechanism of driving forces and different treatment modalities to ease this burden. The above mentioned research article is also part of this effort.

Keywords: tRNAArgCCG; tRNAGluUUC; tRFs; MDA-LM2; CNLM1a.

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STATE OF THE FIELD

The role of transfer RNAs in protein synthesis is well established but still genomes reveal considerable deviations across their coding sequences for particular codons. The findings from a decent number of studies[4,5] highlighting role of tRNA in different phases of tumorigenesis are as follows:

- Significant correlation was found between tRNA type and custom codon showing predisposition of exceedingly expressed tissue-specific proteins
- The rate of translation may effectually be controlled by tRNA content for a subsection of endogenous proteins
- Microarray profiling of tRNA is the technique especially for several human cell lines and samples described discrete tRNA signatures to associate with hall mark of proliferation and differentiation.
- Protein expression may be affected by intonations
- Codon optimality is considered as a keyfactor of mRNA solidity.

AIM OF THE PAPER

In light of above stated findings, authors were of idea that the monitoring magnitudes of inflections of tRNA and their impending undeviating part in gene expression and human ailments is ill defined so they aimed to perform an impartial study of tRNA in both benign and malignant breast cell lines.

The above aim is part of research on an important enabling hallmark of genomic instability and mutability which provide cancer cells with genetic alterations that drive tumor progression.

BRIEF SUMMARY OF THE RESULTS

Authors conceived a promising idea of using available breast cell lines and found out several tRNA classes inhuman cell lines. These were five cell lines namely a non-malignant epithelial cell line (MCF10a) along with MDA-231 and CN34 which were poorly metastatic. Correspondingly exceedingly metastatic cell lines like MDA-LM2 and CNLM1a were also used. They found that MDA-LM2 and CNLM1a which were highly metastatic exposed analogous variations in their tRNA comparative to their isogenic paternalcell lines. Through loss-of-function and gain-of-function experimentations, an instrumental role for two particular RNAs (tRNAGluUUC and tRNAArgCCG) was recognized as developers of metastasis in cancer of breast. Amplified expression of these tRNAs redesigned protein expression through the undeviating intona-

tion of ribosome possession and transcript stability of precise transcripts supplemented for codon complementary to these tRNAs. Improved expression of a particular tRNA enhanced the target gene expression. The unique promoters of metastasis were established in this regard and regulatory tRNA in combination with upstream tRNAs form a tRNA-activated pathway indicative of cancer advancement. TRNAGlu UUC is considered as driver of metastasis by directly activating EXOSC2 and augmenting GRIPAP1.

MAJOR CONTRIBUTIONS

In my view, major contribution of this paper to science is to establish role of tRNA as driver of breast cancer progression. I thought that this paper published in June, 2016 should be read with a paper "Functional Genomic Landscape of Human Breast Cancer Drivers, Vulnerabilities, and Resistance" published also in Cell by Marcotte et al.[6] where they adopted genome-wide pooled shRNA library for screening of 77 breast cancer lines.

Epithelial cells in breast cancer exhibit upregulation of tRNAs but its validation and identification of reliable mechanism is very demanding. This is due to tRNA modification and stable cDNA libraries cannot be produced. Cozen et al. and Zheng et al.[7,8] presented procedures in which not bacterially encrypted demethylase treatment was used. This was done before reverse transcription to increase the value of cDNA library but in current research, Goodarzi et al.[1] established a novel method for measurement of tRNA pool in which specialized pairs of DNA probes were used for every tRNA. By using this approach, tRNAArgCCG and tRNAGluUUC were recognized which showed upregulation in breast cancer cell lines. They additionally perceived that exceedingly metastasis exhibiting cells with high concentrations of tRNAArgCCG and tRNAGluUUC revealed ominously conceded colonization in mice lungs. Contrariwise, overexpression of tRNAArgCCG and tRNAGluUUC in poorly metastatic cells improved their metastatic capability in lungs. Constant with these verdicts, authorsdisclosed that the concentration of these tRNAs were increased in breast cancer with metastasis.

Another strength of the paper is establishing clinical association with advancement of breast cancer in humans. It was achieved by measuring tRNAs levels in a cohort study of primary tumors that had not undergone metastasid accompanied by analyzing clinical metastasis (n = 23) and witnessed substantial upregulations of tRNAArgCCG and tRNAGluUUC in the metastatic primary tumors comparative to non-metastatic ones. Moreover, a new tRNA profiling of both metastatic and non metastatic cell lines revealed that particular tRNAs were showing upregulation in metastatic breast cancer cells and derived metastasis by increasing stability and translation of copiessupplemented for their related codons.

Generally, these findings inspire us to contemplate tRNAs more as regulatory elements of specific gene expression in spite of governing only protein synthesis as regulatory factors.

FUTURE RESEARCH QUESTIONS

1. What is the mechanism of upregulation of particular tRNAs?
2. Which transcription factors are responsible for upregulation?
3. What will be the effect on steadiness of matured tRNAs?
4. What will be the effect of modulation of tRNA on target gene expression?
5. Are similar mechanism is exhibited by any other tRNAs which are responsible for phenotype variation?
6. tRNAs have the ability of producing small RNA fragments (tRFs). In this case question arisethathow tRFs keep their place in current scenario?

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

AUTHORS CONTRIBUTION

ZR and SY equally contributed in critical write up.

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