Role of Pseudogenes in Cancer Stem Creation Via High Nitric Oxide (HNO) Adaptation

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ABSTRACT

Gene chip analysis of ten HNO adapted cell lines (Squamous cells: SCC-016, SCC-040, SCC-056, SCC-114, SCC-116; Adenocarcinomas: A549, BT20, Hs578, MCF7, and T47D) was carried out. Known pseudogenes were identified in each line, as well as their coding counterparts.

The adenocarcinoma cell lines had no up regulated pseudogenes, while they had the following down regulated pseudogenes: RP6-159A1.2, RP11-255N24.3, AC004490.1, LDHBP, RP11-572H4.2. The squamous cell carcinomas (SCCs) had the following up regulated pseudogenes: RPL37AP1, AC138972.1, RP11-641D5.1, AC005534.6, AC022431.1, RPL26P12, and they had these down regulated pseudogenes: RP6-159A1.2, RP11-255N24.3, RBMXP1, RP11-20O23.1, RP11-551G24.2. All cell lines adhered to the hypothesis that an increase in a pseudogene expression also had an increase in the corresponding gene.

The high level of pseudogenes could be due to low levels of microRNA; low expression of microRNA could then be due to high levels of ceRNA. In cases when the pseudogenes increase in expression (possibly due to HNO interference) they, like BRAF, take the functionality of ceRNA which in turn decreases microRNA expression. Although a pseudogene may not have any direct translational significance, it can act as ceRNA to facilitate the over expression of the coding gene in a feedback loop.

INTRODUCTION

Although pseudogenes were traditionally thought to have no functional significance, evidence by Karreth et al. suggests that pseudogenes may contribute to the development of cancer as ceRNA (coding endogenous) mediates microRNA sequestration. Karreth et al. also observed a parallel dysregulation with the BRAF gene and its pseudogene. Specifically, high levels of the BRAF pseudogene (entailing a high amount of the regular BRAF gene) lead to the development of aggressive malignancies similar to human diffuse large B cell lymphoma. Therefore, pairs of coding genes and their pseudogenes in oncogenic dysregulation of ten HNO adapted cell lines needed to be detected in order to better understand the relationship between genes and pseudogenes.

HYPOTHESIS/OBJECTIVE

With HNO, ceRNA and microRNA are affected such that pseudogenes (and coding analogs) are overexpressed ultimately yielding cancer.

METHODS

Gene chip analysis in the Radosevich Lab at UIC allowed the examination of ten HNO adapted cell lines, five squamous and five adenocarcinomas (SCC-016, SCC-040, SCC-056, SCC-114, SCC-116, A549, BT20, Hs578, MCF7, and T47D). Known and processed pseudogenes were sought in each line as well as coding counterparts.

RESULTS

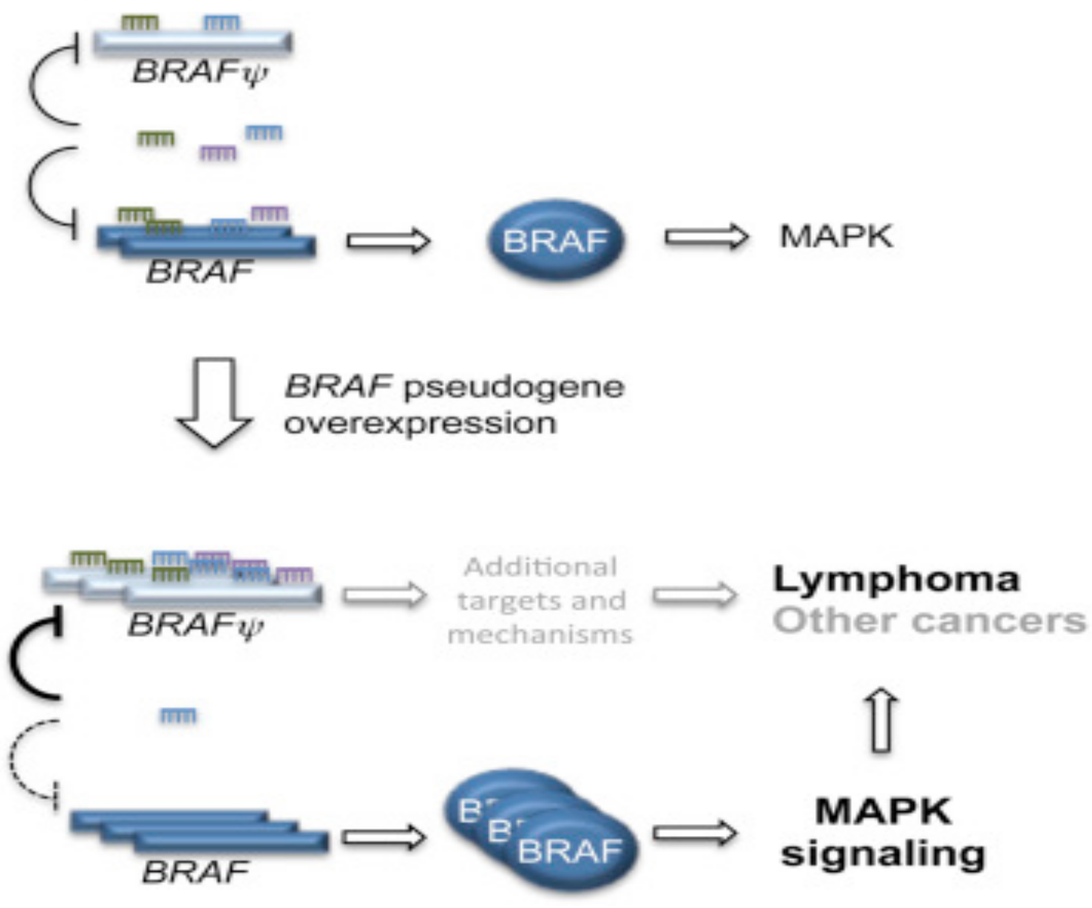

Figure 1. Represents Karreth et al.'s study regarding BRAF and BRAF pseudogene inception and lead up to cancer.

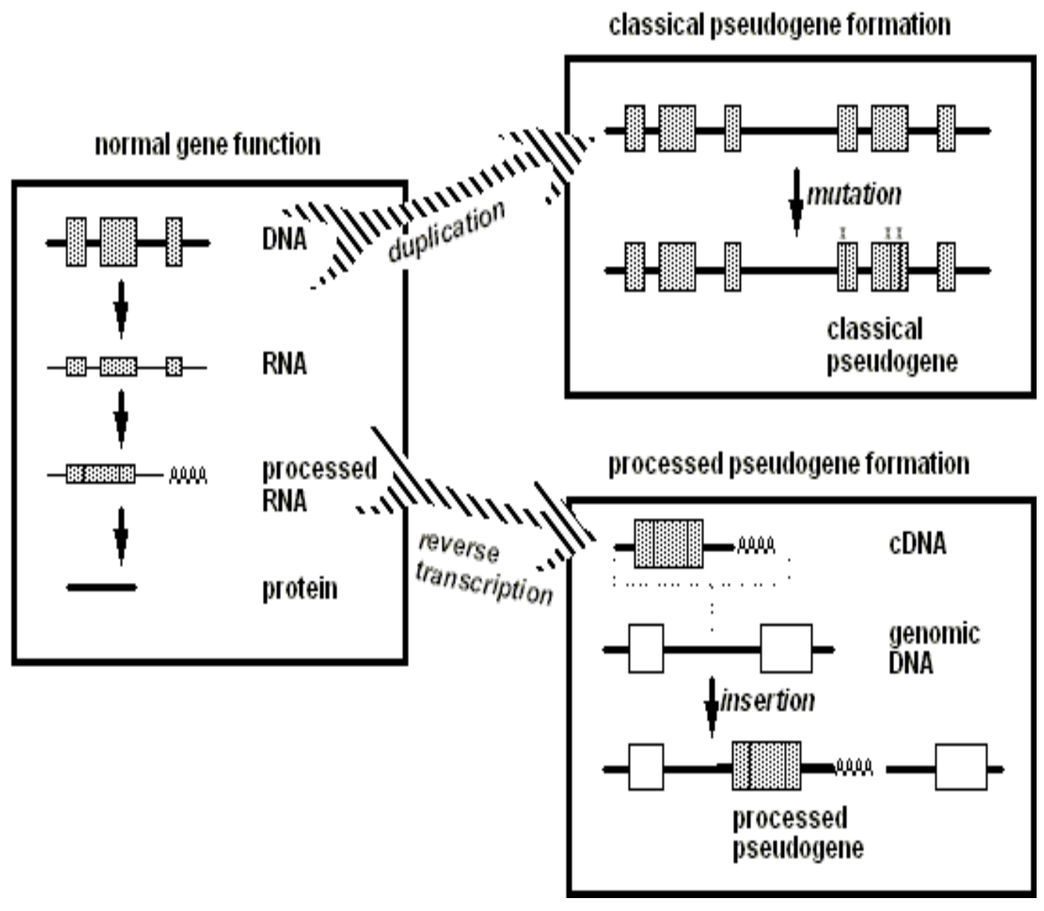

Figure 2. Illustrates possible routes of pseudogene formation as well as the role of ceRNA in its synthesis.

- The ACC cell line upregulated had no pseudogenes; ACC down had RP6-159A1.2, RP11-255N24.3, AC004490.1, LDHBP, RP11-572H4.2; SCC Up had RPL37AP1, AC138972.1, RP11-641D5.1, AC005534.6 , AC022431.1, RPL26P12; and SCC down had RP6-159A1.2, RP11-255N24.3 , RBMXP1, RP11-20O23.1, RP11-551G24.2. All cell lines adhered to the hypothesis that an increase in a pseudogene also increased the expression of the corresponding coding gene.

CONCLUSION

Beyond microRNA having a greater affiliation for pseudogenes, other cellular substances may do the same. The antisense gene (AC004490.1 in ACC down) could also parallel the processes between ceRNA, microRNAs, and pseudogenes. The high level of pseudogenes could be due to low levels of microRNA; low expression of microRNA could then be due to a high level of ceRNA. Such symptoms could be hallmarks for cancerous cells.

Moreover, in cases when the pseudogenes increase in expression (possibly due to HNO interference) they, like BRAF, take the functionality of ceRNA which in turn decreases microRNA expression. Hence, although the pseudogene may not have any translational significance, it acts as ceRNA to facilitate the overexpression of the coding gene in a feedback loop (and pseudogene) which leads to oncogenic threats.

ACKNOWLEDGMENTS

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