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The Human Chromosome 21 Gene TIAM-1 Over-Expressed in Down Syndrome Could be a Valuable Predictive Biomarker and a Potential Therapeutic Target for Treatment of Multiple Clinical Tumors and Cancers

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Abstract

Down syndrome, the triplication of human chromosome 21, is the most frequent genetic disorder associated to numerous diseases with hard impact on public health. Remarkably, the over-expression of most genes on this chromosome causes transcriptional alterations and dosage imbalance of proteins on other chromosomes that impair several genetic networks and signalling pathways. Interestingly, some crucial chromosome 21 genes such as TIAM-1 (T-cell lymphoma invasion and metastasis inducing factor 1) play important roles and regulates multiple signalling pathways involved in cell shape, cell polarity, cell migration, cell adhesion, cell invasion, cell growth and survival and consequently TIAM-1 could be a useful predictive biomarker and a potential therapeutic target for treatment of aberrant developmental cell processes and for treatment of multiple tumors and cancers.

Keywords: Down syndrome; Chromosome 21 TIAM-1 gene; Therapeutic Gene Target; Cancer Treatments

Abbreviations: TIAM-1: T-cell Lymphoma Invasion and Metastasis Inducing Factor 1; GEF: Guanine Nucleotide Exchange Factor; RNAi: RNA Interference; EMT: Epithelial Mesenchymal Transition.

Introduction

Down syndrome or Trisomy 21, a genetic disorder caused by an extra copy of chromosome 21 in all cells generated by a chromosomal non-disjunction during meiosis, is associated to a complex phenotype, the main features of which are the morphological abnormalities of head and limbs, short stature, joint hyperlaxity, hypotonia, frequent occurrence of visceral malformation, skeletal defects, haematological and endocrinal alterations, increased risk of leukaemia, early occurrence of an Alzheimer-like neuropathology and mental retardation [1,2]. Remarkably, the genetic over-expression, caused by trisomy 21, determines alterations in transcriptional level of most genes on chromosome 21 and their dosage alterations determine transcriptional variations of several genes located on other chromosomes affecting several molecular pathways involved in different developmental cell processes, tumors and cancers [3,4].

Among the important chromosome 21 genes, TIAM-1 (T-cell lymphoma invasion and metastasis inducing factor 1)

has been identified to have significant roles in the progression of epithelial cancers. Interestingly, this key gene encodes a RAC-1 specific guanine nucleotide exchange factor (GEF) and regulates RAC-1 signalling pathways that affect cell shape, cell polarity, cell migration, cell adhesion, cell invasion, cell growth and survival.

In human breast carcinomas, a close correlation was observed between an increased TIAM-1 expression and an increased tumor status suggesting that increased TIAM-1 expression and/or activity may promote progression of breast carcinomas [5]. Tumors that occur in TIAM-1$^{(-/-)}$ mice are more likely to progress suggesting that, in skin carcinogenesis, TIAM-1 is an inhibitor of tumor development [6]. Colon carcinoma cell lines selected for increased metastasis in nude mice express more TIAM-1 protein than their parental line indicating that TIAM-1 may have a role in the progression and metastasis of colon carcinomas and that TIAM-1 regulates cell adhesion, migration and apoptosis in colon tumor cells [7-10].

To test the hypothesis that TIAM-1 is a determinant of proliferation and metastasis in colorectal cancer, RNA interference (RNAi) study examined the effect of the inhibition of TIAM-1 expression on proliferation and metastasis and it has been found that the silencing of TIAM-1 resulted in the effective inhibition of in vitro cell growth and of the invasive ability of colorectal cancer cells. This suggests that TIAM-1 plays a causal role in the metastasis of colorectal cancer and that RNAi-mediated silencing of TIAM-1 may provide an opportunity to develop a new treatment strategy for colorectal cancer [11]. TIAM-1 mRNA and protein levels were significantly elevated in 9 human hepatoma cell lines compared to the normal primary human hepatocyte suggesting that TIAM-1 overexpression in malignant neoplasms could be a novel effective biomarker for tumors including hepatocellular carcinoma [12]. TIAM-1 expression is frequently up-regulated in breast cancer and correlated with clinicopathological parameters, suggesting that TIAM-1 could be a useful predictive biomarker and a potential therapeutic target for treatment of patients with breast cancer [13].

The specific genetic variants identified within the domains of TIAM-1 gene that signal to the upstream regulator RAS and downstream effectors molecule RAC are involved in neuroblastoma indicating that TIAM-1 genetic variants improve clinical outcome in neuroblastoma and could be a potential target for therapeutic interventions [14]. Interestingly, it has been established that TIAM-1 knockdown inhibited the migratory and invasive ability of thyroid cancer, suppressed epithelial mesenchymal transition (EMT) and inhibited Wnt/beta-catenin signalling in vitro, and also suppressed liver metastasis development in vivo. The effects of TIAM-1 on metastasis and EMT mediated by the Wnt/B-catenin pathway was reversed by RAC-1 silencing, indicating that the metastasis effect of TIAM-1 is mediated by the activation of RAC-1. These findings suggest that TIAM-1 may be a predictive factor and a potential therapeutic target for treatment of patients with thyroid cancers [15].

Conclusion

Some interesting over expressed human chromosome 21 genes, such as TIAM-1, specific to different Down syndrome associated clinical diseases characterized by aberrant developmental cell processes could provide interesting developmental genetic model to study different genetic networks and signalling pathways involved in cell shape, cell polarity, cell migration, cell adhesion, cell invasion, cell growth and survival and could be a useful predictive biomarker and a potential therapeutic gene target for treatment of aberrant developmental cell processes and of multiple tumors and cancers.

References

1. Korenberg JR, Chen XN, Schipper R, Sun Z, Gonsky R, et al. (1994) Down syndrome phenotypes: The consequences of chromosomal imbalance. Proc Natl Acad Sci 91(11): 4997-5001.

2. Rachidi M, Lopes C (2010) Molecular and Cellular Mechanisms Elucidating the Neurocognitive Basis of Functional Impairments Associated with Intellectual Disability in Down syndrome. American Journal of Intellect Dev Disabil (115): 83-112.

3. Rachidi M, Lopes C (2007) Mental retardation in Down syndrome: From gene dosage imbalance to molecular and cellular mechanisms. Neuroscience Research 59(4): 349-369.

4. Rachidi M, Lopes C (2009) Gene Expression Regulation in Down syndrome: Dosage Imbalance Effects at Transcriptome and Proteome Levels. Handbook of Down syndrome Research, Edition Nova Science Publishers, Inc., pp: 55-87.

5. Adam L, Vadlamudi RK, McCrea P, Kumar R (2001) TIAM-1 overexpression potentiates heregulin-induced lymphoid enhancer factor-1/beta-catenin nuclear signaling in breast cancer cells by modulating the intercellular stability. J Biol Chem 276(30): 28443-28450.

6. Malliri A, vander Kammen RA, Clark K, Van DV, Michiels F, et al. (2002) Mice deficient in the RAC activator TIAM-1 are resistant to RAS-induced skin tumours. Nature 417(6891): 867-871.

7. Morikawa K, Walker SM, Nakajima M, Pathak S, Jessup JM, et al. (1988a) Influence of organ environment on the growth, selection, and metastasis of human colon carcinoma cells in nude mice. Cancer Res 48(23): 6863-6871.

8. Morikawa K, Walker SM, Jessup JM, Fidler IJ (1988b) In vivo selection of highly metastatic cells from surgical specimens of different primary human colon carcinomas implanted into nude mice. Cancer Res 48(7): 1943-1948.

9. Minard ME, Herynk MH, Collard JG, Gallick GE (2005) The guanine nucleotide exchange factor TIAM-1 increases colon carcinoma growth at metastatic sites in an orthotropic nude mouse model. Oncogene 24(15): 2568-2573.

10. Minard ME, Ellis LM, Gallick GE (2006) TIAM-1 regulates cell adhesion, migration and apoptosis in colon tumor cells. Clin Exp Metastasis 23(5-6): 301-313.

11. Liu L, Zhang Q, Zhang Y, Wang S, Ding Y (2006) Lentivirus-mediated silencing of TIAM-1 gene influences multiple functions of a human colorectal cancer cell line. Neoplasia 8(11): 917-924.

12. Chen B, Ding Y, Liu F, Ruan J, Guan J, et al. (2012) TIAM-1 overexpressed in most malignancies, is a novel tumor biomarker. Mol Med Rep 5(1): 48-53.

13. Li Z, Liu Q, Piao J, Hua F, Wang J, et al. (2016) Clinicopathological implications of TIAM-1 overexpression in invasive ductal carcinoma of the breast. BMC Cancer 16(1): 681.

14. Sanmartin E, Yanez Y, Formes-Ferrer V, José L Zugaza, Adela Cañete, et al. (2017) TIAM-1 variants improve clinical outcome in neuroblastoma. Oncotarget 8(28): 45286-45297.

15. Liu L, Wu B, Cai H, Ma Y, Zhu X, et al. (2018) TIAM-1 promotes thyroid carcinoma metastasis by modulating EMT via Wnt/beta-catenin signalling. Exp Cell Res 362(2): 532-540.