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Down syndrome Provide Genetic Models and Key Roles of Human Chromosome 21 Gene Targets in the Elucidation of Molecular Pathways Associated to Cell Cycle Alterations, Leukaemia and Cancer for Development of Potential Drugs and Therapeutics

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Abstract

Trisomy 21 or Down syndrome, caused by the triplication of human chromosome 21, is the most frequent genetic disorder with hard impact on public health. The overdosage of genes on this chromosome determines transcriptional alterations and dosage imbalance of a lot of proteins affecting several molecular pathways involved in several human diseases. Interestingly, some key human chromosome 21 genes play important roles in cell cycle and cell growth and could, with the recent progress in the developmental genetics, provide significant elucidation of molecular mechanisms involved in Down syndrome associated diseases related to cell cycle alterations, leukaemia, tumors and cancers, in the perspective of development of new drugs and treatments.

Keywords: Down syndrome; Human Chromosome 21 genes; Mouse Genetic Models; NF-κB signaling pathway; Wnt/beta-catenin signalling pathway; Cell Cycle; Leukaemia; Cancers; Therapeutic Gene Targets; Treatments

Abbreviations: DYRK1A: Dual-specificity tyrosine[Y]-Regulated Kinase; AML1: Acute Myeloid Leukaemia 1; TIAM-1: T-cell Lymphoma Invasion and Metastasis factor 1; RNAi: RNA interference; EMT: Epithelial Mesenchymal Transition; SIM2 gene: Single Minded 2; Shh: Sonic hedgehog.

Introduction

Down syndrome or Trisomy 21, determined by the triplication of human chromosome 21, is the most frequent genetic disorder with hard impact on public health. This genetic disorder causes a complex phenotype, the main features of which are the morphological abnormalities of head and limbs, short stature, joint hyperlaxity, hypotonia, skeletal defects, frequent occurrence of visceral malformation, increased risk of leukaemia, haematological and endocrinal alterations, early occurrence of an Alzheimer-like neuropathology and mental retardation [1].

The genetic over dosage, 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 cell cycle alterations, leukaemia, tumors and cancers [2,3].

Interestingly, some key human chromosome 21 genes and oncogenes or tumor suppressor genes located on the human chromosome 21 play important roles in cell cycle and cell growth and could, with the recent progress in the developmental genetics, contribute significantly to the elucidation of molecular mechanisms involved in Down syndrome associated diseases related to cell cycle alterations, leukaemia, tumors and cancers, in the perspective of development of new drugs and treatments [4].

Remarkably, the comparison of normogenic versus trisomic subjects showed that the famous Trisomic mouse models Ts65Dn as well as Down syndrome fetuses had a larger percent number of cells in G2 phase of cell cycle compared with controls, and an opposite result is found for the number of cells in the M phase of cell cycle. A longer time spent by proliferating cells in G2 phase result in a longer cell cycle and a reduced proliferation rate [5].

Importantly, one central member of the phosphorylation pathways that control the cell cycle is encoded by the chromosome 21 gene DYRK1A, a member of the DYRK (Dual-specificity tyrosine[Y]-Regulated Kinase) subfamily [6]. Homozygous null Dyrk1A mutant mouse embryos (Dyrk1A-/-) present delayed general growth with an overall reduction in organ growth, including neurogenesis decrease in the brain [7]. DYRK1A overexpression was associated with an increase in phosphorylation of the Forkhead transcription factor FKHR and with high levels of cyclin B1, suggesting a correlation in vivo between DYRK1A overexpression and cell cycle protein alteration. In addition, an altered phosphorylation of transcription factors of CREB family (cyclic AMP response binding protein) was observed, supporting a role of DYRK1A overexpression in the neuronal abnormalities seen in Down syndrome and indicating that this pathology is linked to altered levels of proteins involved in the regulation of cell cycle [8]. This suggests a central role of DYRK1A in the pathways of cell cycle control and its overexpression participate to neurogenesis alteration in Down syndrome patients [9]. The treatment of DYRK1A transgenic mice with inhibitory Dyrk1A shRNA rescues the brain defects and restores cognitive impairments induced by the overexpression of DYRK1A gene and indicates DYRK1A as a therapeutic target in the mouse models of Down syndrome [10,11].

Significantly, Down syndrome children have an approximately 20-fold increased risk of developing acute lymphoblastic leukaemia and acute myeloid leukaemia compared to normal children [12]. The increased transcription of oncogenes and tumor suppressor genes located on the human chromosome 21 have important roles in leukaemia, tumors and cancer that are related to an alteration of the cell cycle.

The chromosome 21 oncogene AML1 (Acute Myeloid Leukaemia 1) named also RUNX1 or CBFA2 is a well-known regulator of hematopoiesis and megakaryopoiesis and the genetic loss-of-function mutations of AML1 cause the autosomal dominant familial platelet disorder with a predisposition to develop acute myeloid leukaemia as is also seen in mouse models [13,14]. The altered function of transcription factor AML1 is closely associated with malignant transformation of hematopoietic cells and AML1 transcripts are down regulated in Down syndrome megakaryoblasts compared to non-Down syndrome megakaryoblasts indicating that AML1 is associated to megakaryocytic lineage [15]. In addition, inherited mutations in AML1 causing haplo-insufficiency with a low level of expression in hematopoietic stem cells lead to a syndrome of familial thrombocytopenia and increased susceptibility to leukaemia [16]. Remarkably, it was found that AML1 inhibits NF-κB signalling through interaction with IκB kinase complex in the cytoplasm and that the inhibition of NF-κB signalling in leukemic cells with mutated AML1 efficiently blocks their growth and development of leukaemia. These results suggest a key role for AML1 as a cytoplasmic attenuator of NF-κB signalling in the repression of myeloid tumors and indicate that NF-κB signaling is one of the promising therapeutic targets of hematologic malignancies with AML1 abnormality [17].

The chromosome 21 gene SIM2 (single minded 2) encodes a helix-loop-helix transcription factor belong to a family of transcriptional repressors involved in the brain development and neuronal differentiation [18,19]. Functional studies indicated that SIM2 protein control the Sonic hedgehog (Shh) expression in the brain involved in cell growth and differentiation in the brain and Sim2 mutant mice are lethal in the early post-natal days and show skeletal alteration due to cell proliferation defects [20,21]. SIM2 gene was expressed in the colon, prostate and pancreatic carcinomas, but not in their corresponding normal tissues, and its expression was seen in a stage-specific manner in colon and prostate tumors [22]. The overexpression of SIM2 was associated with tumors of the colon, pancreas and prostate [23,24]. The antisense inhibition of SIM2 expression in a colon cancer cell line resulted in inhibition of gene expression, growth inhibition and induction of apoptosis in vitro as well as inhibition of tumour growth in nude mouse tumoriginicity models. The induction of apoptosis by the antisense SIM2 could involve a block of cell cycle, induction of differentiation or the activation of apoptotic cascades [23]. The stimulatory effect of SIM2 antisense on tumor cell apoptotic regulation and inhibition of cell cycle by SIM2 indicate that inhibition of tumor growth by antisense blocking of SIM2 in colon cancer may be due to an influence on cell cycle regulation [25,26]. These results suggest that SIM2 might have both diagnostic and therapeutic utility. The gene expression profiling demonstrated that SIM2 is

among the highly up-regulated genes in 29 prostate cancers [27]. SIM2 was significantly co-expressed and increased in prostate cancer and the increased expression of SIM2 protein is a novel marker of aggressive prostate cancer [28]. Interestingly, SIM2 has been identified as a potential biomarker and immunotherapy target in prostate cancer and has also been identified as a predictive biomarker for uterine cervical squamous cell carcinoma [29,30].

The chromosome 21 gene TIAM1 (T-cell lymphoma invasion and metastasis 1) has been identified to have significant roles in the progression of epithelial cancers. In human breast carcinomas, a close correlation was observed between increased TIAM1 expression and increased tumor grade suggesting that increased TIAM1 expression and/or activity may promote progression of breast carcinoma [31]. Tumors that do occur in Tiam1$^{(-/-)}$ mice are more likely to progress suggesting that, in skin carcinogenesis, Tiam1 is an inhibitor of tumor development [32]. Colon carcinoma cell lines selected for increased metastatic potential in nude mice express more TIAM1 protein than their parental line [33-36]. This indicates that TIAM1 may have a role in the progression and metastasis of colon carcinomas and that TIAM1 regulates cell adhesion, migration and apoptosis in colon tumor cells. To test the hypothesis that TIAM1 is a determinant of proliferation and metastasis in colorectal cancer, RNA interference (RNAi) study examined the effect of the inhibition of TIAM1 expression on proliferation and metastasis. It has been found that the silencing of TIAM1 resulted in the effective inhibition of in vitro cell growth and of the invasive ability of colorectal cancer cells. This suggests that TIAM1 plays a causal role in the metastasis of colorectal cancer and that RNAi-mediated silencing of TIAM1 may provide an opportunity to develop a new treatment strategy for colorectal cancer [37]. TIAM1 mRNA and protein levels were significantly elevated in 9 human hepatoma cell lines compared to the normal primary human hepatocyte suggesting that TIAM1 overexpression in malignant neoplasms could be a novel effective biomarker for tumors including hepatocellular carcinoma [38]. TIAM1 expression is frequently up-regulated in breast cancer and correlated with clinicopathological parameters, suggesting that TIAM1 may be a useful prognostic biomarker and potential therapeutic target for patients with breast cancer [39]. Remarkably, it has been shown that TIAM-1 promotes thyroid carcinoma metastasis by modulating epithelial mesenchymal transition via Wnt/beta-catenin signalling suggesting TIAM-1 as a predictive factor and a potential therapeutic target for treatment of patients with thyroid cancers [40].

Conclusion

These numerous genetic molecular studies are of the most interest and indicate that the Down syndrome could provide an interesting model for the role of aneuploidy in leukemogenesis, tumorigenesis and cancerigenesis and could be considered as a developmental genetic model to investigate and decipher the genetic networks involved in these different diseases. Some key human chromosome 21 genes play important roles in cell cycle and cell growth and could, with the recent progress in the developmental genetics, provide significant advancement and elucidation of molecular and cellular mechanisms involved in the Down syndrome associated diseases related to cell cycle alterations, leukaemia, tumors and cancer, in the perspective of development of new drugs and treatments.

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