The Egyptian Journal of Medical Human Genetics (2014) 15, 209–210

Ain Shams University

The Egyptian Journal of Medical Human Genetics

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www.sciencedirect.com

EDITORIAL

The blessing effect of an extra copy of chromosome 21

It has long been known that Down syndrome (DS) children have an increased risk of leukaemia. On the other hand, reports of solid malignancies are rare. Large population-based and/or tumour registries have shown that solid tumours occur significantly less frequently in DS children and adults in comparison with individuals without trisomy 21. Among 2814 individuals from different age groups with DS registered in a Danish study, only 24 cases of solid tumours were identified, whereas 47.7% cases would have been expected [1]. A British registry of 11,000 childhood solid tumour cases identified only seven tumours in DS children [lymphoma (3), teratoma (1), glioma (2), and fibrosarcoma (1)] [2]. This is true also in adult tumours. Among 1278 women with DS registered in the Danish Cytogenetic and Danish Cancer Registries, no cases of breast cancer were identified, while at least seven cases would have been expected [1].

The protective effect of the extra copy of chromosome against the development of certain malignancies was documented in neuroblastoma: The S-100b protein (encoded by a chromosome 21-localised gene) is higher in DS patients which may contribute to its lower incidence. This protein can inhibit the growth and induce death of human and murine neuroblastoma cell lines [3,4].

The presence of an extra copy of chromosome 21 also protects against the progression of tumours where several genes are involved, all mapped to chromosome 21: *COL18A1* gene, encoding endostatin which is a soluble 20 kd cleavage product of collagen XVIII. It is a potent angiogenesis inhibitor for many different types of solid tissue tumours in both human and animal models [5]. Zorick et al. found that endostatin is significantly higher in DS patients and suggested that individuals with serum endostatin levels higher than 20 ng/ml might be less prone to the development of solid tumours than those with lower levels and therefore, it will be important to evaluate the use of endostatin levels as a predictive test [6].

Endostatin was also found to inhibit tumour lymphangiogenesis by decreasing the vascular endothelial growth factor C (VEGF-C) levels in tumours, apparently via inhibition of mast cell migration and adhesion [7].

These data suggested that endostatin is a good candidate for cancer therapy in humans. A phase III clinical trial was carried out on 493 histology or cytology confirmed stage IIIB and IV none small cell lung patients. Patients were treated with Endostar, a recombinant endostatin product in combination with the standard chemotherapeutic regimen. This addition resulted in significant and clinically meaningful improvement in response rate, median time to progression, and clinical benefit rate compared with the chemotherapeutic regimen alone [8].

The extra copy of chromosome 21 protects also against tumour progression through another two genes: Down syndrome critical region 1 (*DSCR-1*, also known as *RCAN1*) gene and dual-specificity tyrosine-phosphorylated and -regulated kinase 1A (*Dyrk1a*) which play a crucial role in inhibiting the growth of new blood vessels [6,9]. These two genes encode proteins that disrupt the calcineurin pathway, which is involved in angiogenesis. Ryeom and Folkman found that DSCR1 protein levels increased in both the tissues of people with DS and in the mouse model of DS. The growth of tumours was also suppressed, and the density of microvessels was statistically significantly lower in the DS mice than in the diploid control mice [10].

Recently, trisomy of the *DSCR1* gene was found to suppress early progression of pancreatic intraepithelial neoplasia driven by oncogenic K-ras [11] and is sufficient to suppress tumour angiogenesis during spontaneous lung tumourigenesis [12].

The DYRK1 gene was suggested to act in concert with *DSCR1* to suppress tumour angiogenesis by further attenuating VEGF-calcineurin-NFAT signalling in endothelial cells [13].

Other genes involved in inhibition of tumour progression were discovered by Reynolds et al., who identified two putative anti-angiogenic genes [14]: *ADAMTS1* which is a protease significantly blocks vascular endothelial growth factor receptor 2 (VEGFR2) phosphorylation with consequent suppression of endothelial cell proliferation [15] and *ERG which is* a transcription factor implicated in endothelial tube formation and angiogenesis [16].

They also identified novel endothelial cell-specific genes, never shown before to be involved in angiogenesis (*JAM-B* and *PTTG1IP*) that, when over-expressed, are responsible for the inhibition of angiogenic responses to VEGF [14].

Peer review under responsibility of Ain Shams University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.ejmhg.2014.01.006

The protective effect of the extra chromosome 21 is also observed in their lower incidence of diabetic retinopathy. The extra amount of endostatin protects individuals with DS from this diabetes complication through the same mechanism of reducing angiogenesis [10]. Endostar, has been considered as one of the most valuable anti-angiogenic agents as it inhibits both the proliferation of the choroid-retinal endothelial cells through limiting the progression of the cell cycle and their migration. Furthermore, it induces the expression of the pigment epithelial-derived factor (PEDF) and suppresses the expression of the vascular endothelial growth factor (VEGF) and the fibroblast growth factor (FGF). Endostar also reduces the expression of the inflammatory mediator tumour necrosis factor-alpha (TNF-alpha), matrix metalloproteinases (MMPs) and vascular cell adhesion molecule-1 (VCAM-1). These findings reveal an integrated role of Endostar in the programme of retinal vascular control and highlight its significant potential for broad clinical application [17].

High levels of endostatatins may also act as antiinflammatory. Recombinant human endostatin was effective in reducing proliferation and inducing apoptosis of synovial fibroblasts and in rheumatoid arthritis in rats. These findings highlight the potential use of endostatin as a treatment for rheumatoid arthritis [18].

As we should expect, individuals with DS have an 80% risk reduction of vascular anomalies. This protective effect is most likely because of increased gene product resulting from an extra copy of chromosome 21. Potential candidate genes on this chromosome include VEGF inhibitors *COL18A1*, *DSCR1*, or *DYRK1A*. Because VEGF is involved in the pathogenesis of both haemangioma and vascular malformations, increased gene product from these genes [19].

Interesting enough, trisomy 21 has an extra neuroprotective mechanism through over-expression of *DSCR1* which improves the outcome following stroke in mice. Mechanisms underlying this protection may involve calcineurin-independent, anti-inflammatory and anti-apoptotic effects mediated by DSCR1 in neurons [20].

Conclusions

As much grief as the family has when they receive the news of having a child with DS, the blessing effect of the extra copy of chromosome 21 (through its role in reducing the incidence and progression of solid tumour, the anti inflammatory effect and the stroke neuro-protection) endorses the human believe that in every tragedy there is a hidden rainbow. There may come a time when scientists induce trisomy 21 in cells as a form of anti-inflammatory or anti cancer therapy.

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Solaf M. Elsayed *

Genetics Unit, Children's Hospital, Ain Shams University, Cairo, Egypt

*Address: Medical Genetics Center, 27 A Baghdad St., Korba, Cairo, Egypt.

Tel.: +20 2 24151999; fax: +20 2 24150977.

E-mail address: elsayed683@yahoo.com

Available online 25 February 2014