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Understanding the Role of Chromosome 21 for Precision Treatment in Down Syndrome Acute Lymphoblastic Leukaemia

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Abstract

Children with Down Syndrome (DS) are predisposed to developing Acute Lymphoblastic Leukaemia (ALL) and experience lower overall survival (75%) compared to children without Down syndrome (85-90%). The mortality rate for paediatric DS-ALL patients is four times higher than non-DS-ALL patients in the first two years after their diagnosis. Increased chemotherapy-related toxicity is experienced by DS-ALL patients, however, new immunotherapies including bi-specific T-cell engagers and chimeric antigen receptor T-cell therapies are being pursued in clinical trials. Fundamental research has identified 31 genes in the Down syndrome critical region of chromosome 21 which play a role in leukaemogenesis. Understanding these genes will be critical to identify the predisposition DS patients have for developing ALL, as well as discovering new targeted therapeutic approaches. The aim is to identify the role(s) of chromosome 21 genes to establish less toxic treatment options for DS-ALL patients.

Keywords: Down syndrome; Leukaemia; Chromosome 21

Commentary

Trisomy of chromosome 21 occurs via nondisjunction at meiosis and results in Down Syndrome (DS) in 1 in 700 births. Chromosome 21 is the smallest human chromosome encoding ~225 genes. Trisomy of chromosome 21 is associated with neurodevelopmental disorders and early onset Alzheimer's disease. Increased expression of β-amyloid precursor protein (*APP*) encoded on chromosome 21 is implicated in Alzheimer's disease providing a mechanism of Alzheimer's development in DS patients [1]. Children with DS are predisposed to developing haematological malignancies and have a 150-fold and 20-fold increased risk of developing Acute Myeloid leukaemia (AML) and Acute Lymphoblastic Leukaemia (ALL), respectively [2]. Acute megakaryoblastic leukaemia (AMKL) is frequently observed in DS patients as trisomy 21 is required for AMKL development. DS-ALL patients have poor survival outcomes and experience significant treatment related-toxicity from contemporary chemotherapeutic regimes. Higher relapse rates and risk of infections are observed in DS-ALL patients compared to non-DS-ALL patients [3]. Therefore, improved treatment strategies are urgently needed to reduce adverse effects and improve survival outcomes.

DS-ALL patients experience toxicity from treatment due to the presence of trisomy 21. The roles of chromosome 21 genes, particularly in the Down syndrome critical region (DSCR) must be investigated to identify new targets for precision therapy (Figure 1). The DSCR encodes many genes involved in cancer associated pathways including cell signalling, proliferation and epigenetic pathways (Table 1) [4]. A number of genes have been identified to play roles in DS-AML, however, these genes do not necessarily have leukaemogenic roles in ALL. For example, *GATA1* mutations are prevalent in 30% of DS children, resulting in a pre-leukaemic haematological disorder called Transient Abnormal myelopoiesis (TAM). DS patients with TAM often undergo transformation to AML at a frequency of 20% [2,5,6]. However, *GATA1* mutations are not observed in DS-ALL patients. ETS-related gene (*ERG*) dysregulation on chromosome 21 has been demonstrated to promote TAM transformation to AML and recently, *DYRK1A* (the dual specificity tyrosine-phosphorylation-regulated kinase 1A) on chromosome 21 was demonstrated to promote AMKL growth [7,8]. These genes have not yet been fully investigated in the context of ALL. The high mobility group nucleosome binding protein 1 (*HMGN1*) has been demonstrated to activate transcription in B-cells and promote B-cell proliferation *in vivo* and may be involved in DS-ALL transformation [4,9].

DS-ALL patients harbour gene fusions involving cytokine receptor like factor 2 (*CRLF2*) at a frequency of 60%, compared to non-DS-ALL patients at 5-16%. *CRLF2* gene fusions are associated with activating mutations in Janus Kinase 2 (*JAK2*), constitutively activating JAK/STAT signalling [3]. JAK2 mutations are observed in 50% of *CRLF2* rearranged ALL patients, however, *RAS* activating mutations are prevalent when *JAK2* mutations are not present [10]. Interestingly, patients with intrachromosomal amplification of chromosome 21 (iAMP21) also have a high incidence of *CRLF2* rearrangements, suggesting a link between genes on chromosome 21 and *CRLF2*. Treatment for other cancers utilise many FDA approved small molecule inhibitors targeting JAK/STAT and RAS signalling that could be re-purposed for use in for a precision treatment approach in DS-ALL. Methotrexate that forms part of many chemotherapeutic regimens inhibits dihydrofolate reductase and interferes with thymidine synthesis to halt DNA replication. This can cause adverse effects for DS patients who have increased expression of genes involved in purine synthesis on chromosome 21 [2].

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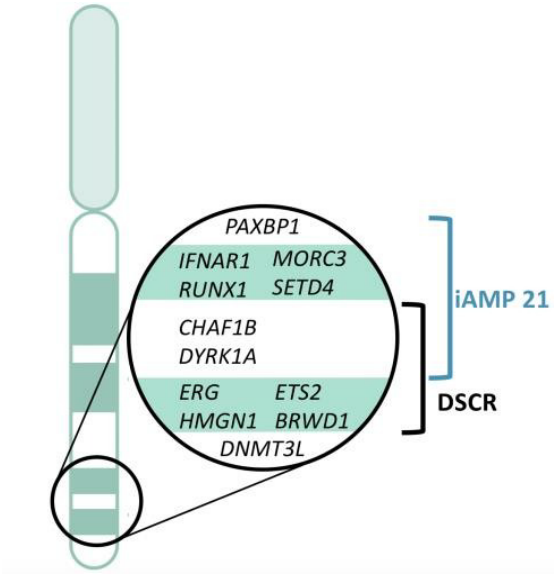

Figure 1: Chromosome 21 schematic depicting critical leukaemic genes located in the Down syndrome critical region and intrachromosomal amplification of chromosome 21 region observed in ALL patients.

Gene	Function
PAXBP1	Binds to PAX3 and PAX7 to regulate transcription
IFNAR1	Activates JAK/STAT signaling
RUNX1	Transcription factor that regulates development of hematopoiesis
MORC3	Chromatin remodeler
SETD4	Methyltransferase
CHAF1B	Chromatin regulator
DYRK1A	Kinase that regulates oncogenes and tumor suppressors
ERG	Hematopoietic oncoprotein
HMGN1	Histone demethylase
ETS2	Transcription factor and oncoprotein
BRWD1	Involved in chromatin regulation and transcriptional activation
DNMT3L	DNA methyltransferase

Table 1: Chromosome 21 genes with functions potentially implicated in leukaemic development or persistence.

Folinic acid (leucovorin) is administered to DS patients (NCT00103285 and NCT00075725) to combat the block in dihydrofolate reductase, as well as risk adapted chemotherapy (NCT01190930 and NCT03286634) which were previously the only precision approaches available for DS patients. Due to the risk of toxicity, DS patients have been excluded from trials of small molecule inhibitors (NCT02723994). However, recent advances have been made in immunotherapies including monoclonal antibodies (mAb), bi-specific T-cell engagers (BiTEs) and chimeric antigen receptor (CAR) T -cell therapies potentiating a new avenue of therapy for DS patients.

Blinatumomab is a single chain antibody construct with bi-specificity, binding to both cytotoxic T-cells through CD3 receptors and B-cells through CD19 receptors (Figure 2). The BiTE engages the immune system to eradicate both B-ALL and normal B-cells which received FDA approval in 2014 [11]. Multiple clinical trials of blinatumomab (NCT03914625, NCT04546399, NCT03117751 and NCT04307576) are currently being established for ALL and DS-ALL patients. Immunotherapies are considered to have less side effects due to their engagement with the patients' immune cells, compared to targeted small molecule inhibitors which are associated with off target effects.

Blinatumomab has been associated with toxicities including Cytokine Release Syndrome (CRS) and neurotoxicity in trials for lymphoma [12]. CRS symptoms can range from headache and fatigue, to multi system organ failure and therefore, must be monitored closely [13]. Despite high response rates, a higher relapse rate has also been observed with the use of blinatumomab. Therefore, blinatumomab is being considered as a bridging treatment prior to haematopoietic stem cell transplant (HSCT), although DS patients have poorer outcomes to HSCT compared to non-DS patients [14].

Trials for the anti-CD19 CAR T-cell, CTL019 (NCT02435849 and NCT02228096), have demonstrated promising results for the treatment of DS-ALL patients with high survival outcomes. Similar rates of toxicities including CRS, neutropenia and neurological effects were observed between DS and non-DS patients. However, a larger patient cohort is needed to determine the safety and efficacy of CTL019 in DS-ALL.

While trials for immunotherapies commence for DS-ALL patients, it is critical to continue investigating chromosome 21 genes and their roles in ALL development or persistence. Previous studies identified the genes responsible for the toxicity DS-ALL patients experience to chemotherapy, and different genes could also affect the

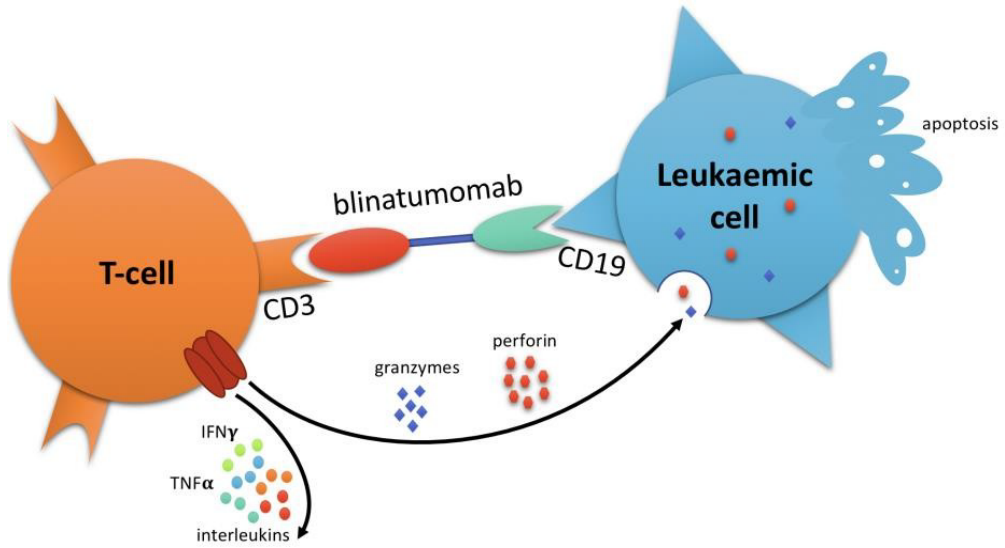

Figure 2: Blinatumomab binds to CD3 and CD19 to link cytotoxic T-cells to leukaemic cells and stimulate the release of interleukins, IFNγ and TNFα, as well as perforin and granzymes to initiate leukaemic cell apoptosis.

efficacy of immunotherapies or targeted approaches. Lessons learnt from the treatment of chronic myeloid leukaemia demonstrate a targeted molecule can revolutionise the treatment of haematological malignancies, transforming poor survival outcomes to a disease now on the brink of achieving treatment free remission [15]. Therefore, the roles of the 31 genes in the DSCR of chromosome 21 need to be fully elucidated to determine their targeting potential and discover the fundamental predisposition DS patients have to developing ALL. Transcriptional activation resulting from increased *HMGN1* expression activates B-cell receptor pathways including SRC kinases in pre-B cells, and JAK/STAT signalling in pro-B cells [9]. Therefore, the investigation of *HMGN1* has led to the identification of potential therapeutic targets including JAK/STAT signalling or protein kinase B (AKT) and BCL6 pathways in DS-ALL.

Interestingly, the gain of chromosome 21 (+21) is the most common cytogenetic abnormality observed in B-ALL patients, suggesting a link between genes located in the DSCR of chromosome 21 and ALL [16]. Investigating the roles these genes play in leukaemogenesis will be of the utmost importance to DS- ALL patient treatment, but also many other subsets of B-ALL patients harbouring +21 or iAMP21. The investigation of targeted therapies is necessary for the treatment of DS-ALL patients who currently experience toxicity to chemotherapy and have poor survival outcomes. While the introduction of immunotherapies is a great advancement for DS-ALL treatment, the fundamental research of DS-ALL aetiology will open new opportunities for safer and more effective treatment.

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