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The acute lymphoblastic leukemia of Down Syndrome – Genetics and pathogenesis

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ABSTRACT

Children with Down Syndrome (DS) are at markedly increased risk for acute lymphoblastic leukemia (ALL). The ALL is of B cell precursor (BCP) phenotype. T-ALL is only rarely diagnosed as well as infant leukemia. Gene expression profiling and cytogenetics suggest that DS-ALL is an heterogeneous disease. More than half of the leukemias are characterized by aberrant expression of the thymic stromal lymphopoietin (TSLP) receptor CRLF2 caused by genomic rearrangements. These rearrangements are often associated with somatic activating mutations in the receptors or in the downstream components of the JAK-STAT pathway. The activation of JAK-STAT pathway suggests that targeted therapy with JAK or downstream inhibitors may be effective for children with DS-ALL. The basis of the increased risk of BCP-ALL and in particular of the CRLF2 aberrations is presently unknown. Neither is it known which genes on the trisomic chromosome 21 are involved.

Individuals with Down Syndrome (DS) have a markedly increased risk for the development of childhood leukemia and a decreased risk for solid tumors (Hasle et al., 2000). Interestingly somatic extra copies of chromosome 21 are commonly found in leukemias (Hertzberg et al., 2007). These observations suggest that both constitutional trisomy 21 (cT21) and somatic trisomy 21 may contribute to leukemia development.

Two types of leukemias are associated with DS. The myeloid leukemias are unique and have received a special WHO classification as "Myeloid Leukemias of Down Syndrome" (ML-DS) (Hasle et al., 2003; Roberts and Izraeli, 2014; Malinge et al., 2009). These are megakaryocytic-erythroid leukemias that are diagnosed before the age of 5 years and are highly curable with chemotherapy. They are often preceded by a congenital transient pre-leukemic phase called "transient myeloproliferative disorder" or "transient abnormal myelopoiesis". Genetically both the transient and the full blown leukemias carries somatic mutation in the transcription factor GATA1, located on chromosome X, that results in expression of a short isoform GATA1s. ML-DS is the only hematological malignancy in which these mutations are detected. The combination of cT21 and the acquired mutation in GATA1 is both necessary and sufficient for the occurrence of the pre-leukemic syndrome. The progression to leukemia is associated with additional mutations mainly in epigenetic regulators (e.g. cohesins) and signaling molecules (e.g. JAK enzymes or RAS) (Yoshida et al., 2013).

In contrast the acute lymphoblastic leukemias of Down Syndrome (DS-ALL) are not a single disease that is unique to DS (Hertzberg et al., 2010). These are B cell precursor leukemias with immunophenotype and clinical presentation that are very similar to the common ALL of children without DS (Buitenkamp et al., 2014). There is no clinical pre-leukemic syndrome, indeed infant ALL is very rare in DS. Unlike ML-DS, DS-ALLs are generally resistant to therapy and are associated with poor prognosis (Buitenkamp et al., 2014; Izraeli et al., 2014). Genetically they are heterogeneous and, unlike GATA1s, all somatic acquired genetic abnormalities in DS-ALL can also be detected in leukemias in individuals without DS (Hertzberg et al., 2010; Izraeli, 2014). This perspective reviews our current knowledge an open questions on the molecular pathogenesis of DS-ALL.

1. Genetic abnormalities associated with DS-ALL

The common genetic subgroups that characterize ALL in children without DS (NDS-ALL) are much less common in DS

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(Buitenkamp et al., 2014; Forestier et al., 2008). The prevalence of ETV6-RUNX1 and high hyperdiploid subgroups is reduced from about 25% each to about 10% in DS-ALL. Yet given the 20 fold increased risk for ALL in DS, it is likely that DS predisposes also for these common genetic subtypes of childhood ALL. Yet in about 75% of DS-ALL the karyotype is normal with the exception of the common presence of an additional X chromosome (Buitenkamp et al., 2014; Forestier et al., 2008).

The breakthrough in deciphering the pathogenesis of DS-ALL occurred with the discovery of JAK2 mutations in about 20% of DS-ALL (Bercovich et al., 2008; Kearney et al., 2009; Malinge et al., 2007). These are activating mutations that most commonly involve the R683 residue in the pseudokinase inhibitory domain of JAK2. Interestingly these mutations are never found in myeloproliferative neoplasms (MPN). Conversely the V617F JAK2 mutation typical of MPN is never detected in ALL. The reason for this tight genotype–phenotype association is still unknown.

The JAK enzymes transfer signals from cytokine receptors. Four research groups discovered in 2009 that the receptor associated with JAK mutations in BCP-ALL is CRLF2 (Hertzberg et al., 2010; Mullighan et al., 2009; Russell et al., 2009; Yoda et al., 2010). CRLF2 heterodimerizes with IL7Ralpha (IL7R) to form the receptor to Thymic Stromal Lymphopoietin (TSLP), a cytokine involved in allergic disorders (reviewed in Tal et al. (2014)). CRLF2 expression in human B cell progenitors is low and its normal role in B cell development is unclear (Payne and Crooks, 2007). CRLF2 is located on the pseudoautosomal domain of the sex chromosomes. Its over expression in DS-ALL is caused by genomic aberrations that either translocate CRLF2 into the IgH chain locus or by a small interstitial deletion upstream CRLF2 that juxtapose it with the constitutively expressed promoter of the P2RY8 gene (Mullighan et al., 2009; Russell et al., 2009).

The high expression of CRLF2 −IL7R dimer, forming the receptor to TSLP, presumably enables expansion of preleukemic cells in response to TSLP in the bone marrow microenvironment. In most of the CRLF2 positive leukemias additional somatic mutations activate the pathway rendering it independent of TSLP. These progression events include somatic mutations in JAK2, or less commonly in JAK1, JAK3 or even loss of function in the SH2B3 gene the encode the JAK inhibitor LNK (Roberts et al., 2014; Loh et al., 2013; Harrison, 2013; Tasian et al., 2012). Recently it has been reported that activating mutations in RAS also occur in CRLF2 positive ALLs in a mutual exclusive manner with JAK mutations (Nikolaev et al., 2014). Thus in about two thirds of CRLF2 expressing ALL there are additional activating mutations in downstream signaling pathways activating JAK-STAT pro-survival signaling.

We and others have discovered a new type of activating mutations in the CRLF2 or the IL7R receptors (Hertzberg et al., 2010; Yoda et al., 2010; Shochat et al., 2014, 2011). Most commonly these mutations introduce cysteine in the extra-cellular domain causing ligand independent dimerization and activation of the receptors. Rarely non-cysteine mutations occur in the transmembrane domain of IL7R. They also cause constitutive dimerization and activation of the receptor in a yet unclear mechanism. The mutations in the receptors are mutually exclusive with mutations in the signaling proteins suggesting that the outcome of all these mutations is the same: constitutive cell-autonomous activation of pro-survival and growth cytokine signaling pathway.

While mutational activation of TSLP or IL7 signaling occurs in about 60% of DS-ALL it is found also in 5–20% of NDS children and adult ALLs respectively (Izraeli, 2014; Roberts et al., 2014). These leukemias are associated with worth prognosis. The development of JAK1/JAK2 inhibitors promises a potential for therapeutic targeting of these leukemias.

2. The role of trisomy 21

At present it is unclear why cT21 predisposes to ALL and specifically to CRLF2 positive ALLs. It is important to remember that cT21 is expressed both in the B cell precursor lymphocytes from which the leukemia evolves and in the microenvironment. This contrasts with sporadic leukemias in which the additional copies of chromosome 21 exist only in the leukemic cells. Interestingly CRLF2 aberrations are more common in a subtype of ALL characterized by intra-chromosomal amplification of a segment of chromosome 21, iAMP21 (Russell et al., 2009; Moorman et al., 2012; Rand et al., 2011). This type of leukemia is discussed in more details by C. Harrison in this edition of EJMG. However CRLF2 aberrations are not detected in high hyperdiploid ALL, a common type of ALL with extra copies of chromosome 21. Hence it is unclear if excess genetic material from chromosome 21 predisposes to the CRLF2 aberration.

Studies of hematopoiesis in human fetal liver of DS have revealed a relative arrest at early B cell development (Roberts and Izraeli, 2014; Roy et al., 2013, 2012). It is possible that the expression of the TSLP receptor caused by the CRLF2 expression is positively selected because it rescues the arrested lymphopoiesis. Conversely it is also possible that compensatory enhancement of postnatal B cell lymphopoiesis predispose for genetic events enhancing their survival.

The study of the pathogenesis of CRLF2 leukemias is limited by lack of a proper cell based or mouse model. The only model has been generated by combining several genetic events. Lane et al. reported the creation of the first animal model of DS-ALL. Disease development required transgenic over expression of CRLF2 and mutated *JAK2* and heterozygous loss of *Pax5* and expression of a dominant negative Ikaros isoform in bone marrow from the mouse model of trisomy 21, the Ts1Rhr mouse (Lane et al., 2014). Loss of B cell differentiation genes such as PAX5 and IKZF1 is common in childhood B cell ALL, including DS-ALL (Buitenkamp et al., 2012; Mullighan, 2012). Further studies by the same investigators suggested a possible role for HMGN1 a chromatin regulator on chromosome 21 (Lane et al., 2014). They showed that in yet unclear mechanism HMGN1 reversed PRC2 mediated suppression of gene expression by reversing the methylation of lysine 27 of histone 3. The relevance of these findings to human DS-ALL is still unclear. While B cell precursors of the Ts1Rhr trisomic mice displayed enhanced self renewal in-vitro and in-vivo human B cell precursors from DS fetal liver grow poorly in-vitro and do not engraft in-vivo (I Roberts personal communications).

Another interesting chromosome 21 gene that has recently emerged as a candidate leukemogenic gene is *DYRK1A* (dual-specificity tyrosine phosphorylation-regulated kinase 1A). DYRK1A together with another chromosome 21 gene, RCAN, suppresses the nuclear factor of activated T cells (NFAT) pathway by phosphorylating NFAT and causing its export from the nucleus to the cytoplasm (reviewed in Birger and Izraeli (2012)). The NFAT pathway has been previously shown to be suppressed in DS which possibly explain some of the neurological defects and perhaps also the repressed angiogenesis and hence decreased risk for solid tumors. Moreover since NFAT pathway is important for T cell development its suppression by DYRK1A and RCAN may explain the lack of T-ALLs and some T cell mediated immune defects in DS. Malinge et al. recently identified DYRK1A as an important regulator of the myeloid leukemia of DS (Malinge et al., 2012). Recently a conditional knockout of DYRK1a, performed by the Crispino group, demonstrated as essential role of DYRK1A in B cell lymphoid development (Thompson et al., 2015). While the role of increased expression of DYRK1A in DS-ALL is unclear, its requirement for B cell development may place it as an interesting candidate for therapy for B-ALL including DS. Furthermore, since DYRK1A may be

also an appropriate target for treatment of the myeloid leukemias and possibly additional defects of DS.

3. Challenges and future perspectives

It is currently unclear why cT21 predisposes to ALL and what is the basis of the close association between cT21 and CRLF2-IL7R-JAK-STAT driven leukemia. Neither is it clear if the leukemogenic role of cT21 share similarities with sporadic ALL with polysomy 21. One of the major obstacle is the lack of appropriate models – mouse or human based – to study that disease. Modern technologies of gene targeting in primary cells and of in-vitro lymphoid differentiation from induced pluripotent cells may be pivotal in solving the mystery of the predisposition of children with DS to ALL.

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