Avances recientes en genética y farmacogenética en leucemia linfoblástica aguda

Recent advances in genetics and pharmacogenetics in acute lymphoblastic leukemia

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Analyses of DNA copy number alterations and gene expression profiling by microarray, and especially next generation sequencing, have revolutionized our understanding of the pathobiology of acute lymphoblastic leukemia (ALL). These studies have not only identified new genetic subtypes, but have characterized each subtype by the constellations of structural and sequence alterations involving key cellular pathways, including lymphoid development, tumor suppression, Ras signaling and kinases, cytokine receptors, transcriptional regulators and chromatin modifications by epigenetic modifiers[1]. All cases of ALL can now be classified according to their specific driver genetic mutations, increasing number of which are now amendable to targeted therapeutics[2]. For example, among the Philadelphia chromosome-like ALL which account for 10% of childhood and up to 30% of young adult B-ALL cases, approximately 10% of the patients have ABL-class fusions that respond to ABL1 tyrosine kinase inhibitors, and approximately 30% of patients have mutations activating the JAK-STAT pathway that may be responsive to treatment with JAK inhibitors[3]. Of interest, a recent study using next-generation sequencing and copy number of alteration analyses to interrogate genomic landscapes of 92 adult and 111 pediatric patients with B-ALL identified not only 29 new in-frame gene fusions, including those involv-

ing *MEF2D* and *ZNF384* with clinical relevance, but also suggested that differences in target cells of transformation between adult and pediatric patients partly account for the age disparity in response to treatment[4]. *MEF2D* gene fusions were found in approximately 3% to 4% of pediatric ALL cases, and were associated with older age at diagnosis (median 12 years), upregulation of B-cell receptor signaling molecules but downregulation of *JAK-STAT* pathway, and poor survival[4-6]. *ZNF384* fusions occurred in 4% of pediatric ALL, and were associated with increased expression of myeloid-associated antigen, high expression of *GATA3* and *CEBPA*, upregulation of *JAK-STAT* pathway, and intermediate outcome[4]. Pharmacokinetic and pharmacodynamic variabilities, some environmental (e.g., hydration status, drug interactions) and others genetic (pharmacogenetics), can influence treatment outcome. The classic example is the relation between the hematopoietic toxicity of thiopurines and inherited polymorphisms in gene encoding thiopurine methyltransferase (TPMT) in Caucasians. However, TPMT deficiency is relatively rare in individuals of East Asian descent. Recently, a genome-wide association study performed by our group found that germline variants in nucleoside diphosphate–linked moiety X-type motif 15 (NUDT15) also strongly predisposed patients to mercaptopurine-related toxicity during ALL therapy, completely independent of TPMT variants[7]. Patients homozygous for the defective allele in *NUDT15* tolerated only 6 mg/m^2/day of mercaptopurine, compared to an average of 67.5 mg/m^2/day for patients with wildtype *NUDT15*. Interestingly, the *NUDT15* risk allele was markedly common in East Asians and thus responsible for their excessive mercaptopurine toxicity[7]. *NUDT15* inherited polymorphisms can also be found in Hispanics with Native American ancestry[8].

Genetic ancestry is associated with many other acute and/or long-term side effects. For example, glucocorticoid-related osteonecrosis is significantly more common in those of European descent than patients of African ancestry and was associated with inherited variations near glutamate receptor genes[9]; asparaginase-related pancreatitis on the other hand was associated with Native American genetic ancestry and more frequent in Hispanics[10]; and vincristine-related peripheral neuropathy was significantly less common in patients of African descent (plausibly due to lower frequency of the toxicity-related risk allele in the *CEP72* gene)[11].

Increasing number of inherited polymorphisms and mutations have been identified to be associated not only with the drug response, resistance and toxicity, but also with the risk of leukemic transformation. For example, germline *TP53* alterations was associated with the development of childhood low-hypodiploid ALL[12]; and germline *ETV6* mutations conferred susceptibility to childhood ALL and familial thrombocytopenia[13]. In fact, up to 5% of children with ALL have inherited cancer susceptibility genes that provide insights into cancer etiology and information to guide the testing, monitoring, and management of not only the patients but also their family members[14].

Recent advances in personalized therapy incorporating the leukemic cell genetics, pharmacogenetics, and optimal therapeutic agents and approaches promise to further improve the cure rate and quality of life of the patients. The major challenges for the coming decades are to develop more tolerable treatment, to devise preventive measures, and to translate gains achieved in higher-income countries to all children worldwide.

Declaración de conflictos de interés:
El autor declara que no posee conflictos de itnerés.

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