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Editorial

Generation of Dyskeratosis Congenital-like Hematopoietic Stem Cells: Editorial

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Dyskeratosis Congenita (DC) is rare telomere biology disorder, which results in different clinical manifestations, including severe bone marrow failure. To date, the only curative treatment for the bone marrow failure in DC patients allogeneic hematopoietic stem cell transplantation. However, due to toxicity associated to this treatment, improved therapies are recommended for DC patients. The generation of DC-like HSPCs constitutes new platform for studying the molecular basis of BMF in DC and also for screening efficacy and safety of hematopoietic therapies for DC patients, including gene therapy and drugs capable of protecting or restoring function of DC HSPCs.

Clinically, DC patients are characterized by the mucocutaneous triad (nail dystrophy, oral leukoplakia, and abnormal skin pigmentation). Nevertheless, Bone Marrow Failure (BMF) is the main cause of early mortality of these patients (80% of the cases) as also occurs in other congenic BMF syndromes. According to inheritance of the disease, three DC variants have been reported: X-linked recessive, autosomal dominant and autosomal recessive. X-linked variant of DC (X-DC) is mainly caused by point mutations in DKC1, which encodes for dyskerin nucleolar protein. Interestingly, the knock-out of Dkc1 has been reported to be embryonic lethal in mice. This observation and fact that only hypomorphic DKC1 mutations have been reported in X-DC patients reveals the critical relevance of DKC1 in the cell biology.

Aimed at generating DC-like human hematopoietic stem cells in which efficacy of innovative therapies could be investigated. Because X-linked DC is the most frequent form of disease and is associated with an impaired expression of DKC1. Moreover, DKC1-interfered human CD34+ cells showed defective clonogenic ability and were incapable of repopulating the hematopoiesis of immunodeficient NSG mice. Development of DC-like hematopoietic stem cells will facilitate the understanding of molecular and cellular basis of this inherited bone marrow failure syndrome and will serve as platform to evaluate the efficacy of new hematopoietic therapies for DC.

Curative treatment for BMF in DC patients is allogeneic hematopoietic stem cell transplantation (alloHSCT) from healthy donors. Apart from the low availability of HLA-matched donors, the outcome of DC patients undergoing alloHSCT is very poor, mainly due to toxicity of conditioning regimens and development of graft versus host disease. New therapies such as gene therapy without cytotoxic conditioning, as recently reported in Fanconi Anemia (FA), would be highly beneficial for DC patients.

Taking into account that periodic BM aspirations are not part of routine follow-up of DC patients, difficulties in the access of HSCs constitute an important limitation in development of new therapies for DC patients. Furthermore, animal models of telomeropathies developed to date do not mimic characteristic BMF of DC patients. Considering that DKC1 is one most frequently mutated genes in DC, purpose of this study was generation of DC-like human HSCs based on interference of DKC1 in human HSCs which would serve as a platform for development of new hematopoietic therapies for DC patients.

To determine whether knockdown of DKC1 affects functionality of human HSPCs, DKC1-interfered CD34+ cells were in vitro cultured for 10 days to evaluate implications in cell growth. In these studies, portion of CD34+ cells at the end of the culture period was similar among different experimental groups.

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