EDITORIAL

Can determination of gene polymorphism be of practical value in tailoring the treatment of HSCT patients?

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Matching the donor and recipient in HLA alleles lowers the risk of HSCT to the level of sibling transplantation. Nonetheless, some patients develop GVHD and suffer from prolonged immune system reconstitution, which causes fatalities. The discovery of the effect of gene polymorphism on the gene-transcribing potential or structure of encoded proteins led to the hypothesis that, in addition to the presence of disparities in HLA specificities, the genetically controlled magnitude and pace of the immune response do play a role.

In spite of more than 15 years of research in the field of gene polymorphism, there is no recommendation for the clinical implementation of the studies. This may be due to the fact that not only one gene's characteristics but those of a number of genes working along the same signaling pathway should be considered, which makes the single-gene polymorphism analysis approach unfeasible. Alternatively it can be assumed that the effect of gene polymorphism-associated features may be seen only in patients with some well-defined clinical situations. Indeed, 13 CA micro-satellite polymorphism at position +875 within the first intron of the *IFN γ* gene of the patients influences the risk of CMV reactivation, but this effect is only clinically relevant if the polymorphic feature, representing a low level of IFN γ production,¹ goes together with low CD4+ lymphocyte count.² On studying the *NOD2/CARD15* gene polymorphism we learned that the presence of SNP 13 (3020insC, Leu1007 fsins C) mutation in patients as well as donors constitutes a risk factor of septic complications in HSCT patients exposed to deadly bacteria.³ *NOD2/CARD15*, if triggered by muramyl dipeptide, activates two pathways: one going to mitochondrial antiviral-signaling protein/Interferon regulatory factors (MAVS/IFR) and the other to nuclear factor κ B and activating protein-1; the latter ones are the transcription factors of several molecules involved in the immune response including IFN γ .⁴ The natural immune (IFN β) response makes the first line of resistance and IFN γ generation alert adaptive immunity. Signal transduction within the cells aimed at activation of different DNA-binding molecules (transcription factors, STATs) uses different pathways employing kinases belonging to several families. Clinical observation of SNPs in the *NOD2/CARD15* gene suggests that single-nucleotide polymorphism (SNP) 13 impairs the natural immunity mechanism, but not the one leading to cytokine production.⁵ This observation helps in understanding the mechanism of frequently fatal septic complications seen in patients with SNP 13. The results of the above-mentioned observations show that the effect of the above-quoted gene polymorphisms may be clinically seen only in situations associated with a higher risk of infections.

Probably the best example of the biological significance of gene diversity in man, depending on the situation they face, is provided by the paper published in this issue entitled 'Caspase-8 polymorphisms result in reduced Alemtuzumab-induced T-cell apoptosis and worse survival after transplantation'.⁶

Apoptosis inevitably regulates the life span of cells. The apoptotic signal is processed within the cells, leading to the sequential activation of caspases executing cell apoptosis.

Caspase 8 has a central position in the apoptotic pathway and six-nucleotide deletion within the promoter region of this gene affects gene transcription, consequently influencing the homeostasis of cells, including lymphocytes and macrophages. Deletion polymorphism of this gene has clinical relevance in the lower susceptibility to some cancers.⁷ The beauty of the above-mentioned paper lies in the fact that it finds the significance of this deletion mutation in the susceptibility to immunosuppression exerted by Alemtuzumab. The mechanism of this immunosuppression depends at least in part on the induction of apoptosis. Quite understandably, donors with six-nucleotide deletion within the *Caspase 8* promoter (rs3834129, -652del AGTAAG) provide the recipients with T lymphocytes resistant to activation-induced cell death. Therefore, Alemtuzumab has a restricted effectivity, which translates into poorer transplantation outcomes in patients who receive transplants from donors with *Caspase 8* deletion mutation. The authors have documented the mechanism involved in resistance to apoptosis of lymphocytes that have the *Caspase 8* mutation, showing it in *in vitro* experiments.

The other important insight offered by the study is that deletion polymorphism of the *Caspase 8* gene can have an opposite effect on the fate of patients, depending on the clinical situation they face. It is known that the presence of deletion mutation making T cells more resistant to activation-induced cell death is associated with reduced susceptibility to some cancers,⁷ which benefits mutation-harboring individuals. On the contrary, as shown in the paper by Shaw *et al.*,⁶ the presence of the mutation in patients in need of Alemtuzumab-induced immunosuppression adversely affects the treatment outcome.

This paper points to the importance of determining the polymorphism of genes encoding proteins relevant for the disease pathomechanism and treatment. If the polymorphism affects the function of encoded proteins, the determination of the allelic diversity of individuals may help in tailoring the treatment to the needs of individual patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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