ZKBS
The Central Committee on Biological Safety

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Position statement of the ZKBS on the classification of genetic engineering operations, in which genes for immunomodulating proteins are inserted into the genome of replication-competent microorganisms

Introduction

A large number of immunomodulatory proteins are currently known (> 60 cytokines and about 50 chemokines). Due to their pleiotropic and redundant mode of action and strong contextual dependence of their properties [1], some of these modulators can have antagonistic effects in immune responses, i. e. they can stimulate or suppress the immune reaction to a certain pathogen.

One example is interleukin-4 (IL-4). Overexpression of IL-4 alters the immune response by shifting the cellular immune response towards the humoral immune response. Thus, administration of tumour cells expressing *il-4* can induce a systemic T-cell-dependent immune response against the tumour cells [2]. However, in a study by Jackson et al. it was found that IL-4 can decisively suppress the cellular immune response against Ectromelia virus (ECTV) [3]. After infection of mice with a recombinant, replication-competent ECTV, into whose genome the murine *il-4* gene had been inserted, an existing immunity was undermined [3]. Mice infected with this recombinant ECTV died, whereas mice infected with a corresponding control virus survived the infection. The insertion of the murine *il-4* gene thus significantly increased the hazard potential of ECTV.

The expression of chemokines by a replication-competent microorganism can also lead to an increase in the hazard potential. Infection of mice with an attenuated *Rabies lyssavirus* strain, into whose genome the gene for the chemokine IP-10 (CXCL10) had been integrated, led to severe weight loss, neurological deficits and the death of three out of ten of the test animals, while infection with the initial strain led to only minor weight loss and transient symptoms such as ruffled fur in one out of ten test animals [4].

Recommendation

For genetic engineering operations, in which immunomodulating proteins are expressed by replication-competent microorganisms, a statement about the mode of action of these proteins cannot be made based on general criteria, but only for individual cases. These works are thus basically not considered to be comparable in terms of the Genetic Engineering Act (GenTG). This also includes corresponding works with chemokines.

Thus, a case-by-case assessment by the ZKBS of genetic engineering operations, in which genes for immunomodulating proteins are inserted into the genome of replication-competent microorganisms, is generally required.

However, a case-by-case assessment by the ZKBS is dispensable in the following cases:

1. Recipient organisms are used that do not pose a risk to humans and animals and cannot permanently colonize or infect humans and animals.

2. Combinations of recipient organisms and immunomodulating genes that have already been assessed by the ZKBS are used (e. g. transfer of the gene for the human protein TRAIL to *Human mastadenovirus C*).

The current data do not allow to provide a final list of genes for immunomodulatory proteins that do not require a case-by-case assessment.

References

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