Abstract of PhD. Thesis

Gene Modified Cellular Vaccines against *bcr-abl*-Transformed Cells

In our laboratory we are focused on the development of therapeutic vaccines against chronic myeloid leukaemia (CML), using as a model system mouse *bcr-abl*-transformed B210 and 12B1 cells. Both these cells are of early B-cell lineage, express BCR-ABL protein and induce leukaemia after i.v. inoculation; the 12B1 cells also induce solid lymphoma-like tumours after s.c. inoculation. Several types of experimental vaccines directed against these *bcr-abl*-transformed cells were developed in our laboratory. Since it has been recognized that BCR-ABL protein does not carry the immunodominant epitope, our attention switched to the development of cell-based vaccines that are capable of inducing immune responses against a whole complex of tumour-associated antigens.

The present work describes studies on experimental cellular vaccines based on the B210 or 12B1 cells, gene-modified to express either IL-2 or GM-CSF or IL-12. For the transfection of these cells, an optimised electroporation method was used. The vaccines were tested in our mouse BALB/c model. All the cell lines derived from B210 cells secreting IL-2, GM-CSF or IL-12 were non-oncogenic. The oncogenicity of the IL-2 producing 12B1 sublines was reduced and most of the animals, which did not develop tumours after administration of these cells, were found resistant to the challenge with the parental cells. On the other hand GM-CSF secreting 12B1 cells maintained their oncogenic potential. In addition to leukaemia and solid tumours, they also induced extensive pathological changes in several organs and accumulation of MDSC in spleens. When testing the effects of cell clones markedly differing in the production of GM-CSF, it became apparent that the pathogenicity was directly related to the extent of the cytokine production. For immunogenicity assays, B210 gene-modified cells were used as live vaccines, while the cell lines derived from 12B1 cells were inactivated by γ-radiation. The immunized animals were challenged s.c. with 12B1 cells. All the cytokine secreting vaccines have higher immunogenic potential than the parental cells. In the immunization/challenge experiments the most efficient vaccines were those secreting GM-CSF. As concerns immunotherapeutic potential, the most favourable results were achieved with the B210 cells secreting IL-2, especially when their administration was combined with chemotherapy.