Abstract

We have used a well characterized transplantable transgenic mouse model which mimics human acute promyelocytic leukemia (APL), both in its biological characteristics and its response to conventional therapeutic drugs. The aim of our study was to better characterize the efficacy of the combined treatment and to determine molecular markers of clinical outcome.

We established a minimal residual disease monitoring based on the high sensitivity of detection of PML-RARα transcripts by polymerase chain reaction (PCR) technology in APL mice. We showed that oncogene-specific PCR-based assays allow, like in patients, the diagnosis, follow-up and prediction of disease evolution. Furthermore, PCR assay was used to assess various tissues and organs for the presence of PML-RARα-positive cells in minimal residual disease free long-term survivors. As expected, majority of mice had no measurable tissue level of PML-RARα demonstrating the efficacy of immunotherapy. However, tracking the oncogene-positive cells reveals for the first time that extramedullary PML-RARα-positive cell reservoirs such as the brain may persist and be involved in the leukemia relapse.

We aimed at investigating the immune responses involved in the anti-leukemic effect of the combined immutherapy. To evaluate the humoral response, we determined the prevalence of anti-RARα antibodies in APL mice as well as in APL patients using specific ELISA. We reported the presence of higher levels of antibodies reacting with PML-RARα and RARα in the sera of treated mice. These antibodies were predictive of better survival. In the APL patient, the data reveal for the first time that antibody response may be detected at diagnosis and enhanced after maintenance therapy. Using complementary cellular methods, we show that APL-specific T cells remain active in vaccinated animals long after the last boost of DNA. The present model was chosen as proof of principle, to investigate the feasibility of inducing immunity against a tumor-specific human fusion protein using DNA delivery. Evidence of induction of humoral and cellular immune response has been obtained. Combining ATRA with DNA resulted in increased APL-specific immune responses, with MHC-restricted CD8+ T cell responses and increased IFN-γ production, which rescue the disease. Together with the finding of a major role of CD4+ T cells in maintaining the durable remissions, our data suggest that in human trials, the combination of ATRA+DNA vaccine should control minimal residual disease.