Institute of DNA Medicine
Department of Oncology

Yoshikatsu Eto, *Professor and Director*
Sadamu Homma, *Associate Professor*
Tetsuro Kikuchi, *Associate Professor*
Mikio Zeniya, *Professor*
Junko Horiguchi-Yamada, *Associate Professor*

General Summary

Our research focuses on tumor immunology and leukemia cell biology. Basic investigations clarified the synergistic effects of a combination of chemotherapy and immunotherapy in cancer treatment. In clinical research, therapy with fusion cells (FCs)—monocyte-derived dendritic cells mechanically fused with patient's tumor cells—continues, on the basis of the results of previous studies, for patients with brain tumors. The dendritic/fusion cell system also provides a mouse model to study the pathophysiology of autoimmune hepatitis.

Research Activities

New functional aspects of anticancer chemotherapeutic agents as activators of host antitumor immunity

Because the action of anticancer chemotherapeutic agents is based on their cytotoxic effects, it is inevitably accompanied by suppression of host antitumor immune activity. In contrast, some anticancer drugs elicit immune-activating effects represented by suppression of the activity of regulatory T cells. Our recent studies have demonstrated that the expression of major histocompatibility complex molecules, co-stimulatory molecules, death receptor molecules, and tumor-associated antigens on tumor cells is significantly up-regulated by treatment with some anticancer chemotherapeutic agents. Importantly, such immune-modulating effects are induced by low doses of these agents, which generate no cytocidal effects on tumor cells or immune suppression. These results would rationalize the possible synergistic effects of combined chemotherapy and immunotherapy for cancer treatment. A phase I clinical study of combination therapy with the WT1 peptide vaccine and gemcitabine for advanced pancreatic cancer is now being performed on the basis of synergism between immunotherapy and chemotherapy.

Clinical immunotherapy for brain tumors

Previous studies have revealed that subcutaneous injection of FCs is safe and elicits no adverse effects in patients. However, because a strong immunomodulator, interleukin 12, has become unavailable for clinical use, we are now combining FC therapy with chemotherapy to enhance the efficacy of the two strategies.

Adhesion-induced differentiation toward megakaryocytes in human leukemia cells

Human leukemia JAS-R cells have megakaryoerythroid features. Some of the cells

adhere to extracellular matrices and undergo dynamic morphological changes. Gene expression patterns compared between adherent and nonadherent cells confirmed these changes to be more megakaryocytic. Furthermore, most alterations of gene expression were also induced by fibronectin-derived Arg-Gly-Asp-Ser (RGDS) peptide, indicating that the integrin signal is relevant to these changes. These studies will disclose the mechanisms of the shift of megakaryoerythroid progenitors to megakaryocytes.

Role of regulatory T cells in the pathogenesis of autoimmune liver disease

We have previously reported that immunization of mice with dendritic cells loaded with well-differentiated hepatocellular carcinoma (HCC) cells followed by administration of recombinant interleukin 12 generated liver-specific inflammatory responses, inducing autoreactive cytotoxic T cells to normal hepatocytes by possible immune cross-talk between hepatocytes and HCC cells. This animal model is useful for analyzing the pathogenesis and pathophysiology of autoimmune liver diseases, such as autoimmune hepatitis. The role of regulatory T cells (Tregs) on the development of autoimmune liver disease was examined using this animal model. Abundant Tregs were observed to have accumulated in the liver at the peak of liver inflammation, whereas the number of Tregs in the spleen significantly decreased, suggesting that Tregs are recruited into liver inflammatory sites from the spleen. The expression of transforming growth factor-beta, a key cytokine for the induction of Tregs, and several Treg-associated chemokines in the liver were found to be enhanced by generation of liver-specific inflammation. These results suggest that Tregs have a homeostatic suppressive effect on autoimmune liver inflammation and that a functional defect of Tregs in patients with autoimmune hepatitis accelerate disease progression.

Publications

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