Current Topics

Target Therapy for Cancer: Anti-cancer Drugs Targeting Growth-Factor Signaling Molecules

Foreword

Fumiaki Ito

Department of Biochemistry, Faculty of Pharmaceutical Sciences, Setsunan University; Osaka 573-0101, Japan.

In contrast to the conventional anti-cancer drugs that act on all dividing cells, thus generating toxic effects and damaging normal tissues, most of the new anti-cancer drugs currently in the developmental stage are based on targeted therapies by means of compounds that inhibit specific target molecules in cancer cells. Molecules controlling cell proliferation and survival, such as tyrosine kinase receptors for growth factors, are among the best targets for this type of therapeutic approach.

Growth factors are a diverse group of regulatory agents that act to control cell proliferation and viability. The majority of growth factors exert their effects through binding to cell-surface receptors having intrinsic tyrosine kinase activity. The binding of these growth factors stimulates receptor activation such as indicated by increased tyrosine kinase activity and induces transmembrane signals from the cell surface to the nucleus. In a variety of cancers, modification of growth-factor production, receptor expression, and alterations in the intracellular proliferation signals have been observed. Loss of regulation of these signals can contribute to uncontrolled growth of cells and play a critical role in directing normal cells to become cancerous. The treatment options for cancer patients have been disappointing, since standard cytotoxic chemotherapy has severe side-effects and is not effective against some types of cancer. However, our understanding of the abnormality of growth factor signals that distinguish malignant cells from their normal counterparts has presented us many molecules for targeting by cancer therapy and has dramatically changed the armamentarium for cancer treatment.

Among current topics of interest, the first two reviews, by Takeuchi *et al.* and Kohno *et al.* provide background for un-

derstanding the signal transduction pathways of growth factors in normal and cancer cells and describe ways in which targeted inhibition of receptor tyrosine kinases (RTKs) of growth factors and the extracellular signal-regulated kinase pathway have been exploited to inhibit cancer growth *in vitro* and *in vivo*. In the third review, Takahashi describes blockade of vascular endothelial growth factor signaling, which plays key roles in both physiological and pathological angiogenesis. This blockade is a promising therapy for cancer patients, because evidence for the importance of the induction and sustenance of angiogenesis by cancer cells is compelling. The aim of the last review, by Nishio *et al.*, is to introduce the clinical applications of microarray analysis for the development of molecularly-targeted treatments in oncology.

As evidenced by the successful use of trastuzumab, a monoclonal antibody against HER2, for the treatment of metastatic breast cancer, and imatinib, a small tyrosine kinase inhibitor targeting BCR-Abl, for that of chronic myeloid leukemia, many targeted anti-cancer drugs are now being used clinically. However, several problems limit the use of anti-cancer drugs targeting growth factor-mediated signaling in tumor therapy. There is a need for new active compounds, since most patients who respond positively eventually suffer relapse as a result of acquired resistance. In the past, the main effort was focused on developing specific compounds targeting single RTKs, but recently, there is a general agreement that compounds targeting multiple RTKs might be more effective. Thus, the rationale for molecularly-targeted therapy is radically shifting. We hope that these four reviews will challenge researchers to devise new strategies toward the curing of cancer patients having various signaling-pathway abnormalities.