

Preface: Practical Molecular Targets for Suppression of Cancer

Screening of anti-cancer agents from natural products began in the 1950s, when cultures of cancer cells became laboratory tools for research. Since then, investigators have searched for cytotoxic drugs directed against cultured cancer cells. Some successes include the approved drugs adriamycin, bleomycin, and vinblastine. In addition to natural compounds, mustard gas, which is lethal, has been used as an anti-cancer agent. Platinum, which is used for electrodes among other things, was also found to be cytotoxic against cancer cells, which led to the discovery of cisplatin. Most of the cytotoxic drugs listed here are still being used as anti-cancer therapeutics in human patients. However, it is clear that their use is not tumor-specific and is limited by the serious toxic side effects they exert on normal tissues.

“Molecular Targeted Therapy” against cancer has recently become available. This therapy is directed against specific targets in cancer cells or environmental cells that are selected on the basis of their activity in cancer progression. Significant advances in the molecular, genetic, and biochemical mechanisms regulating cancer progression have been made during the last 20 years. For instance, many cancer suppressor genes and oncogenes have been discovered, and many of these have been shown to be involved in the pathogenesis of various human cancers.

More recently, the concept of cancer stem cells has gained popularity and acknowledgement among cancer researchers. Cancer tissue is now considered to consist of a large number of bulk cancer cells and a small number of cancer stem cells. Following anti-cancer therapy, most bulk cancer cells are removed, while a small number of resistant cancer stem cells grows to form the cancer tissue again. Therefore, the suppression of cancer stem cells is considered essential for future cancer therapies, and the development of new drugs is being directed at specific molecular targets in cancer stem cells.

Furthermore, not only the cancer cell itself but also environmental factors such as inflammatory cells have also gained attention as therapeutic targets. For instance, the inhibitor of Abl kinase on chronic myelogenous leukemia has been a great success as a molecular targeted anti-cancer drug. However, therapeutic target drugs against other leukemia and tumors are limited at the present time.

In this issue, several selected reviews are presented on novel molecular targets and their suppression in various cancers. In “*Growth Factor Signaling Regulates Breast Cancer Stem Cells*,” Dr. Gotoh discusses the concept of cancer stem cells and their resistance to various therapeutic agents, and are responsible, in large part, for tumor relapses and metastasis. Dr. Gotoh has found that heregulin (HRG) alone can induce tumor cell formation from breast cancer stem cells. The HRG-PI3 kinase-Akt-NF- κ B pathway plays a role in their maintenance. In “*Current Molecular Targets of Lymphomas*,” Dr. Horie discusses the typical discrepancy between the classification of and treatment strategies for lymphomas. Exploration of addictive molecules based on the pathological classification might be an efficient way to establish molecular-targeted therapies for lymphomas. In “*Current Molecular Targets for Urological Cancer*,” Dr. Horiguchi discusses the molecular targets, multiple kinase inhibitors (MKIs), mammalian target of rapamycin (mTOR) inhibitors, and conventional COX inhibitors used to treat advanced renal cell carcinoma. In “*Apoptosis as a Practical Target for Identifying Anticancer Agents of Marine Origin*,” Dr. Ohno discusses recent drug discoveries in marine organisms. For example, eribulin mesylate, a synthetic analog of halichondrin B isolated from *H. okadae* Kadota, has been developed as an anticancer drug. Novel cytotoxic substances like halichonines, bisbromoamides, and biselyngbyasides have been isolated from marine organisms as apoptosis-inducing agents.

In “*Molecular Targets for Suppression of Metastasis: Recent Cellular Observations*,” Drs. Simizu and Niwa introduce novel molecular targets for cancer metastasis and suggest that NF- κ B, K(upside⁺) channels, GAG-degrading enzymes, and protein glycosylation may be useful targets for suppression of metastasis. Dr. Kawada and colleagues, in “*Modulation of Tumor–Stromal Cell Interactions: A New Anti-Tumor Strategy Targeting the Tumor Microenvironment*,” introduce new strategies targeting the tumor–stromal cell interactions. They discuss targets and small molecules that can modulate the tumor–stromal cell interactions. As reported in “*Peritoneal NF- κ B as a Possible Molecular Target for Suppression of Various Cancers and Inflammation*,” Dr. Umezawa has investigated the new NF- κ B inhibitor, dehydroxymethyl-epoxyquinomicin (DHMEQ), which directly binds to a specific cysteine residue of the Rel family proteins to inhibit their DNA-binding activity. DHMEQ showed potent anti-inflammatory and anticancer

activities in many animal models. He presents a novel hypothesis, namely, that the inflammatory cells in the peritoneal cavity appear important for the regulation of peripheral inflammation and tumor growth. In “*Roles Each of Snail, Yin Yang 1 and RKIP in the Regulation of Tumor Cells Chemo-immuno-resistance to Apoptosis*,” Dr. Bonavida and colleagues discuss the findings of new targets in cancer cells that are dysregulated compared to their expressions in normal cells. They have identified three interrelated gene products involved in resistance, namely, Snail, YY1 and RKIP that are components of the dysregulated NF- κ B/Snail/YY1/RKIP loop in many cancers. Targeting any of these three gene products can simultaneously inhibit tumor cell resistance and metastasis.

Guest Editor:

Kazuo Umezawa, Ph.D.

Department of Molecular Target Medicine Screening
Aichi Medical University School of Medicine,
Aichi, Japan