Thalidomide, Cyclooxygenase-2, and Angiogenesis: Potential for Therapy

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Very few drugs in modern history have had a history similar to that of thalidomide. First introduced in the late 1950s in Germany (1), thalidomide soon became available in a total of 46 countries, including Canada and the United Kingdom but not the United States. Originally, it was marketed as an over-the-counter sedative-hypnotic and antiemetic drug for use in pregnancy. Thalidomide was withdrawn in the early 1960s after reports of teratogenicity and phocomelia associated with its use (1). In response to this tragedy, the United States Congress enacted legislation in 1962 that required drug manufacturers to provide substantiation to the United States Food and Drug Administration of a drug’s safety and efficacy before marketing (2). In addition, for the first time informed consent was required from patients participating in studies of a new drug (2).

Fortunately, research into the effects of thalidomide was not halted. In 1965, Sheskin (3) reported a dramatic therapeutic effect of thalidomide on erythema nodosum leprosum, an inflammatory manifestation of leprosy. This finding prompted evaluation of the drug for use against other diseases. Calabrese and Fleischer (4) reviewed the numerous and diverse inflammatory and autoimmune conditions against which thalidomide has been found to be effective. These include cutaneous lupus erythematosus, conditions associated with HIV infection such as aphthous ulcers, wasting syndrome and diarrhea, and Behçet’s syndrome (4). In 1998, thalidomide was approved by the Food and Drug Administration for the treatment of erythema nodosum leprosum (4), which remains the sole approved indication. Several immunomodulatory and anti-inflammatory properties of thalidomide have been discovered, including inhibition of leukocyte chemotaxis, alternation of tumor necrosis factor-α-induced adhesion molecule density on leukocytes, reduction of phagocytosis by polymorphonuclear cells, enhancement of interleukin-4 and interleukin-5 production, inhibition of IFN-γ and IFN-12 production, and inhibition of tumor necrosis factor-α production by reducing the half-life of mRNA (4).

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2 The abbreviations used are: COX, cyclooxygenase; LPS, lipopolysaccharide.

D’Amato et al. (5) were the first to describe the antiangiogenic effects of thalidomide. In a rabbit model, they demonstrated an inhibitory effect of the drug on basic fibroblast growth factor-induced corneal neovascularization. Recent interest in the antiangiogenic activity of thalidomide has led to studies of the drug in the treatment of numerous hematological and solid malignancies. Singhal et al. (6) reported significant antitumor activity of thalidomide in patients with refractory multiple myeloma. Others demonstrated its activity in Kaposi’s sarcoma (7). Thalidomide is currently being evaluated in the treatment of numerous hematological and solid malignancies. In the United States, more than 20 clinical trials include thalidomide in their regimen, alone or in combination with other antineoplastic drugs. Its use is highly appealing because thalidomide is one of the few putative antiangiogenic agents that is an oral drug, although initial results as a single agent have been somewhat disappointing (8, 9). These studies, however, have looked at patients with end-stage disease making their chance for success less likely.

COX, a key enzyme required for prostaglandin synthesis, is transcribed from two distinct genes (10). COX-1 is expressed constitutively in most tissues, whereas COX-2 is induced by a variety of stimuli. COX-2 expression is markedly increased in 85–90% of human colorectal adenocarcinoma, whereas COX-1 levels remain unchanged (10). Epidemiological studies have reported a significant reduction in the risk of developing colon, breast, and lung cancer in persons who were treated with aspirin which inhibits cyclooxygenase (11). Furthermore, Oshima et al. (12) reported that in mice null for COX-2, the number and size of intestinal polyps are dramatically reduced. In addition, treating these mice with a selective COX-2 inhibitor reduced the number of polyps more significantly than did treatment with sulindac, which inhibits both isoenzymes (12). Steinbach et al. (13) treated patients with familial adenomatous polyposis with celecoxib, a selective COX-2 inhibitor, and found a significant reduction in the number of colorectal polyps. Clinical correlates between COX-2 up-regulation and poor prognosis have been reported in several cancers, such as carcinoma of the head and neck (14) and lung cancer (15). Tsujii et al. (16) suggested that COX-2 modulates production of angiogenic factors by colon cancer cells, thus affecting tumorigenicity. Together, these results suggest that COX-2 may contribute to the development of cancer. Its selective blockade may have an important role in cancer prevention and by extrapolation cancer treatment—most likely through an effect on prostaglandins, thereby preventing angiogenesis and stimulating immune surveillance and apoptosis (17, 18).

The article in this issue by Fujita et al. (19) raises several...
important issues relevant to the treatment of cancer patients in the 21st century. They provide more evidence for the rehabilitation of thalidomide. Their results provide important insight into a novel mechanism, which suggests that one action of thalidomide might be through the COX-2 pathway. This study clearly demonstrated that thalidomide modulates expression of COX-2. The investigators also demonstrated that thalidomide inhibits LPS-mediated induction of COX-2 and prostaglandin E\(_2\) synthesis in a dose-dependent manner. Thalidomide also suppressed LPS-mediated induction of COX-2 mRNA expression. Using nuclear run-off assays, the authors determined that thalidomide did not alter the \(\text{de novo}\) synthesis of COX-2 mRNA induced by LPS. Furthermore, transient transfection studies confirmed that thalidomide did not affect LPS-mediated induction of COX-2 transcription or LPS-mediated stimulation of COX-2. These findings suggested that thalidomide suppresses LPS-mediated induction of COX-2 by a posttranslational mechanism. Indeed, the investigators demonstrated that thalidomide enhanced the rate of COX-2 mRNA degradation. Structural analogues of thalidomide (ImiDs) had similar actions on suppression of COX-2 and prostaglandin E\(_2\) synthesis by LPS. This represents strong supporting evidence for the action of thalidomide on angiogenesis inhibition.

The inhibition of angiogenesis represents an exciting new target for cancer treatment; however, most tumors are biologically heterogeneous and contain multiple subpopulations of cells with different properties (20). Of special interest is endothelial cell diversity. Although most solid tumors are highly vascular, their vessels are structurally and functionally abnormal. They are disorganized, tortuous, and dilated with an uneven diameter and excessive branches and shunts. Consequently, tumor blood flow is chaotic and leads to hypoxic and acidic regions in tumors (21). In addition, tumor vessels differ from normal blood vessels in their cellular composition, permeability, stability, and growth regulation (22) as well as response to antiangiogenic molecules (23). An explanation for this diversity has been suggested to be at the molecular level, where tumor and normal endothelium are distinct (24). Taken together, these observations suggest that strategies for targeting endothelial cells must take into account their molecular diversity and the organ specificity of the vasculature (25). Since the proangiogenic mechanisms are diverse, it will be important to have a wide range of different inhibitors.

The therapeutic implications of this work are enormous, as clinicians now have at their disposal multiple new “targeted” therapies for cancer. Results for initial trials with these agents in many cases have been disappointing, but one must keep in mind that identifying the specific biological characteristics of certain tumors and their endothelium will be essential to enable physicians to tailor a specific therapy suitable to each specific patient. In regard to the findings of Fujita \textit{et al.} (19), we suggest that patients with high COX-2 levels and those with high levels of basic fibroblast growth factor may benefit from a mixture that includes thalidomide and selective COX-2 inhibitors. In fact, with multiple antiangiogenic and anti-signal transduction agents now available, we predict that ultimately therapy will include a mixture of these agents (Fig. 1) designed specifically for a patient based on the precise characteristics of a tumor. Certainly, knowing more specifically the mechanism of action of any given agent makes a rational combination possible. Depending on the precise setting of their use (advanced or minimal disease), they will be introduced with or without chemotherapy. Further study is necessary to prove this hypothesis, but the work presented in this article moves this type of study closer to reality.

Fig. 1 Tumor biology has become part of pathological staging. Accordingly, in addition to conventional chemotherapy, patients will soon routinely be treated with specific small molecules targeted against distinct proteins manifested by the tumor and its blood vessels. Targeting in this way would also prevent new metastases and help eradicate existing ones. RTK, receptor tyrosine kinase.
giving us yet one more weapon in the fight against metastatic cancer.

References
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