HIGHLY ACTIVE ANTICANCER CURCUMIN ANALOGUES

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Abstract: Curcumin, a compound in the human food supply, represents a near-perfect starting point for drug discovery. Consequently, a number of research groups have taken the natural product as a starting point to prepare and biologically evaluate a wide variety of curcumin analogues. One widely used structural modification truncates the central conjugated β-diketone in curcumin to the monocarbonyl dienone. A diverse array of the latter compounds exhibit cytotoxicities against an equally diverse set of cancer-related cell lines. Importantly, these compounds still retain toxicity profiles in rodents comparable to the parent natural product, whereas some analogues (e.g., EF-24, 41) exhibit good oral bioavailability and good pharmacokinetics in mice. Thiol conjugates of EF-24 analogues have been prepared that address stability and solubility issues while demonstrating cellular activities similar to the unmodified dienones. In parallel experiments, the factor VIIa–tissue factor complex (fVIIa-TF) has been exploited to develop a targeting strategy for the analogues. In particular, the EF24-FFRck-fVIIa protein conjugate is not only somewhat more effective relative to the drug alone against breast cancer and melanocyte cells. Both simple curcumin analogues and the protein conjugate evidence antiangiogenic activity in cell culture. The implication is that the fVIIa-TF targeting process, like the dienone drugs, permits a double-pronged attack with the potential to destroy a tumor directly by apoptosis.

1. INTRODUCTION

Many chemotherapeutic approaches to the range of diseases that fall in the cancer category have been explored. Perhaps the oldest of these involves the use of natural products. Because compounds made by plants and microorganisms often serve to attract allies or repel, disable, or kill competitors, it is not surprising that natural products have proved to be a rich source of potential anticancer therapies. However, a delicate balance must be struck between a compound’s cancer-fighting capabilities and its toxicological profile for it to progress from a lead to a clinically useful agent. As a consequence, many promising natural product leads had to be structurally modified (natural product optimization) to produce compounds that exhibit more favorable pharmacologic profiles.

Today, the screening of natural products represents one of many approaches used to discover new drugs. Other methods include, inter alia, computer-assisted
small-molecule drug design, combinatorial synthesis/high-throughput screening and the development of monoclonal antibodies. However, just as with natural products, drug candidates developed using these approaches can exhibit varying types of toxicity that manifest themselves as undesirable side effects. For example, Gleevec, a small-molecule drug used in treating chronic myeloid leukemia (CML), is generally well tolerated with only mild side effects.1 Similarly, the antibody Herceptin exhibits drug-induced complications in only 1–4% of patients.2 By contrast, many natural-product-derived chemotherapeutics are accompanied by significant toxicities. Taxol (paclitaxel, PTX), almost completely water insoluble, is delivered in a vehicle formulation of 50% ethanol and 50% polyethoxylated castor oil (Cremophor EL). The vehicle has been associated with various side effects, including hypersensitivity in 41–44% of all patients,3 whereas PTX shows both neurotoxicity and cardiotoxicity in a subset of patients. Doxorubicin, a potent broad-spectrum inhibitor of human tumors, also exhibits severe adverse side effects. Among other things, the compound has been cited as the cause of irreversible degenerative cardiomyopathy and congestive heart failure.5 Clearly, these serious side effects limit the overall clinical utility of these compounds.

In contrast to natural products that are prone to serious side effects, curcumin (1, Figure 1), the compound that imparts the color and spicy flavor to both turmeric and curry powder, is nontoxic. In the general population, it is consumed daily as a dietary spice at levels up to 100 mg/day. In clinical trials, it has been administered at up to 8 g a day without showing untoward side effects.7 This yellow spice has a long history in Eastern cultures as a treatment for a multitude of ailments, most commonly inflammation. Recently, curcumin has emerged as a key weapon in the fight against cancer. As a pleiotropic anticancer agent, the compound operates by a number of mechanisms as detailed in recent reviews.6,8,10 Curcumin is cytotoxic to a variety of tumor cells, exhibits antimetastatic activity, inhibits the survival factor nuclear factor-κB (NF-κB), blocks angiogenesis, and is a potent antioxidant. Together, these findings imply that curcumin is a rare example of a substance that possesses both chemotherapeutic and chemopreventative properties without debilitating consequences for the patient.

Although the effects of curcumin on cellular pathways continue to be studied, there has been much research devoted to developing and understanding the structure–activity relationships (SARs) responsible for the drug’s anticancer properties. By synthesizing families of analogues and subjecting them to biological

![Figure 1. Curcumin (1) and selected general structural permutations accomplished through analogue synthesis (2). (See also Plate 5 in the Color Plate Section.)](image-url)