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Commentary

Host Modulation Therapy for Dermatologic and other Collagenolytic Diseases

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DESCRIPTION

For decades, after the discovery by Gross et al. [1] of the first (of dozens) of human and animal tissue-generated matrix-metalloproteinases (MMPs), academics and industry have attempted to develop safe medications to dampen the excessive levels and activity of these calcium and zinc-dependent proteolytic enzymes during a variety of diseases [2,3]. The rationale for this drug development strategy was based on:

(1) The knowledge that collagen, the major structural protein of all the connective tissues throughout the body, both calcified (such as bone, dentin and cementum) and non-calcified (such as skin, tendons, ligaments, cornea of the eye, cartilage of the joints), is unusually resistant to a variety of human tissue-derived proteolytic enzymes.

(2) the discovery by Gross, et al. of a tissue-derived proteinase, collagenase, able to degrade the triple-helical collagen molecule under physiologic conditions of pH (7.6) and temperature (37°C).

Soon thereafter, it was recognized that dozens of MMPs are generated by mammalian including human tissues (3 collagenases, 2 gelatinases/type IV collagenases, stromelysins, etc.), and these can degrade all the constituents of connective tissues including collagens, proteoglycans, etc. As a result, numerous experimental medications were developed to inhibit pathologically elevated MMPs including hydroxamic acid peptides and polyphenolics. However, only low-dose NON-antibiotic formulations of a tetracycline, doxycycline, have been approved by the FDA and other governmental agencies as a systemically administered (oral route) medication: These include Periostat® and Oracea®. The former is a 20 mg capsule (in contrast to the 100 mg formulation used as an antibiotic which can induce antibiotic side-effects) administered once/12 h (b.i.d.). This novel formulation produces blood levels of ~0.5 µg/ml which are too low to function as an antibiotic, but does decrease excessive MMPs during chronic periodontitis. The latter, is a 40 mg sustained delivery formulation administered once/day, and produces the same low NON-antibiotic blood level; this is FDA-approved for the treatment of acne/rosacea patients. In this regard, Monk, et al. described a number of collagen-destructive diseases affecting the skin which responded favorably to host modulation therapy [4]. However, the most widely recognized is the reduction of erythema, pustules and papules in patients with rosacea.

Later on, Golub et al. [5], recognizing the site on the tetracycline molecule responsible for its antibiotic activity, ie., the di-methylamino group on carbon-4 of the A ring, then removed this side-chain to generate a series of NON-antibiotic tetracycline compounds as novel MMP-inhibitors. The most potent was CMT-3, a 6-demethyl 6-deoxy 4-de-dimethylamino tetracycline. With support from the NIH and from industry, this compound was found to be relatively safe (however, it did result in increased incidence of sunburn, requiring sunscreen application by human subjects) and effective in some clinical trials involving patients with the cancer, Kaposi's sarcoma-angiogenic lesions were reduced by approximately 40% [6].

More recently, using this drug development strategy to develop MMP-inhibitor drugs, Golub and his colleague, Francis Johnson, Ph.D. (Professor of Chemistry and Pharmacology, Stony Brook University), then developed a 2nd group of medications. These are the chemically-modified curcumins (CMCs), and are based on a natural food spice (turmeric, curcumin). Like the tetracyclines, they bind Ca++ and Zn++ to inhibit MMPs. Through this process, they ultimately generated a more potent triphenolic, triketonic chemically modified curcumin (CMC 2.24), a phenylamino carbonyl curcumin, which was found to be safe and effective *in vitro*, in cell culture and tissue culture, and *in vivo* using various animal species, including mice, rats, rabbits, and most recently, dogs [4]. Currently, in collaboration with Scaduto, CEO Traverse Biosciences, Inc. and CMTx, Inc., these compounds are being investigated and prepared for initial clinical trials to test for safety and efficacy in a variety of collagenolytic diseases including arthritis, pulmonary disease, and cancer, and impaired wound healing in skin during diabetes [3].

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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