Putting the Brakes on Cylindromatosis?
Sunil R. Lakhani, M.D.

A man cannot become a competent surgeon without the full knowledge of human anatomy and physiology, and the physician without physiology and chemistry flounders along in an aimless fashion, never able to gain any accurate conception of disease, practicing a sort of popgun pharmacy, hitting now the malady and again the patient, he himself not knowing which.

— Sir William Osler (1849–1919)

In patients with familial cylindromatosis, or “turban tumors,” numerous benign skin adnexal tumors develop, principally on the head and neck (Fig. 1). This rare disorder is caused by a mutation of the CYLD gene and has a variable penetrance. Thanks to three recent studies and, in particular, to the work of Brummelkamp and colleagues, we now have a more accurate conception of the disease process and thus a hope of developing a mechanism-driven therapy.

In the normal course of cellular homeostasis, proteins are inactivated by the attachment of ubiquitin moieties (a process called ubiquitination). These moieties act as tags by which the protein-transport machinery ferries the proteins to the proteosome for degradation. Antagonizing this process are enzymes that remove ubiquitin from proteins; CYLD is an example of a de-ubiquitinating enzyme.

Since there was already some evidence implicating de-ubiquitinating enzymes in tumor formation, Brummelkamp et al set out to identify those that might modulate the tumor necrosis factor α (TNF-α) pathway — a key pathway of tumor formation. They identified sequences specific to various de-ubiquitinating enzymes and then designed a set of sequence-specific molecules (silencing RNAs) to block their expression. Suppression caused an increase in the level of nuclear factor κB (NF-κB) — a key transcription factor that sits at the end of the TNF-α pathway and inhibits apoptosis. Thus, the authors found that CYLD puts the brakes on NF-κB, indicating that the loss of CYLD may promote tumor formation by increasing the levels of NF-κB and thereby preventing cell death.

How does this discovery translate into potential therapy? A closer look at the TNF-α pathway suggests that CYLD and aspirin have a similar effect on NF-κB levels, although they act on different parts of the pathway. When TNF-α binds its receptor, a
molecule called TNF-receptor–associated factor 2 (TRAF-2) binds to the cytoplasmic end of the receptor, where it is ubiquitinated (Fig. 2). Ubiquitination of TRAF-2 leads to the activation of the inhibitor of κB kinase complex, which in turn leads to the activation of NF-κB, and, thus, to cell survival. CYLD acts like a brake near the beginning of the pathway—it de-ubiquitinates TRAF-2 and thus prevents the activation of the inhibitor of κB kinase complex (and hence of NF-κB). Mutation of the CYLD gene is analogous to faulty brakes on a car, but instead of a pile-up of cars, a pile-up of cells results.

Aspirin and its derivatives represent another brake: they inhibit the release of NF-κB and its translocation to the nucleus, hence preventing cell proliferation. Because this second brake acts on parts of the pathway downstream of that engaged by CYLD, it may compensate for CYLD dysfunction. Thus, topical application of aspirin may be an easy and acceptable treatment; phase 1 trials are already under way. Whether aspirin will cure patients of cylindromatosis remains to be seen—it is perhaps a better candidate as a preventive agent. In any case, it is gratifying that studies such as that by Brummelkamp et al.² lead us toward promising medications and away from “popgun pharmacy.”

From the Breakthrough Breast Cancer Research Centre, Institute of Cancer Research, and the Royal Marsden Hospital—both in London.


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Figure 2. Tweaking the Tumor Necrosis Factor α (TNF-α) Pathway.

The TNF-α pathway is implicated in inflammation and oncogenesis. Binding of TNF-α leads to a series of events, such as the ubiquitination of TNF-receptor–associated factor 2 (TRAF-2), that ultimately increases the expression of nuclear factor-κB (NF-κB). This transcription factor drives the synthesis of proteins that support cell survival, which may in turn lead to tumor formation. Brummelkamp et al.² have recently demonstrated that CYLD, which is mutant in patients with familial cylindromatosis, represses the TNF-α pathway by antagonizing the ubiquitination of TRAF-2. Because aspirin and its derivatives also repress the pathway, they may represent a potentially easy way to prevent cylindromatosis. Ik denotes the inhibitor of κB complex, Ub ubiquitin, and P phosphate.