TGF-β-Induced Cataract-Like Changes in Lens Epithelia

To the Editor:

In their article, Liu et al[1] reported that transforming growth factor β (TGF-β) might be involved in the occurrence of lens changes resembling those found in subcapsular cataracts, and suggested that investigations of this cytokine in the ocular media may provide important insights into cataract etiology. Considering this problem, it is worth mentioning that Štambuk et al[2] have recently observed marked differences in cataract morphology and aqueous humor interleukin 4 (IL-4) levels, when they compared the groups of patients with uncomplicated senile cataracts and those with cataracts complicated by previous anterior uveitis of unknown etiology. In the latter group, the prevalence of subcapsular (mostly posterior) opacities was followed by a significant rise in aqueous IL-4, regardless of the fact that in all subjects the uveitis was in complete clinical remission ranging from 8 months to 7 years before the cataract surgery, i.e., aqueous humor collection.[2] This situation was also followed by abnormally high aqueous IgG and β_2-microglobulin findings, despite the lack of clinical signs of active ocular inflammation.[2-4]

Considering the results of Liu et al[1] and Štambuk et al,[2] it seems that further comparative investigations of TGF-β and IL-4, and their local interactions, in various cataract groups have been justified. Of particular interest is the question whether, in chronic or recurrent ocular inflammation followed by subcapsular cataract formation,[2] the compensatory rise of aqueous TGF (perhaps as a synergistic[5] and eye-protecting response[6]) to heightened aqueous IL-4,[2-4] might contribute to the cataract formation according to the mechanism described by Liu et al.[1] As has recently been established, such TGF-β activity could originate from its local production in distinct localizations of the anterior eye segment.[1,6-8]

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The authors reply:

In this letter, Dr. Štambuk offers speculations stimulated by our report that TGF-β induces cataract-like changes in lens epithelial explants.[1] He draws attention to his own recent studies, which show elevated levels of interleukin-4 (IL-4) in aqueous humor of patients undergoing cataract surgery subsequent to uveitis, compared with patients with uncomplicated senile cataracts.[2] In essence, he seems to be suggesting that the induction of cataract by TGF-β, as we have proposed,[1] may be enhanced (directly or indirectly?) by increases in IL-4 in patients who have suffered uveitis. Because we did not have access to several key publications he cites, it is not appropriate that we comment in detail on his suggestions; however, the following general remarks may be of interest.

For many years, researchers have been reporting that changes in levels or properties of certain biologic molecules are associated with various kinds of cataracts. In humans, such studies are inevitably limited to analysis of cataractous lenses or ocular media collected at the time of surgery. Dr. Štambuk's studies fall into this category. Such studies undoubtedly add to our knowledge about cataract, but great care is needed in interpreting them. The data are collected long after the events that initiated the formation of the cataract (for example, in Dr. Štambuk's study there was a delay of 8 months to 7 years), and there is no way of determining whether such changes occurred before, during, or after these events. Hence, it is impossible to establish from this type of study

whether there is a correlation (let alone a causal relationship) between changes in the level or properties of the molecule of interest and the development or progression of the cataract.

Our studies of TGF-β are in a different category. We have shown that both TGF-β1 and TGF-β2, molecules known to be present in or near the lens, initiate events that lead to dramatic changes in lens explants from postnatal and adult rats.[1] These include rapid formation of spindle-shaped cells, capsule wrinkling, deposition of extracellular matrix and "apoptotic" cell death.[1] Moreover, the effects of TGF-β are completely blocked by a pan-specific antibody against TGF-β. As reviewed in that report, all these changes are characteristic of various forms of cataract.

Ongoing work in this laboratory has confirmed and extended this study, providing us with convincing evidence, both molecular and morphologic, that TGF-β can rapidly induce cataractous changes in lens cells. These results will be published in due course. The cataract-like changes induced by TGF-β have been demonstrated in adult rat lens explants, which consist only of lens epithelia attached to their capsule, and in a serum-free culture system. No concomitant inflammatory response or exogenous supply of IL-4 or other modulatory factors is required.

TGF-βs are ubiquitous molecules, with a great diversity of actions, known to interact with many other biologic molecules.[3,4] Interactions between IL-4 and TGF-β have been widely studied in macrophages. Although, as in the study cited by Dr. Štambuk,[5] such interactions may sometimes lead to enhancement of TGF-β activity, this is not always the case; often TGF-β action is suppressed by IL-4.[6] Their combined effects on lens epithelial cells remain to be determined. Thus, there is no evidence for direct involvement of IL-4 in inducing cataractous changes in lens cells. TGF-β bioavailability is enhanced during wound healing as part of the inflammatory response[3,7] and there is an established association between inflammation and cataract,[8] but the molecular mechanisms involved remain to be determined.

If TGF-β does indeed induce cataractous changes in lens cells in vivo as in vitro, then there are many ways in which its action could be enhanced, leading to increased likelihood of cataract. These may include activation of latent TGF-β, stimulation of autocrine or paracrine production of TGF-β, or an increase in the concentration of a molecule that potentiates TGF-β activity. No doubt, many researchers with an interest in the pathology of the lens will be stimulated to speculate about the possible involvement of his or her "molecule of interest" in a TGF-β-mediated pathway of cataractogenesis via one or more of these mechanisms.

Naturally, we will be delighted if our discovery that TGF-β induces cataract-like changes in lens epithelial explants paves the way for new ways of thinking about cataract research in laboratories throughout the world. If we are to make real progress in understanding the events that underlie the induction and subsequent progression of a cataract, more than speculation will be needed, however. We will also need the ingenuity to devise appropriate ways of testing promising hypotheses experimentally.

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