Commentary (Weitberg): Chronic Inflammation and Cancer

In this article, Drs. Shacter and Weitzman present a thoughtful, comprehensive review of the role of chronic inflammation in the multistep process of carcinogenesis. Their cogent discussion encompasses the basic science, clinical correlates, and treatment implications of this subject. It is well balanced, highly informative, and indicative of the complexity of the biochemical events that transpire as chronic inflammation results in malignant transformation of target cells.

The association between chronic inflammation and tumorigenesis continues to be well documented in the literature,[1,2] even though the full spectrum of intra- and extracellular intermediates in this process remains to be elucidated. The ones that have been elucidated, however, likely participate in the initiation as well as promotion and progression of carcinogenesis. This is evidenced by their similarities to other chemical carcinogens as discussed in this review article. These proneoplastic inflammatory mediators include the reactive oxygen and nitrogen intermediates, prostaglandins, and cytokines that act via several mechanisms to promote the transformed phenotype. It is probable that multiple molecular and biochemical events must occur over time for cancer to develop (eg, DNA damage, promotion of cell proliferation and angiogenesis, inhibition of repair enzymes, inhibition of apoptosis).[3]

Cause and Effect Not Established

Although the association between chronic inflammation and cancer is well described, cause and effect remain to be proven, perhaps because definitive causative inflammatory mediators have not been completely identified. One can imagine extracellularly generated radical species that interact with the cell membrane to produce a series of intracellular radicals, which careen through the cytoplasm, initiating serial oxidation-reduction events that terminate at the site of nuclear DNA. In the process, cell signals are distorted, repair mechanisms interrupted, and DNA damaged. Some cells die, some repair the damage faithfully, but others miscue, and the preneoplastic genotype eventuates. Obviously, identifying the causative intermediate in this process is difficult, and thus, establishing the link between inflammation and cancer has been elusive.

An especially interesting aspect of research in this area involves the role of stimulated human phagocytes whose normal salutary biological role is to thwart infection. The chronicity of that stimulation, however, may result in too much of a good thing, with DNA damage being induced in the target cells, as in ulcerative colitis. This is aptly discussed by the authors, although notably only a minority of patients with ulcerative colitis develop malignancies.

Inhibition of Chronic Inflammatory Sites

As the mechanisms for carcinogenesis in chronic inflammatory states are better defined, targets for inhibition of this process will be more fully elucidated. Drs. Shacter and Weitzman appropriately review the known anticancer effects of antioxidants and oxygen radical scavengers in the reliable clinical trials published to date. The results are inconclusive, but we have yet to define the effective doses of these agents based on measurement of biological end points. As demonstrated with vitamin C, its pro- and antioxidant effects are dose-dependent, and thus, more is not necessarily better. Mechanism-based chemoprevention trials should be refined (eg, using animal models involving transgenic mice), so that the expected molecular or biochemical effect of the agent being studied can be measured and correlated with its anticancer effect or lack thereof.[4,5]

The suggestion that antioxidants may enhance the effects of antineoplastic therapy is interesting, clinically important, and addressed by the authors in this review. They note that oxidants may interfere with the induction of apoptosis by chemotherapeutic agents and that this effect is
reversible with antioxidants. Since inflammation commonly accompanies neoplasia in vivo, oxidative stress may be an important determinant of the success of therapy, and antioxidants may be useful adjuncts to that therapy. Further investigation of this subject is warranted and has important clinical implications.

This comprehensive overview provides useful information for both those unfamiliar with and those intimately involved with this area of research.

**References:**


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