Letters to the Editor

Telomere Length Abnormalities and Human Cancer

With great interest we read the article by Meeker et al. (1) on abnormalities of telomere length occurring early in the initiation of epithelial carcinogenesis. From in situ assessment of telomere length in formalin-fixed human surgical specimens of epithelial cancer precursor lesions, it was concluded that this methodology may be useful as an early biomarker for monitoring disease prevention strategies and for improved early diagnosis.

Telomeres are distinctive structures of a repetitive DNA sequence and associated proteins, which allow cells to distinguish chromosome ends from DNA double-strand breaks. Telomere alterations are observed in senescence and during the immortalization process and may be caused by shortening or direct damage and usually lead to chromosomal instability.

Recent data support the view that immune activation and inflammation and thereby evolving oxidative stress are deeply involved in the development and progression of cancer (2, 3). The tumor microenvironment includes various inflammatory cells, which participate strongly in tumorigenesis and progression of the disease. As Meeker et al. stated, immune activation and inflammation could be involved in telomere shortening. Indeed, telomere shortening was observed in chronic or acute inflammation (e.g., ulcerative colitis, a chronic inflammatory condition predisposing for cancer; ref. 4). An association between telomere abnormalities and immune activation and inflammation is very intriguing to us, because earlier we have found variables of immune activation, such as neopterin, to be sensitive predictors of outcome in several human malignant tumors (5–7). In a similar way, cytokine-inducible expression of indoleamine-2,3-dioxygenase, an enzyme converting tryptophan to kynurenine, was recently observed as an early abnormality in tumorigenesis (8). Likewise, an accelerated tryptophan catabolism predicts shortened survival in patients with cancer (6, 9) and is characteristic for diseases associated with immune activation. For the expression of indoleamine-2,3-dioxygenase and in the increased production of neopterin, pro-inflammatory cytokine IFN-γ is primary (7, 9). IFN-γ is an important mediator of antitumoral defense, which on the one hand enforces forward-regulatory T-cell response mechanisms and on the other hand induces several antiproliferative enzymes in addition to indoleamine-2,3-dioxygenase. IFN-γ also induces high output of cytoidal reactive oxygen species (10). Overall, IFN-γ is probably the most potent growth inhibitor.

At first glance, it is astonishing that shortened survival in cancer patients is associated with higher degree of immune activation and increased formation of IFN-γ. However, it is no surprise that such a potent cytokine has its side effects, and available data imply that IFN-γ released within antitumoral immune response could accelerate the course of malignant process (e.g., by inhibiting T-cell responsiveness; ref. 8). Telomere abnormalities could represent another consequence of chronic immune activation in cancer patients.

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