

The immortalized chondrocyte: art without sacrifice.

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J Clin Invest. 1994;[94\(6\)](#):2173-2173. <https://doi.org/10.1172/JCI117575>.

Editorial

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Chondrocytes compose and remodel articular cartilage in response to sensory cues provided by mechanical forces, existing matrix structure, growth factors, and cytokines in their avascular, non-innervated environment. However, articular cartilage chondrocytes are essentially sacrificed to their art, living as a normally sparse population of individually confined cells that rarely divide and decline in proliferative potential and number with aging (1).

Inherent limitations in the regenerative potential of articular cartilage are compounded by the susceptibility of the cartilage matrix to inflammatory injury (1). In this regard, exogenous IL-1 β is a particularly potent inhibitor of collagen II and proteoglycan synthesis by chondrocytes, and at higher concentrations IL-1 induces elaboration of metalloproteinases and active degradation of matrix (1). Chondrocytes also have the capacity to directly initiate and amplify inflammatory injury by expressing IL-1 and other inflammatory cytokines (1, 2).

Phenotypic instability and other limitations inherent in the use of monolayer-cultured chondrocytes released from human articular cartilages (3) hinder studies to develop improved means to protect and/or regenerate the cartilage matrix. Because the applicability of culturing intact cartilage slices (2) is limited, investigators have attempted to use a variety of transformed and immortalized chondrocyte lines to further understand the functions of articular chondrocytes, an approach supported by experience with other tissues (3, 4). In this issue of *JCI*, Goldring et al. (3) describe what is by far the most successful strategy for chondrocyte immortalization. Using vectors containing SV40 DNA sequences, this group has obtained immortalized chondrocyte lines from human costal cartilage that are phenotypically stable for at least 40–80 passages, and, under defined serum-free conditions, elaborate cartilage matrix constituents including collagen II (3). Furthermore, the immortalized chondrocytes demonstrate cartilage-specific gene regulation and responsiveness to IL-1 that includes transcriptional suppression of the expression of the gene for collagen II, and up-regulation of the level of mRNAs for certain metalloproteinases (3).

The work by Goldring et al. provides not only a novel system for in vitro studies on molecular regulation of chondrocyte gene expression but also a significant testing ground for development of targeted pharmacologic means to regulate matrix production and to potentially regenerate cartilage. Because collagen II gene expression in adults is largely restricted to articular cartilage, the capacity of immortalized chondrocytes to be efficiently transfected, and to express genes driven by regulatory sequences from the collagen II gene (3), also can be used to screen for potential effects on in vivo matrix regula-

tion in cartilage-specific transgene expression systems (5) (e.g., using genes for IL-1 antagonists or metalloproteinase inhibitors) (1). Immortalized chondrocytes also may be useful in addressing other clinically pertinent problems, including the mechanisms regulating genes that mediate the pathologic deposition of calcium pyrophosphate dihydrate and basic calcium phosphate crystals in articular cartilage (6), and the basis for the effects on cartilage matrix of certain antirheumatic drugs (7).

SV40-immortalized chondrocytes appear to lose several constitutive functions (3), and the validity of findings to be obtained using monolayer-cultured immortalized chondrocytes, as described in this issue of *JCI*, will generally require scrutiny under more physiologic experimental conditions. The relatively unconstrained proliferative potential of SV40-immortalized chondrocytes also impels constant consideration of Lec's dictum that "the first requisite for immortality is death." Factors that determine chondrocyte senescence, and the effects on chondrocyte proliferative potential of IL-1, nitric oxide (8) and other mediators, also must continue to be investigated as potentially important factors in certain diseases of cartilage.

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