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REGULATION OF SYNTHESIS OF CHONDROITIN SULFATE PROTEOGLYCAN

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Since chondroitin sulfate proteoglycan is the end product of a complex biosynthetic pathway (1), a number of possible sites exist at which the rate of its metabolism may be controlled in the intact cell. These include, among others, formation of core protein, maintenance of levels of requisite nucleotide sugars and the sulfate donor-PAPS, and synthesis and coordination of specific glycosyltransferases and sulfotransferases. In a continuing study of the regulation of these biochemical events, a model system using embryonic chick chondrocytes in monolayer culture has been developed, in which each phase of synthesis of this complex macromolecule can be separately assessed. Concurrent with the morphological differentiation of chondrocytes in monolayer, a change occurs in the rates of glycosaminoglycan and collagen synthesis by the progeny of the chondrocytes (2, 3). Levels of three of the chondroitin sulfate glycosyltransferases and both sulfotransferases, assayed in a cell-free system during the growth cycle, were found to be closely correlated with the quantity of synthesized chondroitin sulfate proteoglycan as measured by sulfate incorporation. However maximum levels of glycosyltransferase and sulfotransferase activities preceeded the maximum rate of chondroitin sulfate synthesis by 2 days. Turnover studies showed that the individual glycosyltransferases decayed with significantly different half-lives, indicating that the glycosyltransferases are not coordinately synthesized and degraded.

In order to identify those sites which may serve as a locus of control, the various steps of synthesis were also examined and compared under conditions in which normal synthesis is perturbed (4, 5). Chondrocyte cultures were stimulated to produce high levels of soluble chondroitin sulfate chains by prolonged treatment with β-xylosides, which have previously been shown to initiate the synthesis of protein-free polysaccharide chains (6). Stimulation of chondroitin sulfate chain synthesis was accompanied by a decrease in $^{35}SO_4$ incorporation into large molecular weight chondroitin sulfate proteoglycan. Additional experiments which examined several of the possibilities that might account for decreased production of $^{35}SO_4$-labeled chondroitin sulfate proteoglycan, suggest it to be the result of an inhibition of galactosyltransferase activity in the presence of normal production and xylosylation of core protein. It would appear from these studies that production of core protein and the sequence of glycosylation reactions may be independently regulated, since neither increased synthesis of chondroitin sulfate chains nor decreased synthesis of chondroitin sulfate proteoglycan alters the level of core protein production.

Additional information on the regulation of the sulfation process has resulted from a determination of the specific lesion responsible for defective proteoglycan synthesis in an animal mutant exhibiting an aberrant cartilage matrix. Activity levels of sulfotransferases, requisite for the sulfation of chondroitin sulfate proteoglycan, were measured in cell-free

homogenates from normal or homozygous brachymorphic mouse epiphyseal cartilage. In the presence of [^{35}S]-PAPS plus an exogenous sulfate acceptor comparable amounts of $^{35}SO_4$ were incorporated into chondroitin sulfate by the two types of cartilage. In contrast, the mutant cartilage catalyzed the conversions of approximately 25% of the $^{35}SO_4$ into chondroitin sulfate as normal mouse cartilage, when synthesis which initiated from ATP and $H_2{}^{35}SO_4$. These results suggest that the production of an undersulfated proteoglycan, which has been reported in brachymorphic mice (7), may result from a defect in synthesis of the sulfate donor-PAPS.

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