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Interference with steps in collagen synthesis as a biochemical mechanism of teratogenesis

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INTRODUCTION

Interference with collagen synthesis and deposition can be expected to play a significant role in teratogenesis, not only because collagen is the most abundant protein in the body, being the major protein constituent of most tissues and organs of mesenchymal origin, but especially because it is involved in important aspects of cell and tissue differentiation including epithelio-mesenchymal interaction, cell adhesion and alignment and cell-cell communication and information transfer. Collagen has unique physicochemical features which contribute to its many functions. These features are related to its unusual primary structure and its unique conformation. The potential of collagen to fulfill its many roles is not fully achieved until a series of post-translational modifications of newly synthesized collagen chains occur, resulting in the attainment of its triple-helical conformation and the subsequent assembly and stabilization of the molecules into aggregates. Steps in the synthesis of collagen are susceptible to many exogenous influences. Our thesis, reviewed in this chapter, is that interference with steps in collagen biosynthesis is a major biochemical mechanism of teratogenesis.

ROLE OF COLLAGEN IN TISSUE DIFFERENTIATION AND DEVELOPMENT

Collagen is present in the earliest stages of embryonic development and, throughout development and growth of the organism, collagen continues to undergo turnover at significant rates, at first to accommodate the morphogenetic changes accompanying tissue remodelling and growth and, in the fully grown adult, as part of normal tissue attrition and renewal. Its involvement in
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many aspects of differentiation, morphogenesis and growth is well docu-
mented.

The significance of collagen in epithelio-mesenchymal interactions was first
recognized by Grobstein\textsuperscript{1-3}. The presence of collagen at the interface between
the epithelium and the mesenchyme has been confirmed\textsuperscript{4,5} and the removal of
collagen at the interface by collagenase has been shown to abolish morpho-
getic interactions\textsuperscript{6}. Collagen involved in such interactions is synthesized
by cells of mesenchymal\textsuperscript{7,8} as well as of epithelial\textsuperscript{9,10} origin. Epithelial collagen
may act as a substratum on which cells align during morphogenesis\textsuperscript{9,11-14}. 
Connective tissue cells are known to migrate in a directed manner and are
frequently seen adjacent to pre-existing collagen fibres during morphogenesis.
The adhesion of cells to collagenous matrices is well known. Collagen sub-
strata are used to grow cells in culture and collagen has been shown to be
involved in the aggregation of platelets. Interaction of cells with collagen may
play a role in spatial pattern formation. Because collagen occurs in highly
organized fibrous networks under physiological conditions, it may direct the
course of morphogenesis by steering cells into appropriate geometric and
appositional patterns. Reddi\textsuperscript{15,16} demonstrated the potential of the collagenous
matrix of bone to alter gene expression in responding fibroblasts and suggested
that the geometric and surface charge characteristics of the matrix may play a
role in such interactions. Although the mechanisms involved in cell attach-
ment to collagen are not fully understood, recent studies\textsuperscript{17} suggest that a
protein meshwork containing fibronectin and collagen associated with the
fibroblast surface may play a role in the binding of the cell to the extracellular
matrix, with collagen–collagen interactions contributing significantly to the
complex. Collagen and collagenous matrices have been shown to promote
differentiation and morphogenesis in a variety of systems including in vitro
chondrogenesis\textsuperscript{18}, bone\textsuperscript{15,16} and eye\textsuperscript{19,20}. It is clear that collagen synthesis and
extracellular aggregation must proceed in an orderly manner for morpho-
genesis to occur normally.

CHEMICAL BIOLOGY OF COLLAGEN

It is now recognized that collagen is not a single protein but rather, a group of
closely related but genetically distinct proteins. The most abundant and widely
distributed collagen, Type I collagen accounts for two of the known chain
types, \(\alpha 1(I)\) and \(\alpha 2\). The triple helix of Type I collagen contains two \(\alpha 1(I)\)
chains and one \(\alpha 2\) chain. Type I collagen is nearly ubiquitous in the body,
being sparse only in cartilage and in basement membranes. Cartilage contains
a distinct type of collagen, Type II collagen whose triple helical molecule is
made up of three identical chains, \(\alpha 1(II)\). Another type of collagen present in
many different tissues, especially those supporting an endothelium such as
blood vessels and skin, is Type III collagen, made up of three \(\alpha 1(III)\) chains.
Type III collagen invariably occurs in association with Type I collagen and it
is apparently a component of reticulin fibres. Type III collagen may play a
role in morphogenesis and development since it occurs in larger proportions
during fetal and early developmental stages but is decreased in adult tissues.
Various basement membranes are comprised of a unique collagen species,