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Extracellular Matrix Remodeling and Metalloproteinase Involvement during Intestine Regeneration in the Sea Cucumber *Holothuria glaberrima*

José L. Quiñones … José E. García-Arrarás [1]

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Abstract

The sea cucumber, *Holothuria glaberrima*, has the capacity to regenerate its internal organs. Intestinal regeneration is accomplished by the thickening of the mesenteric border and the invasion of this thickening by mucosal epithelium from the esophagus and the cloaca. Extracellular matrix (ECM) remodeling has been associated with morphogenetic events during embryonic development and regeneration. We have used immunohistochemical techniques against ECM components to show that differential changes occur in the ECM during early regeneration. Labeling of fibrous collagenous components and muscle-related laminin disappear from the regenerating intestine and mesentery, while fibronectin labeling and 4G7 (an echinoderm ECM component) are continuously present. Western blots confirm a decrease in fibrous collagen content during the first 2 weeks of regeneration. We have also identified five 1,10-phenanthroline-sensitive bands in collagen gelatin zymographs. The gelatinolytic activities of these bands are enhanced during early stages of regeneration, suggesting that the metalloprotease activity is associated with ECM remodeling. Inhibition of MMPs *in vivo* with 1,10-phenanthroline, p-aminobenzoyl-Gly-Pro-D-Leu-D-Ala hydroxamate or N-CBZ-Pro-Leu-Gly hydroxamate produces a reversible inhibition of intestinal regeneration and ECM remodeling. Our results show that significant changes in ECM content occur during intestine regeneration in the sea cucumber and that the onset of these changes is correlated to the proteolytic activities of MMPs.

Keywords

echinoderm; extracellular matrix remodeling; ECM; epithelial tubular outgrowth; fibrosis; holothuroid; intestine regeneration; metalloproteases; metalloprotease inhibitors; morphogenesis; organogenesis; 1,10-phenanthroline; zymograph

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1 To whom correspondence should be addressed. Fax: (787) 764-3875. E-mail: jegarcia@upracd.upr.clu.edu.