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Demonstration of the extrinsic coagulation pathway in teleostei: identification of zebrafish coagulation factor VII.

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Abstract

It is not known whether the mammalian mechanism of coagulation initiation is conserved in fish. Identification of factor VII is critical in providing evidence for such a mechanism. A cDNA was cloned from a zebrafish (teleost) library that predicted a protein with sequence similarity to human factor VII. Factor VII was shown to be present in zebrafish blood and liver by Western blot analysis and immunohistochemistry. Immunodepletion of factor VII from zebrafish plasma selectively inhibited thromboplastin-triggered thrombin generation. Heterologous expression of zebrafish factor VII demonstrated a secreted protein (50 kDa) that reconstituted thromboplastin-triggered thrombin generation in immunodepleted zebrafish plasma. These results suggest conservation of the extrinsic coagulation pathway between zebrafish and humans and add credence to the zebrafish as a model for mammalian hemostasis. The structure of zebrafish factor VIIa predicted by homology modeling was consistent with the overall three-dimensional structure of human factor VIIa. However, amino acid disparities were found in the epidermal growth factor-2/serine protease regions that are present in the human tissue factor-factor VIIa contact surface, suggesting a structural basis for the species specificity of this interaction. In addition, zebrafish factor VII demonstrates that the Gla-EGF-EGF-SP domain structure, which is common to coagulation factors VII, IX, X, and protein C, was present before the radiation of the teleosts from the tetrapods. Identification of zebrafish factor VII significantly narrows the evolutionary window for development of the vertebrate coagulation cascade and provides insight into the structural basis for species specificity in the tissue factor-factor VIIa interaction.

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