

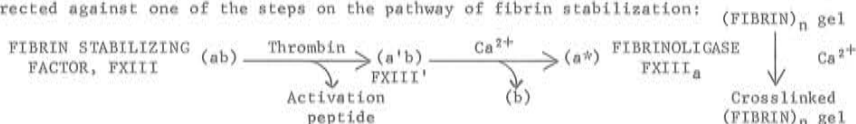
THE BIOCHEMISTRY OF FIBRIN CROSS-LINKING. Russell F. Doolittle. Department of Chemistry, University of California, San Diego, La Jolla, California U.S.A.

The final steps in the formation of a fibrin clot involve the factor XIII-catalyzed introduction of covalent peptide bonds. These bonds are the result of the condensation of specific lysine and glutamine sidechains in  $\gamma$ -chains on the one hand and  $\alpha$ -chains on the other. Function apart, these bonds have provided great insight into the way the individual molecular units are arranged in the fibrin polymer. Thus, the reciprocal pairing of the carboxy-terminal segments of  $\gamma$ -chains to yield  $\gamma\gamma$  dimers indicates that all molecules in the polymer have the same orientation, and, because of the dimeric nature of the fibrinogen molecule, the abutting chains of neighboring molecules are therefore antiparallel. Until now the three-dimensional involvement of  $\alpha$ -chains--which in contrast to  $\gamma$ -chains become multimerically cross-linked--has been completely mysterious. Recently, however, we have isolated those portions of  $\alpha$ -chains involved in multimeric cross-linking by fragmenting fully cross-linked fibrin with cyanogen bromide. Thus, we were able to identify the linked fragments as two segments which, when not cross-linked, have mol. wts. of 29,000 and 6,000 respectively. The latter fragment has amino-terminal leucine and is thought to be the carboxy-terminal penultimate CNBr fragment in the  $\alpha$ -chain. It is linked in equimolar quantities to the large mol. wt. glutamic acid-ending fragment. The total mol. wt. of the multimerically linked units is greater than 500,000. The nature of the fragment network is such that the orientation of the  $\alpha$ -chains in fibrin could be either parallel or antiparallel. In either case the architecture is well suited to lateral cross-linking between fibrin polymers.

PHYSIOLOGICAL AND CLINICAL SIGNIFICANCE OF FIBRIN. L. Lorand.

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Disorders of fibrin stabilization are hemorrhagic conditions in which the patient's plasma clot is lacking in inter-fibrin  $\gamma$ -glutamyl- $\epsilon$ -lysine isopeptide linkages. The primary defect occurs either because no fibrinoligase (FXIII<sub>a</sub>) activity can be generated or because the enzyme cannot act on fibrin in the patient's plasma. Distinction is made between hereditary disorders (Class I) and those appearing later in life because of an acquired inhibitor (Class II) directed against one of the steps on the pathway of fibrin stabilization:



Of the genetic deficiencies (Class I), Type I is characterized by a lack of zymogen activity in plasma and Type II by the unreactivity of the cross-linking sites of the patient's fibrin ["dysfibrin(ogen)emias"] towards fibrinoligase.

There are three varieties of Class II abnormalities. In Type I, the acquired inhibitor interferes with zymogen activation. Type II inhibitors affect transamidation by competing against fibrin for the enzyme. The Type III inhibitor combines with fibrin rendering it unreactive towards fibrinoligase. The Type I and III inhibitors appear to be autoimmune antibodies. (Ann. N. Y. Acad. Sci., 202, 6, 1972).

Differential diagnostic criteria for this family of molecular disorders will be discussed.