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Aldolase and Protease: Unsuspected Structural Homology

Neurath, Walsh, and Winter (*1*) have reviewed the structural homologies between functionally related proteolytic enzymes. Similar sequences were found to be present around one of the functional histidine residues in chymotrypsin, trypsin, elastase, and an α-lytic protease from *Sorangium* sp. (*2*). We now call attention to an unexpected homology between this region of the proteases and a sequence in the Schiff base-forming aldolases. Despite the apparent unrelatedness of the two classes of enzymes, there may be similar roles for histidine residues in the catalytic mechanisms. Histidine appears to participate in the obligatory proton transfer in discharge of the acyl-enzyme intermediate formed in protease catalysis (*3*, *4*); it has also been found essential (although perhaps indirectly) for protonation and discharge of the Schiff base carbanion intermediate formed when aldolase reacts with its substrate (*5*). We therefore examined these proteins for homologous sequences.

The sequences that demonstrate the best homology are shown in Fig. 1. They include the single histidine residue in the α-lytic protease of *Sorangium* (*2*), and a portion of the polypeptide chain in the vicinity of the active site of rabbit liver and rabbit muscle aldolases (*6*). The sequence around the histidine residue in the protease is homologous to those around the "functional" histidine in the mammalian proteases (*1*, *2*); the histidine in the aldolase sequence is eight residues removed from the lysine residue which forms the Schiff base with the substrate.

	1	2	3	4	5	6	7	8
Chymotrypsin:	Val-	Thr-	Ala-	Ala-	His-	Cys-	Gly-	Val
α-Lytic protease:	Val-	Thr-	Ala-	Gly-	His-	Cys-	Gly-	Thr
Aldolase (liver):	Val-	Thr-	Ala-	Gly-	His-	Ala-	Cys-	Thr
Aldolase (muscle):	Val-	Thr-	Pro-	Gly-	His-	Ala-	Cys-	Thr

Fig. 1. Homology of sequences in enzymes.

The degree of correspondence of this section of the protease with liver aldolase (two differences) is the same as that of the protease with chymotrypsin (two differences) and greater (*1*) than that of the protease with trypsin (four differences). The differences at positions 6 and 7 are compatible with mutational changes of one and two nucleotides, respectively (*7*). The apparent homology between the two proteins decreases beyond this region, although relatedness still may be detected if one considers the residues found at corresponding positions in the other proteases (*1*) as alternatives, and evaluates the extent of nucleotide substitution required to account for observed differences.

In addition to the sequences presented in Fig. 1, we have found other regions in the structures of trypsin and chymotrypsin (*8*) which may reflect homologies with elements in the aldolase structure. In order to evaluate the significance of such possible homologies, and to determine whether they represent the result of divergent or convergent evolution, or mere coincidence, it would be desirable to compare the two classes of structures with the aid of a computer program of the type developed for homology detection in other proteins (*9*).

The possibility that the observed homology is a reflection of divergent evolution in which selective pressure has preserved the sequence around the histidine residue might suggest that this residue is essential in aldolase as it is in the proteases. Although the location of the essential histidine residue or residues in aldolase is not yet known, preliminary experiments (*4*) suggest that at least one may be located within ten residues from the active site lysine residue. The mechanism of aldolase action, which shares some elements of base-catalysis and proton transfer with that of the proteases, has been recently reviewed (*10*).

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