Abstract Human kallikrein-related peptidases (KLKs) are (chymo)-trypsin-like serine proteinases, which are expressed in a variety of tissues such as prostate, ovary, breast, testis, brain, or skin. While their physiological functions have been elucidated only partially, many of the KLKs appear to be useful prognostic cancer markers, showing distinct correlations between their expression levels and different stages of cancer. Recent advances in the purification of 'new-type' recombinant KLKs allowed the solving the crystal structures of KLK4, KLK5, KLK6, and KLK7. Along with these data, enzyme kinetic studies and extended substrate specificity profiling have led to an understanding of the nonprime side substrate preferences of KLK4, 5, 6, and 7. Shape and polarity of the specificity pockets S1 to S4 explain well their substrate preferences. KLK4, 5, and 6 exhibit a trypsin-like specificity with a strong preference for Arg at the P1 position of substrates. In contrast, KLK7 displays a unique chymotrypsin-like specificity for Tyr, which is also preferred at P2. All four KLKs show little specificity for P3 residues and have a tendency to accept hydrophobic residues at P4. Interestingly, for KLKs 4, 5, and 7 extended charged surface regions were observed that serve most likely as exosites for physiological substrates.
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