Abstract:

Including the true tissue kallikrein KLK1, kallikrein-related peptidases (KLKs) represent a family of fifteen mammalian serine proteases. While the physiological roles of several KLKs have been at least partially elucidated, their activation and regulation remain largely unclear. This obscurity may be related to the fact that a given KLK fulfills many different tasks in diverse fetal and adult tissues, and consequently, the timescale of some of their physiological actions varies significantly. To date, a variety of endogenous inhibitors that target distinct KLKs have been identified. Among them are the attenuating Zn(2+) ions, active site-directed proteinaceous inhibitors, such as serpins and the Kazal-type inhibitors, or the huge, unspecific compartment forming ?(2)-macroglobulin. Failure of these inhibitory systems can lead to certain pathophysiological conditions. One of the most prominent examples is the Netherton syndrome, which is caused by dysfunctional domains of the Kazal-type inhibitor LEKTI-1 which fail to appropriately regulate KLKs in the skin. Small synthetic inhibitory compounds and natural polypeptidic exogenous inhibitors have been widely employed to characterize the activity and substrate specificity of KLKs and to further investigate their structures and biophysical properties. Overall, this knowledge leads not only to a better understanding of the physiological tasks of KLKs, but is also a strong fundament for the synthesis of small compound drugs and engineered biomolecules for
pharmaceutical approaches. In several types of cancer, KLKs have been found to be overexpressed, which makes them clinically relevant biomarkers for prognosis and monitoring. Thus, down regulation of excessive KLK activity in cancer and in skin diseases by small inhibitor compounds may represent attractive therapeutical approaches.