Regulatory KLK cascades in normal physiology and disease

Kallikrein-related peptidases constitute a single family of 15 (chymo)trypsin-like proteases (KLK1-15) whose aberrant regulation has been associated with diverse diseases, such as cancer, inflammation, neurodegeneration, hypertension, renal dysfunction and skin disorders. In addition to their established clinical applications as biomarkers, recent studies have revealed pleiotropic roles of KLKs in important (patho)physiological processes. Co-ordinated activation and control of KLK activity is achieved via complex regulatory cascades, referred to as the “KLK activome”. Proteolytic activities produced by KLK zymogen activation via the KLK activome are involved in processes of skin desquamation, innate immunity, hypertension, semen liquefaction, neurodegeneration, and tumor-promoting or -inhibiting effects. Notably, certain KLKs exert pleiotropic functions by activating molecules involved in multiple processes, e.g. cathelicidin, which is involved in skin desquamation and innate immunity. Consequently, KLKs are emerging as attractive targets for diagnosis and for therapeutic intervention in a number of human pathologies.