ЖУРНАЛ ЭВОЛЮЦИОННОЙ БИОХИМИИ И ФИЗИОЛОГИИ, 2020, том 56, № 7, с. 783

МАТЕРИАЛЫ КОНФЕРЕНЦИИ И ШКОЛЫ

EVOLUTION OF ECTOPEPTIDASES AND THEIR FUNCTIONS

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DOI: 10.31857/S0044452920072115

The ubiquity and diversity of peptidases is indicated by the existence of some 28000 specific peptidases and their homologs characterized in more than 6000 known organisms. In the human genome of approximately 24000 protein-coding genes, 686 genes of putative peptidases are known alongside 423 of non-catalytic homologues. Many of these are orphan peptidases for which the biologically active peptide substrates have not yet been identified. Such a profusion of proteolytic events requires specifically controlled regulation. Hence, while genes for peptidases constitute about 2.8% of the human genome, a significantly higher number (7.4%) of genes encode protein inhibitors of peptidases. Turning off peptide signaling is principally mediated by a group of cell-surface peptidases whose active sites face the extracellular space (ectopeptidases). Two groups of metallopeptidases are the best characterized as peptide degrading enzymes: the neutral endopeptidase or neprilysin (NEP) family and the angiotensin converting enzyme (ACE) family. NEP and its homologs are important in degrading both brain peptides (e.g., enkephalins, tachykinins) and cardioactive peptides (e.g., atrial natriuretic peptides, angiotensins, endothelin). They also metabolize the Alzheimer's amyloid β-peptide (Aβ). In the cardiovascular system, ACE and ACE2 act to counterbalance each other in controlling angiotensin peptide levels but may also participate in metabolism of other peptides. ACE2 is also a receptor for the coronaviruses that cause SARS and COVID-19. Prolyl-directed peptidases such as dipeptidyl peptidase IV and prolyl oligopeptidase play highly specific roles in peptide metabolism. This talk will summarize current developments in our understanding of evolution of ectopeptidases, regulation of these key mediators of peptide signaling, their roles in human diseases and potential therapeutic values.

Supported by RFBR 19-015-00232, state assignment (AAAA-A18-118012290373-7).