MOLECULAR CELL BIOLOGY OF OLIGOPEPTIDASES

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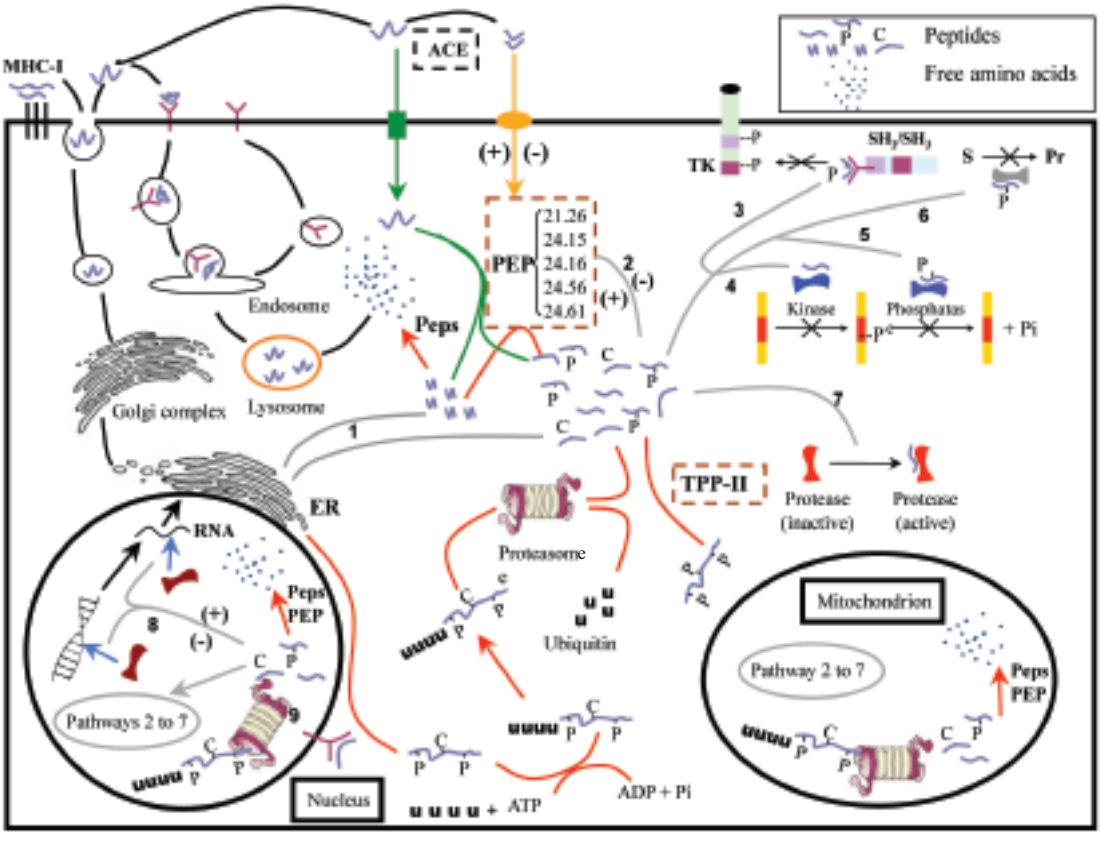
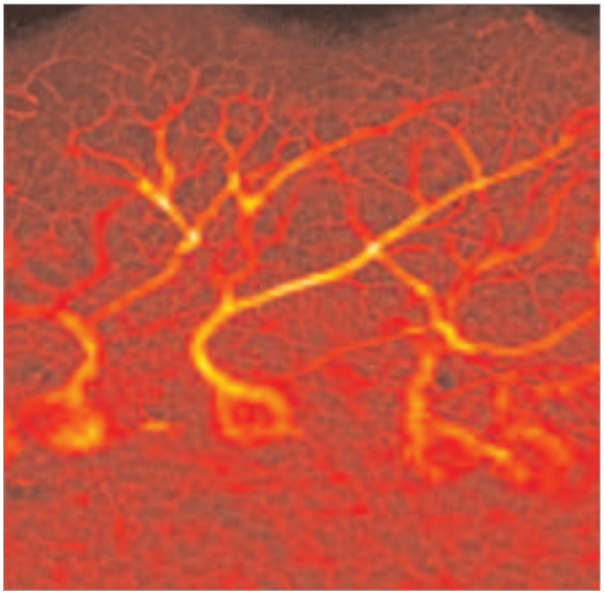


Diagramatic scheme showing oligopeptidases in the cell

Endo-oligopeptidases is a denomination coined by Camargo and cols. (Oliveira, et al., 1976) to describe the substrate specificity of two enzymes named endo-oligopeptidases A and B, which cleave only short peptides (from 5 to 17 amino acids). At this time we intend to keep on investigating the cell biology and function of endo-oligopeptidases EP24.15 (EC 3.4.24.15) and EP24.16 (EC 3.4.24.16). The primarily intracellular location (e.g., cytosolic, nuclear, mitochondrial) of peptidases such as EP24.15 (EC 3.4.24.15) and EP24.16 (EC 3.4.24.16) suggests additional functions besides extracellular neuropeptide/hormone metabolism/processing. In collaboration with the laboratories of Professors Antonio C.M. Camargo (Butantan Institute) and Célio Silva (FMRP, USP), we have shown that oligopeptidases such as EP24.15 play an important intracellular role in degrading peptides released by the 268 proteasome. Thus, the aim of the present project is to investigate the molecular cell biology of endo-oligopeptidases EP24.15 and EP24.16.

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

We have developed knockout animals for the neurolysin endopeptidase, and we are in the final phase of obtaining knockout animals for the thimet oligopeptidase. We are concluding studies which suggest high concentration of intracellular peptides, with biological activity capable of altering the signaling of receptors coupled with G proteins (GPCRs) and tyrosine kinases. We have obtained specific conformation anti-GPCR antibodies which were used for the identification of hemopressin as an inverse agonist of type-1 cannabinoid (CB1) receptors. Another 25 peptides had their GPCRs identified, thus composing a new group of molecules with potential therapeutical use.



Oligopeptidases: presence in rat brain neurons is shown by immunohistochemistry suggesting a physiological role in brain peptide degradation (Massarelli et al., 1999)

MAIN PUBLICATIONS

Demasi M, Piassa-Filho GM, Castro LM, Ferreira JC, Rioli V, Ferro ES. 2008. Oligomerization of the cisteynil-rich oligopeptidase EP24.15 is triggered by S-Glutathionylation. *Free Radical Biology & Medicine*, **44**:1180-1190.

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Dale CS, Pagano R De L, Rioli V, et al. 2005. Antinociceptive action of hemopressin in experimental hyperalgesia". *Peptides*. **26(3)**:431-436.

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