UNIVERSITY OF CYPRUS
DEPARTMENT OF BIOLOGICAL SCIENCES

The Department of Biological Sciences cordially invites you to the thesis defense of the PhD candidate

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entitled

"Computational approaches for the identification of LIR-motifs in selective autophagy receptor and adaptor proteins"

Abstract

Macroautophagy (hereinafter autophagy) is a catabolic, cellular homeostasis mechanism conserved throughout the eukaryotes. Under stress conditions, double membraned vesicles (autophagosomes) isolate cytoplasmic material, eventually targeted to the lysosome/vacuole for degradation, thus recycling structural blocks for use by the cell. Selective modes of autophagy are facilitated by receptor proteins capable of binding specific cargos via cargo-specific interactions. These receptors bind to members of the Atg8 protein family (conjugated to the autophagosome membrane) via short linear motifs (LIR-motifs). Furthermore, protein adaptors interact with Atg8 proteins via LIR-motifs for performing other autophagic functions. At the initiation of this PhD project approximately 25 selective autophagy receptors/adaptors had been characterized along with their LIR-motifs.

We set to develop computational methods and tools for characterizing LIR-motifs, aiming to broaden our knowledge on selective autophagy receptors/adaptors. Based on previous attempts to describe LIR-motifs, we propose a generic regular expression (xLIR) aspiring to achieve absolute sensitivity. Expectedly, this approach leads to many false positive hits without any biological relevance. We systematically examined additional sequence-derived features to reduce false positives.

Knowing that:

a) autophagy proteins are enriched in intrinsically disordered regions (IDRs), and
b) short linear motifs are often found in IDRs

we confirm these observations in our reference autophagy receptor/adaptor dataset and, consequently, apply these principles as filters, leading to increased specificity. We also demonstrate that using a profile representation of LIR-motifs (in the form of a PSSM) further increases specificity, yielding high quality predictions. This work led to the first method of its kind reported in the literature, now freely available for use by the research community via the iLIR web server.

In our quest for deeper understanding the relationships between aminoacid sequences and the structural features of proteins with functional LIR-motifs (and to further improve iLIR efficiency):

a) We systematically study different data resources regarding IDRs, proposing multi-scheme predictions, each suited for different applications aiming at higher specificity/sensitivity.
b) We compiled a comprehensive collection of experimentally determined 3D-structures of Atg8 proteins and LIR-motifs. Following data pre-processing for defining the LIR-motif interaction interfaces, we conduct peptide docking experiments, illustrating that this approach is useful for predicting LIR::Atg8 binding-specificity. We develop a specialized database for storing this information, facilitating downstream analyses, which we plan to make freely available for use.

It is difficult to make successful long-term predictions in a rapidly developing field like autophagy. The increasing number of selective autophagy receptors/adaptors discovered (often using the methods/tools developed for this thesis) opens exciting research perspectives. Access to substantially broader reference datasets enables (or, better, requires) development of more sophisticated methods/tools (e.g. based in machine-learning techniques) to successfully capture hidden dependencies between sequence-features and functional properties of LIR-motifs. Combined with the increasing availability of -omics data, we envisage cutting-edge research towards elucidating regulation of autophagy in different cell types, tissues and developmental stages. In addition, the discovery of novel molecular entities (e.g. ncRNAs) with active roles in autophagy guarantees further 'surprises' but also new data material and research directions for experimentation, in vivo, in vitro or in silico.

Tuesday, December 11, 2018 at 12:00
Building ΘΕΕ01, Room 020 (Panepistimioupoli Campus)

The presentation is open to the public.