Volume 52(2):333-356, 2008
Acta Biologica Szegediensis
http://www.sci.u-szeged.hu/ABS

The *lemming* gene encodes the Apc11 subunit of the anaphase-promoting complex in *Drosophila melanogaster*

Olga Nagy

Institute of Biochemistry, Biological Research Center, Hungarian Academy of Sciences, Szeged, Hungary

The ubiquitin-mediated proteolysis of regulatory proteins plays an essential role in regulating the eukaryotic cell cycle. A multi-subunit complex called the anaphase-promoting complex/cyclosome or APC/C plays a key role in this process as an ubiquitin-protein ligase. By targeting mitotic regulatory proteins for degradation, it regulates chromosome segregation and exit from mitosis. The APC/C contains at least 11 subunits, most of which are evolutionarily conserved from yeasts to humans (Castro et al. 2005). The role of most of the subunits within the APC/C complex is still poorly understood.

We have isolated and characterized hypomorph and null alleles of the *lemming* (*lmg*) gene. They show different pupal and pharate-adult lethal phenotypes. Larval neuroblasts from *lmg* mutants show mitotic defects including high mitotic index, chromosome overcondensation, metaphase-like arrest and frequent aneuploid and polyploid cells. Beside the mitotic phenotype, we observed elevated level of apoptosis in *lmg* mutant neuroblasts. Immunostaining of *lmg* mutants shows abnormal cyclin A and cyclin B accumulation in the metaphase arrested mitotic cells.

The *lmg* gene was cloned by plasmid rescue. The predicted coding region consists of 255 nucleotides, and encodes a small, 10 kDa polypeptide containing a RING-finger motif. The Lmg protein shows more than 50% sequence identity and more than 80% sequence homology with the Apc11 subunits of the budding yeast and human APC/C.

Yeast two hybrid experiments revealed that the Lmg protein specifically interacts with a protein identified as the *Drosophila* orthologue of the Apc2/Mr subunit of the yeast and human APC/C (Kashevsky et al. 2002). This interaction was underlined by the synergistic genetic interaction between hypomorph alleles of *lmg* and *mr*.

When introduced and expressed in budding yeast cells, the *lmg* gene was able to fully complement the proliferation defect of yeast temperature sensitive *APC11-myc9* mutant. This result demonstrates that the *lmg* gene product from the fruit fly can functionally replace the yeast APC11 protein.

These phenotypic and functional assays indicate that the *lmg* gene encodes the Apc11 orthologue of the *Drosophila* APC/C. Our work represents the first genetic study of this subunit of the APC/C in a multicellular organism.

Castro A, Bernis C, Vigneron S, Labbé JC, Lorca T (2005) The anaphase-promoting complex: a key factor in the regulation of cell cycle. Oncogene 13;24(3):314-325.

Kashevsky H, Wallace JA, Reed BH, Lai C, Hayashi-Hagihara A, Orr-Weaver TL (2002). The anaphase promoting complex/cyclosome is required during development for modified cell cycles. Proc Natl Acad Sci U S A 99:11217-11222.

Supervisor: Péter Deák
E-mail: nagyo@brc.hu

Network evolution and related models in biology

Sergiu Netotea

Bioinformatics Group, Biological Research Center, Hungarian Academy of Sciences, Szeged, Hungary

Every complex natural system is characterized by several things: redundancy - that ensures information has several good options for circulating across a system, decoupling - the capacity to separate into functional parts that can work even if they are separated, modularity – the property of subparts to work independently and have specific functions, and feedback control – a basic mechanism that allows a system to observe its fitness, making it able to adapt to external or internal pressures. We are investigating how can the properties of general complex systems be measured in evolving networks, and what are the similarities and differences to naturally occurring networks.

Many biological networks evolve using a tradeoff between two basic properties: efficiency, which deals with the capacity of using resources to the maximum extent, and robustness, that deals with resistance to various external pressures. A conceptually simple model of evolution is explained, the outcome of it is however surprising: highly evolved networks have some properties far from many naturally occurring networks.

Simulations of network evolution were done using both a distributed evolutionary algorithm and a random rewiring of the links without the possibility to backtrack in the case of finding a better fitted network, storing the network structures. The efficiency was expressed as computing the number and length of shortest paths, and the robustness by evaluating the efficiency cost of attacking the most central nodes. We used both directed and undirected networks. The resulted over-all topology is showing a highly connected central core surrounded by a dense periphery connected only to the core. Many biological networks have scaled node distributions; this implies that their evolution is never completed, or that it acts modular, in subparts of the network. Several examples are discussed.