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

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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.

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Network evolution and related models in biology

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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.

The network of protein folding pathways is a particularly interesting one in terms of evolutionary fitness. The number of possible folding states a protein can have during its folding process is huge but the protein is folding extremely quickly, and this is an unsolved problem of today science. Groups of proteins form complexes that generally interact weakly but sometimes the bond can have high specificity. These complexes together can establish a strong structure, but to attain it they need to go through a network of states in a similar manner to protein folding. We are investigating ways to model this in terms of network evolution.

Also not every evolved system is suitable to be expressed as a proper network, but the evolutionary mechanism remains the same. We investigate the fitness of different populations of bacteria forming fractal shaped colonies using an agent based model that simulate the behavior of individual bacteria and the diffusion and sensing of different substances across the medium.

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Axonal and dendritic effects of neurogliaform cells in rat and human neocortex

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Neurogliaform cells have a unique position among cortical interneurons (Kawaguchi 1995) because they can elicit combined GABAA and GABAB receptor-mediated inhibition on pyramidal cells (Tamas et al. 2003). Moreover, they establish electrical synapses with each other and with other interneuron types (Price et al. 2005; Simon et al. 2005).

We measured the pre- and postsynaptic effects of neurogliaform cells applying simultaneous whole-cell recordings in layers I-IV of rat somatosensory cortex and in human association cortex *in vitro*.

Apart from the GABAA receptor mediated component in postsynaptic responses, single action potentials in neurogliaform cells elicited GABAB receptor mediated responses in neurogliaform, regular spiking and fast spiking interneurons in rat cerebral cortex.

Neurogliaform cells recorded in human cortical brain slices evoked GABAA and GABAB receptor mediated slow inhibition in various types of inteneurons and one of them established heterologous electrical coupling. These are the first multiple patch clamp recordings which analyse the functions of neuorgliaform cells in human cortex (Oláh et al. 2007).

These cells can effectively recruit GABAB receptors not only on classical postsynaptic compartments like dendritic spines and shafts but on presynaptic axon terminals as well. This presynaptic inhibitory effect can reduce synaptic transmission and this is reflected in the altered paired pulse ratios and reduced amplitudes of the evoked postsynaptic potentials. In one case we show phamacological dissection of this presynaptic modulation by applying GABAB receptor antagonist.

Our results highlight the peculiar role of neurogliaform cells in cortical circuits and extend their contributions to slow inhibition in cortex.

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