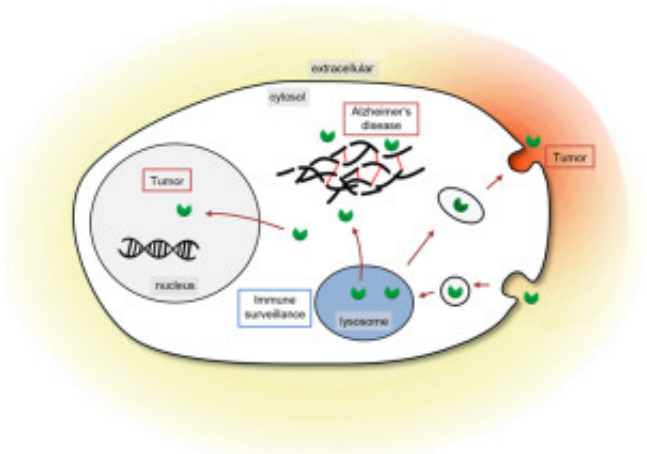
Smart legumain drugs: Blocking the right activity at the right time, at the right place



Proteins enable a diverse spectrum of complex chemical reactions that are important for our body to function properly. Some of these chemical reactions require special ingredients, such as energy. Others must proceed in strictly confined reaction chambers within the cells of our body as they could be harmful to other compartments of the cell. Chemical reactions must, therefore, be controlled and enabled by specialized molecules known as enzymes, the chemists among our body's proteins.

Legumain is such a molecular chemist with tasks in cellular waste recycling and safety maintenance. To do so, legumain is usually confined to lysosomes, cellular recycling centres for dispensable and damaged proteins, where it degrades waste proteins and participates in the immune surveillance of the degraded fragments for possible threats.

We found that legumain can moonlight and, rather than degrade proteins, assemble new proteins and protein complexes within the cell. The assembly program is triggered by pH which is acidic in the lysosome, but neutral in most other cellular compartments. Therefore, location is of particular importance for legumain, as a cellular relocation will often trigger a switch from the degradation to the assembly program. Indeed, such relocation was found in pathological situations, in particular in cancer and Alzheimer's disease. In either situation legumain was found translocated from the cells' lysosome.

These findings provide new treatment options. Legumain's moonlighting activity can be exploited as a diagnostic sensor of the disease state and provides a target point for therapeutic intervention. Future smart drugs will capitalize on the distinct enzymatic activities of legumain. Such smart drugs are not inactivating legumain completely, but only stop the enzymatic activity relevant for the disease in question. It is about doing the right thing at the right place at the right time.

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