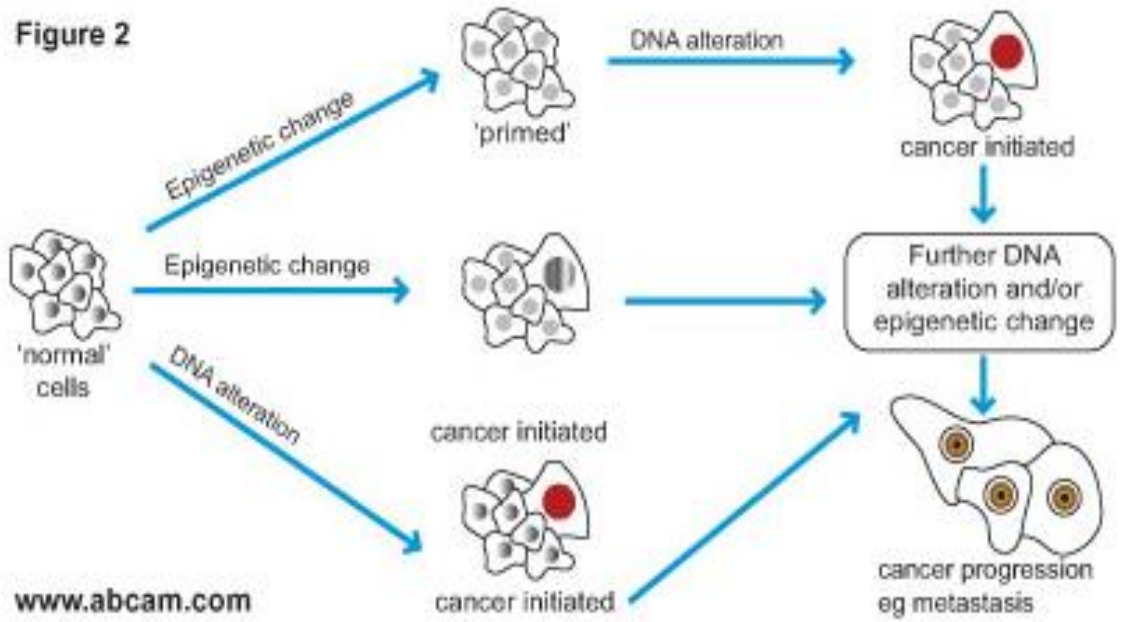
Malignant transformation
Metabolism

MUDr. Jaromír Gumulec, Ph.D.
Dept. Of Pathological Physiology
Faculty of Medicine – Masaryk University

Malignant transformation

- The process of tumor formation is a **complex** involving multiple alterations of cells and their physiologic control mechanisms.
- The complexity of this process is reflected in the **long time periods** required for most human cancers to develop.
- Multi-step tumor progression can be depicted as a form of **Darwinian evolution** occurring within tissues.
- Some of the critical changes occurring during tumorigenesis are **epigenetic** and the rate of genetic diversification can occur very rapidly.

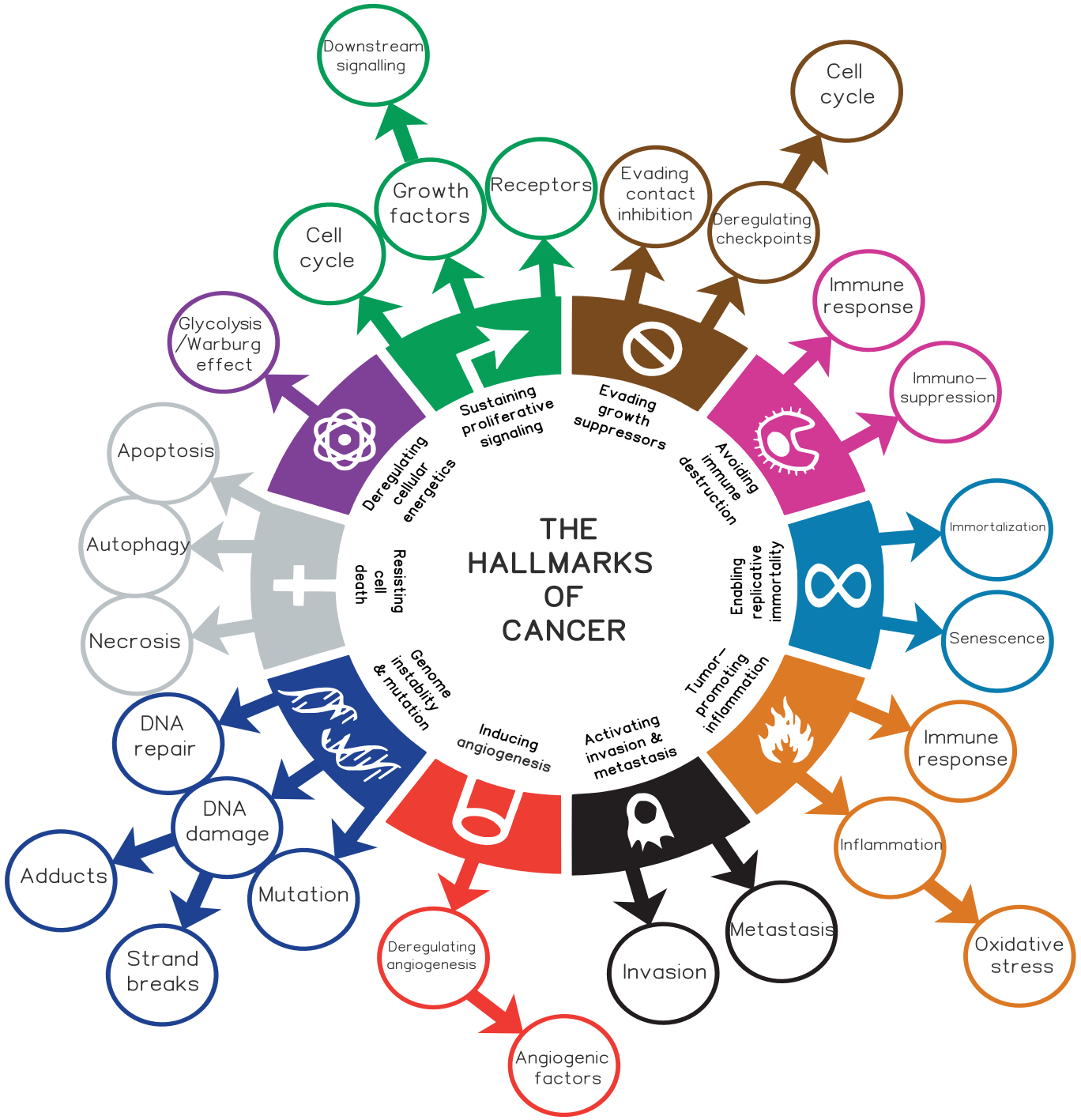


Genetic alteration can appear
– (1) due to internal errors during DNA replication and cell division
– (2) as a consequence of exposure to the external factors (**carcinogens**)
physical – e.g. UV and ionising light
chemical – organic substances, toxins, heavy metals
biologic – some RNA and DNA viruses

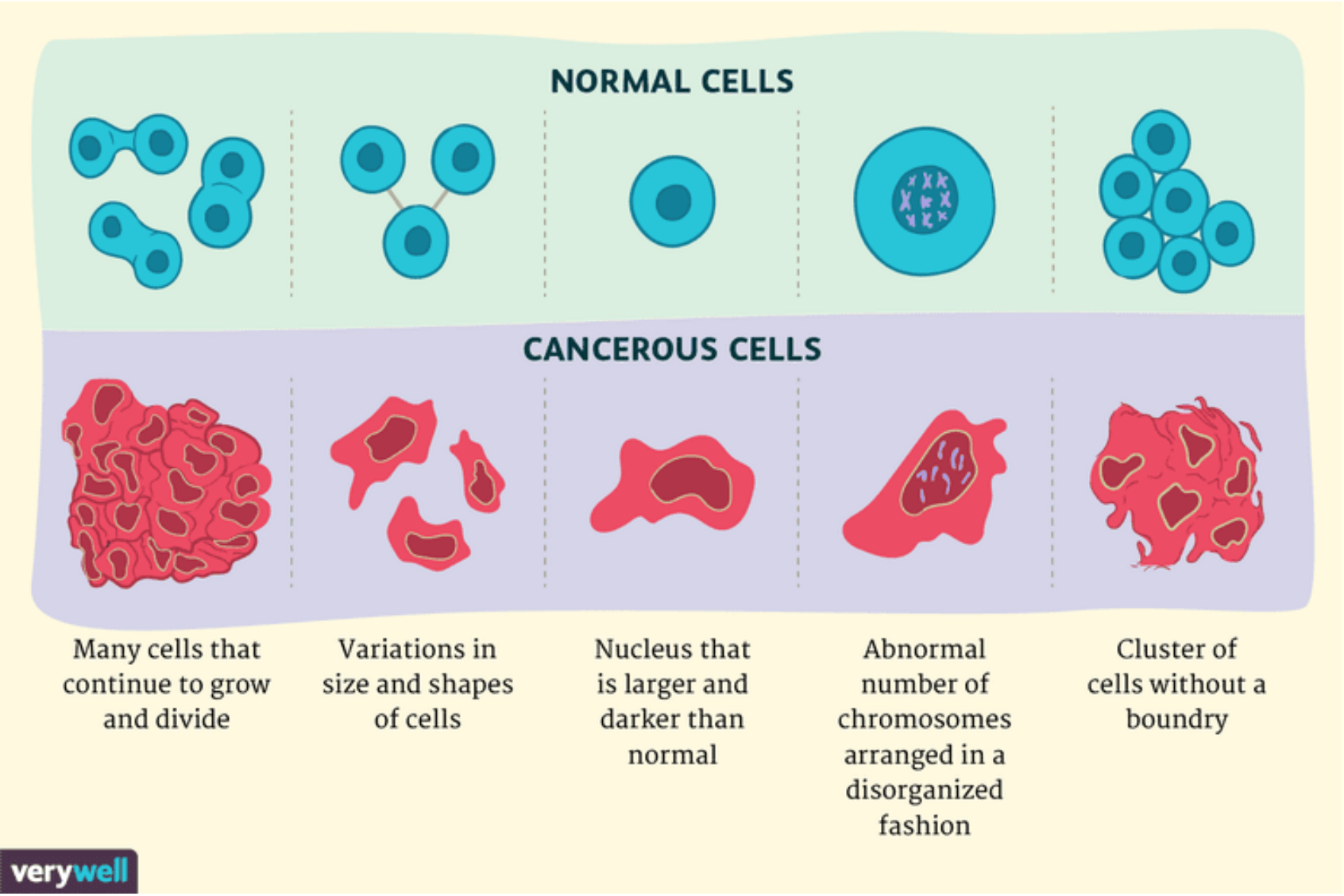
Hallmarks of cancer

Continual unregulated proliferation of cancer cells (sustaining proliferative signaling and evading growth suppressors)
Replicative immortality
Genome instability
Resisting cell death and senescence
Inducing angiogenesis
Inflammation
Avoiding immune destruction
Altered metabolism
Invasion and metastasis

All these features do not have to be newly evolved, because they are part of physiological processes such as embryogenesis and wound healing. Cancer cells only use these processes in wrong intensity, time, and place. Cancer is a disease of regulation.



Cancer cell

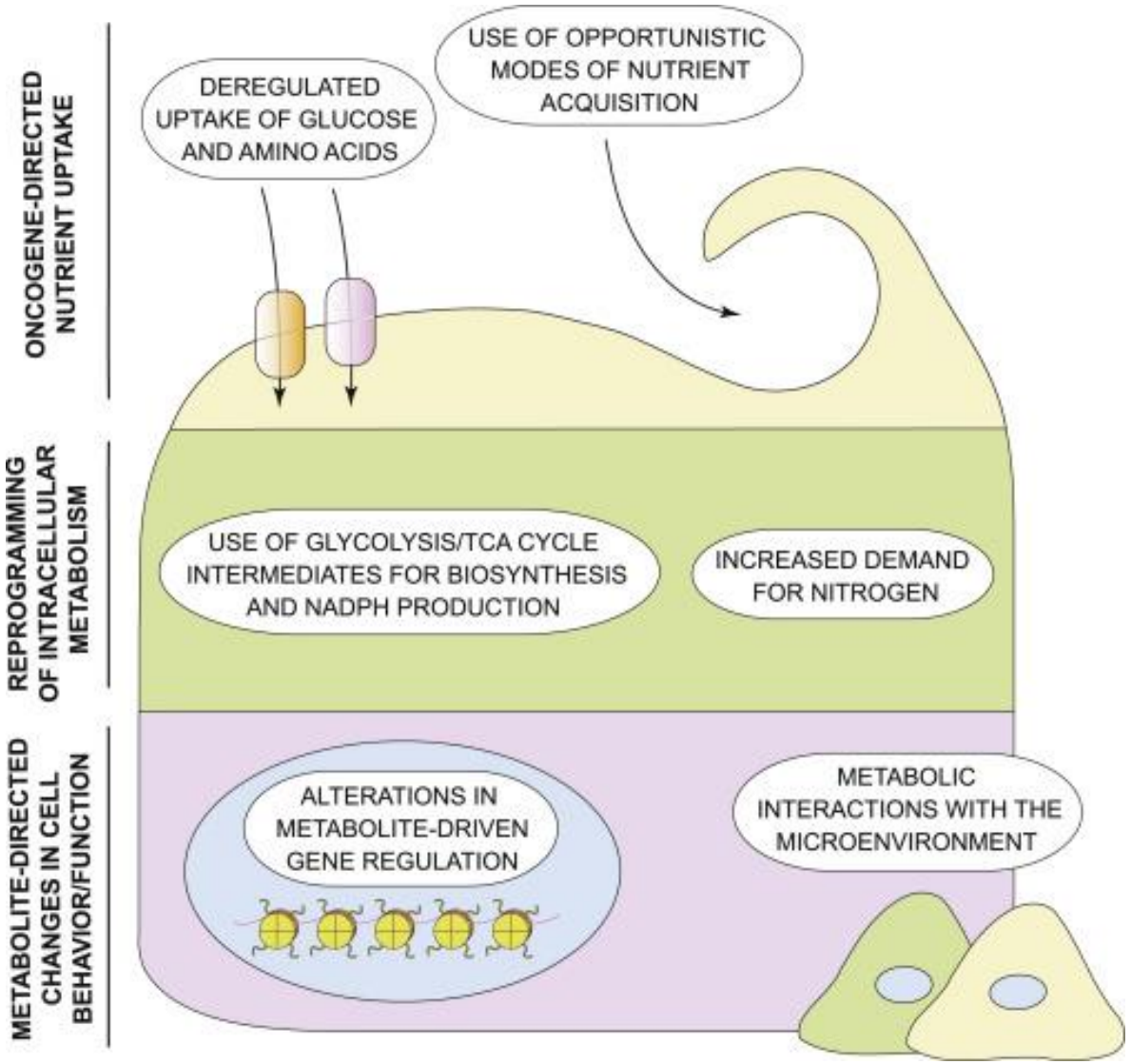


Cancer cells divide excessively - they have too many “GO” signals or not enough “STOP” signals and can also ignore “DIE”, “ DIFFERENTIATE “, or “GROW OLD” signals.

Altered metabolism

The ability to acquire necessary nutrients from a nutrient-poor (low glucosis) and hostile (hypoxia, oxidative stress) environment and utilize these nutrients to maintain viability and build new biomass.
Cancer-associated metabolic reprogramming have profound effects on gene expression, cellular differentiation, and the tumor microenvironment.
These adaptations involve an ability to access normally inaccessible nutrient sources.

Hallmarks of cancer metabolism



(1) deregulated uptake of glucose and amino acids
(2) use of opportunistic modes of nutrient acquisition
(3) use of glycolysis/TCA cycle intermediates for biosynthesis and NADPH production
(4) increased demand for nitrogen
(5) alterations in metabolite-driven gene regulation – metabolites influence enzymes involved in deposition and removal of epigenetic marks.
(6) metabolic interactions with the microenvironment.

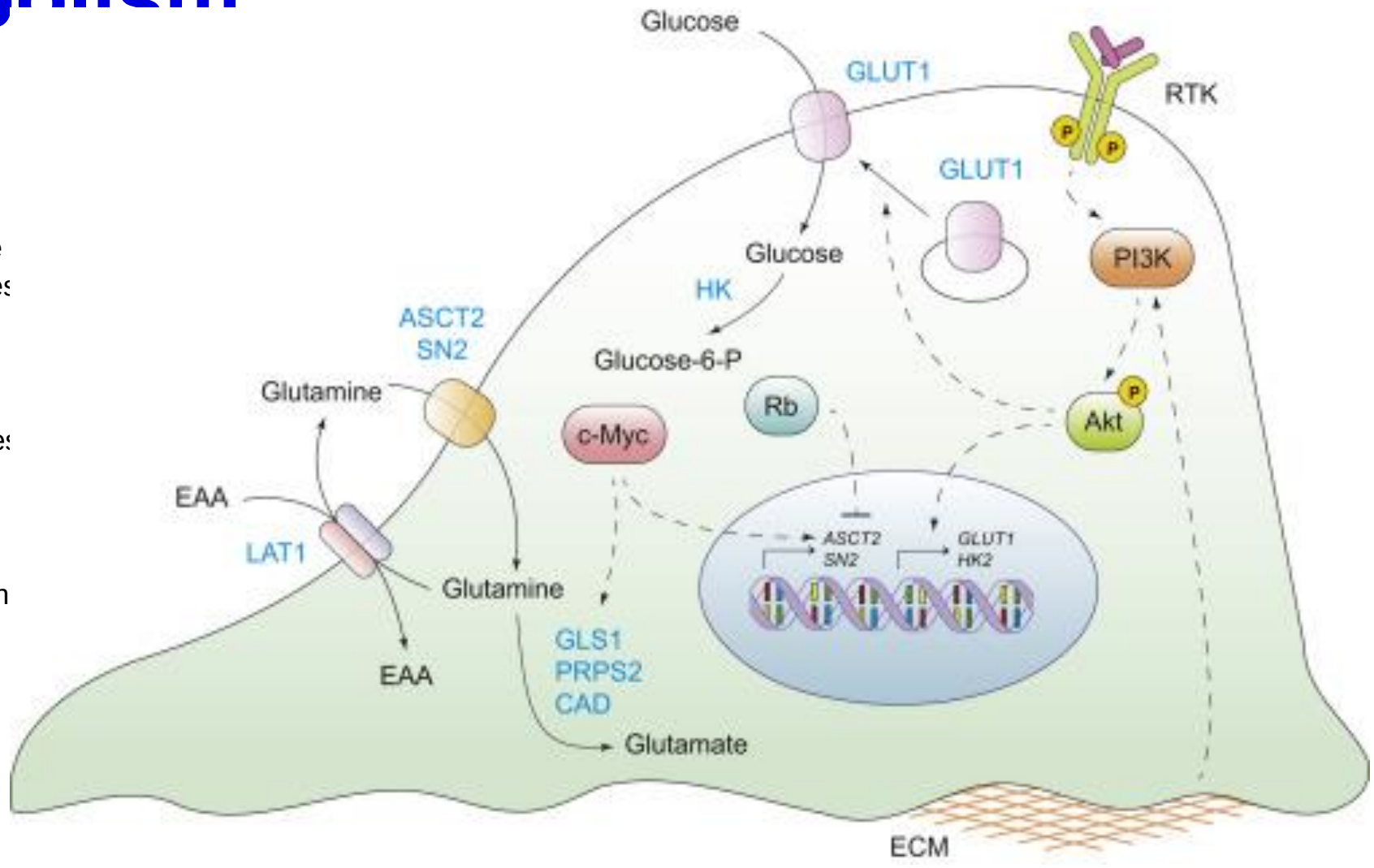
Altered metabolism

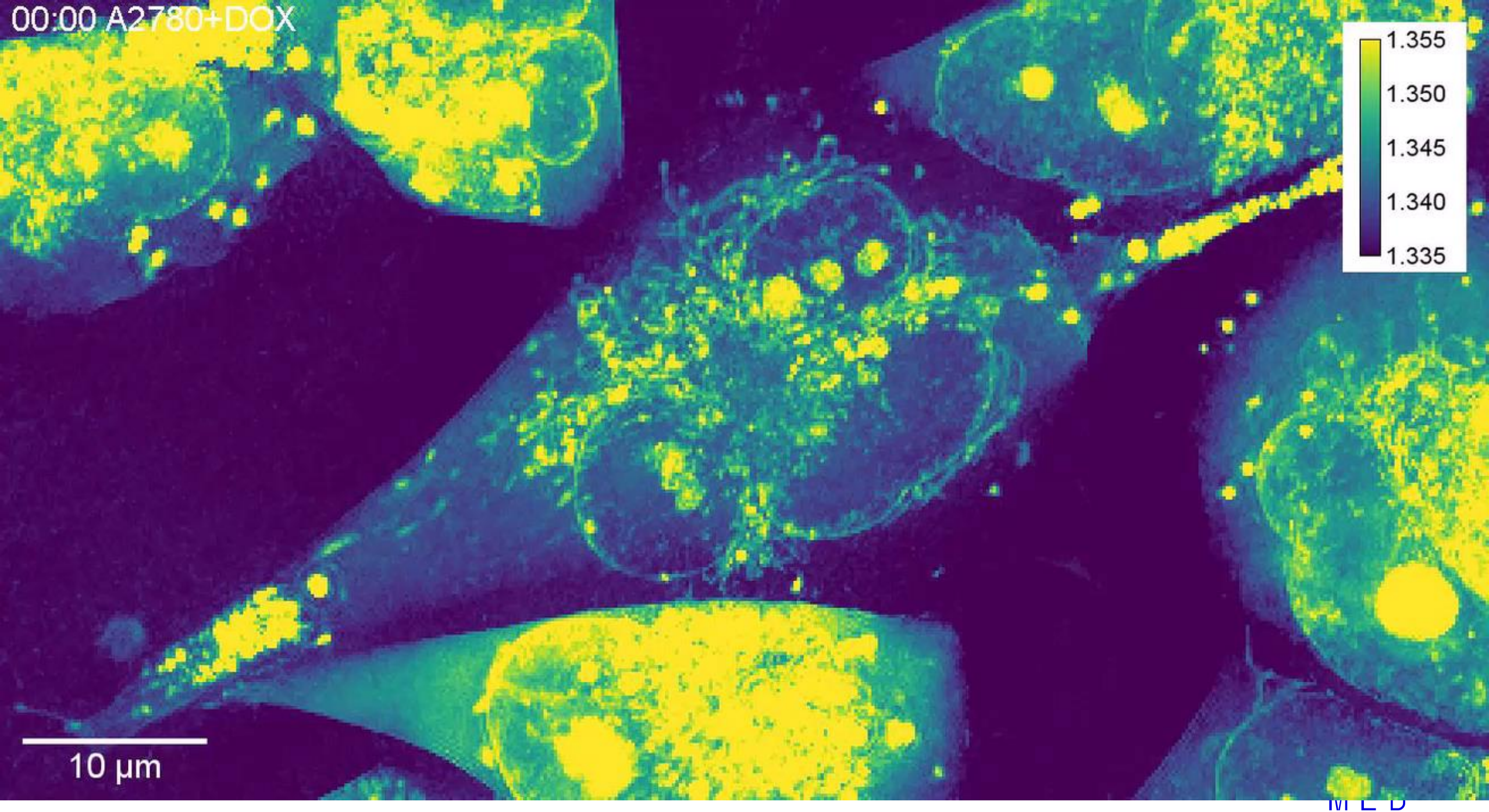
Two principal nutrients that support survival and biosynthesis are **glucose** and **glutamine**. Glutamine provides the nitrogen required for the biosynthesis of purine and pyrimidine nucleotides and nonessential amino acids.

Warburg effect - a markedly increased consumption of glucose by some tumors in comparison to the nonproliferating normal tissues

Positron emission tomography (PET)-based imaging of the uptake of a radioactive fluorine-labeled glucose analog, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) has been successfully used in the clin for tumor diagnosis.

Oncogenic signaling proteins - Ras upregulate *GLUT1* mRNA expression and increase cellular glucose consumption.

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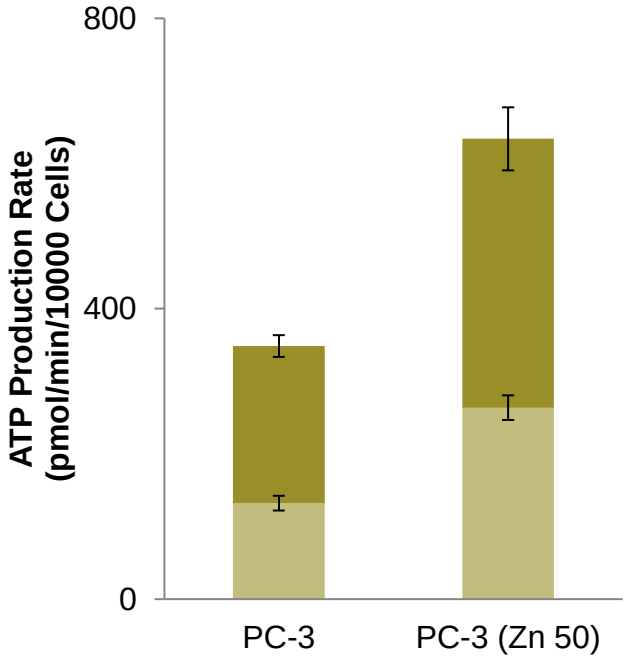
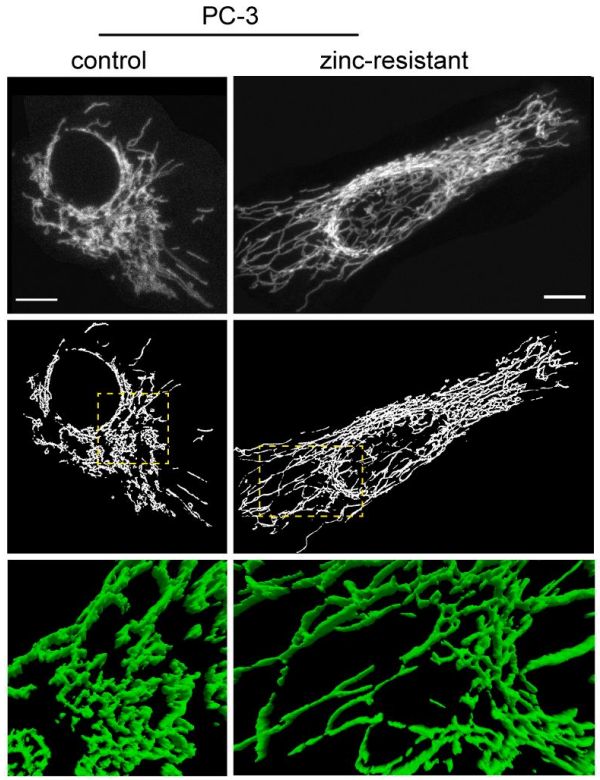
10 µm





Bilions of ATP

Our metastatic prostate cancer cells produce 3 bilions of molecules of ATP every second.

The resistant ones produces roughly doble 6 bilions of ATP. Every second.

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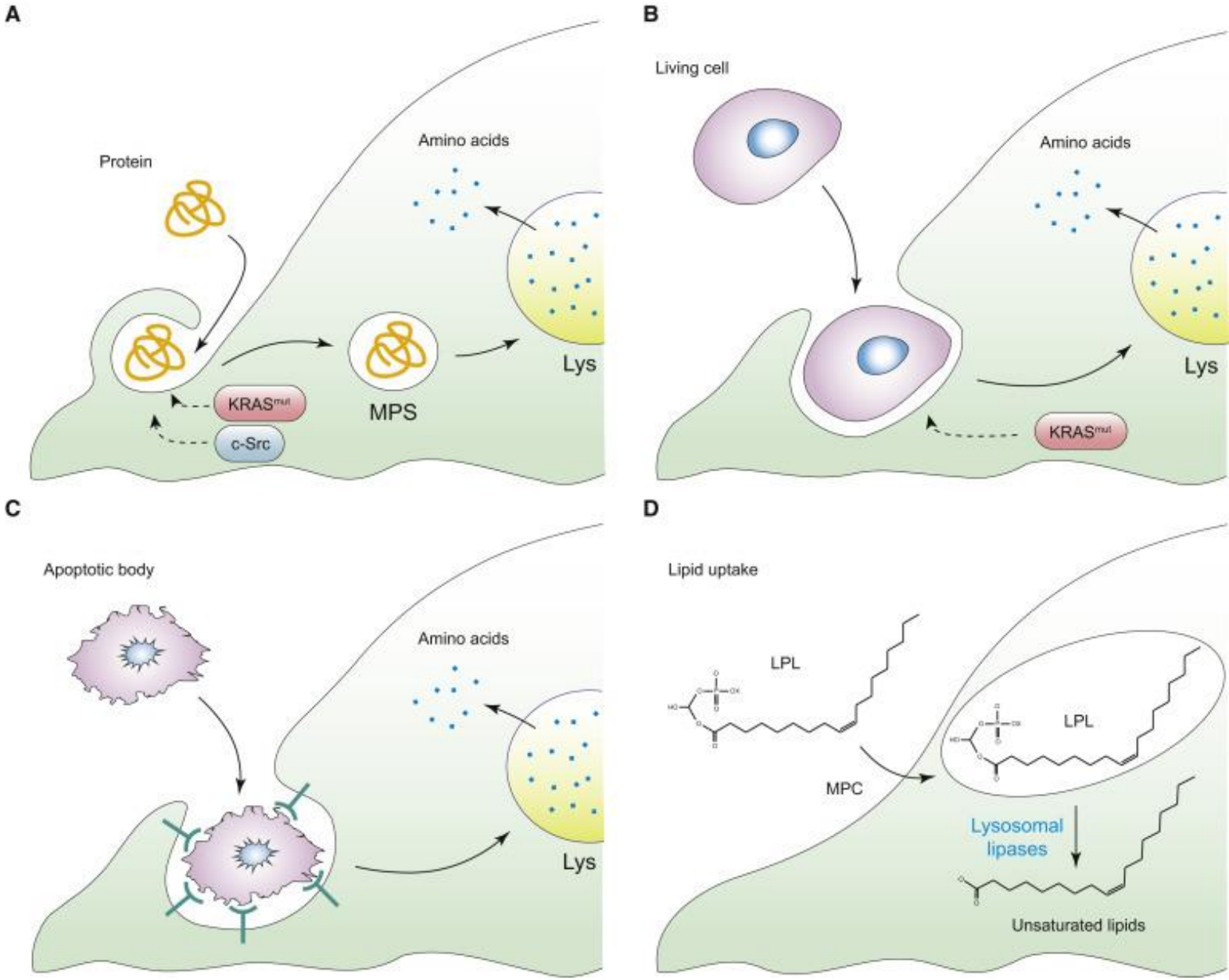
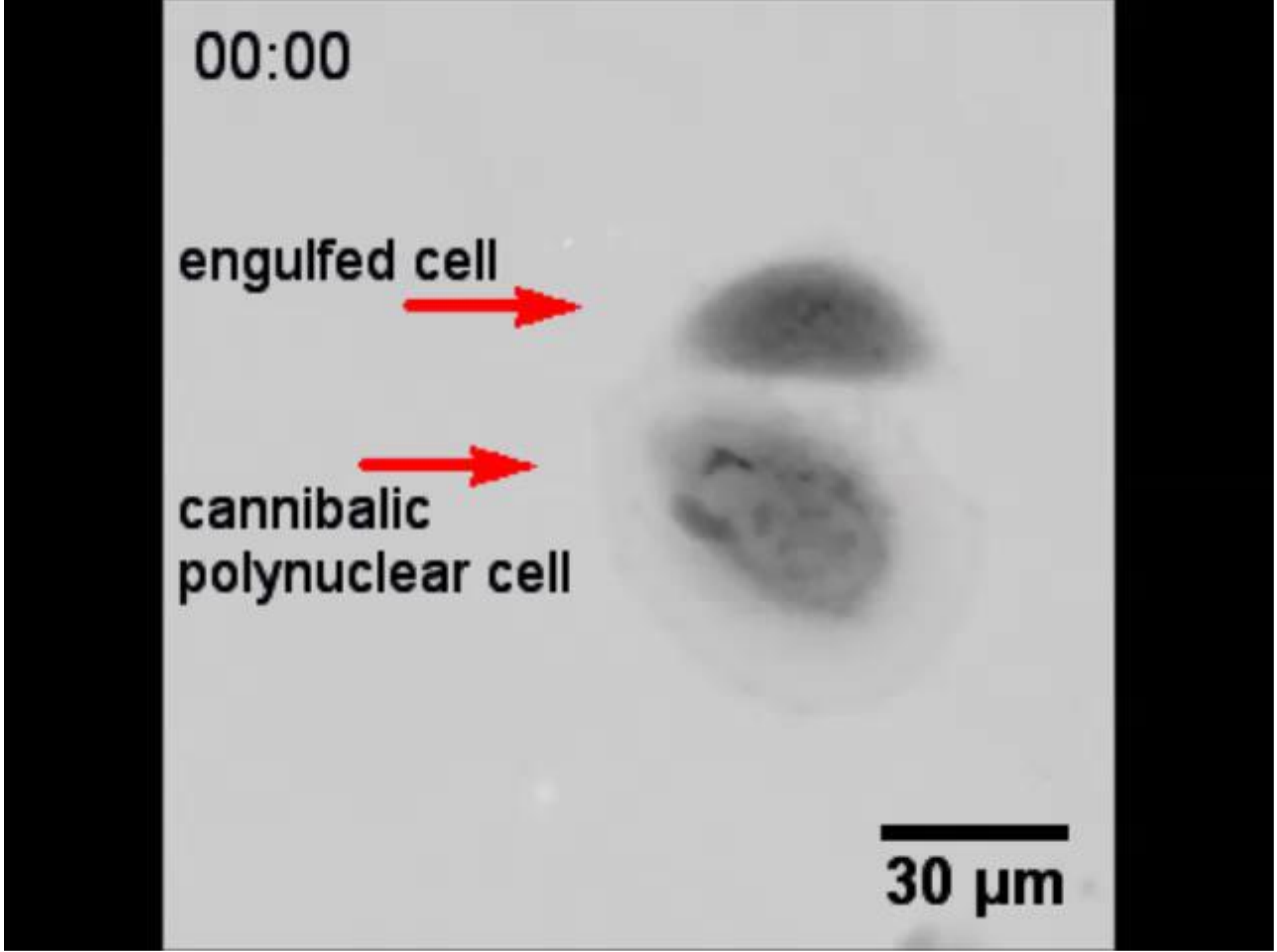
Use of opportunistic modes of nutrient acquisition

Ras or c-Src oncogenes allow to recover free amino acids through the **lysosomal degradation of extracellular proteins**.
Macropinocytosis.
Macroautophagy (autophagy cannot supply cells with new biomass and thus cannot support proliferation in nutrient-poor conditions).
Phagocytosis of apoptotic cellular corpses.
Canibalism.

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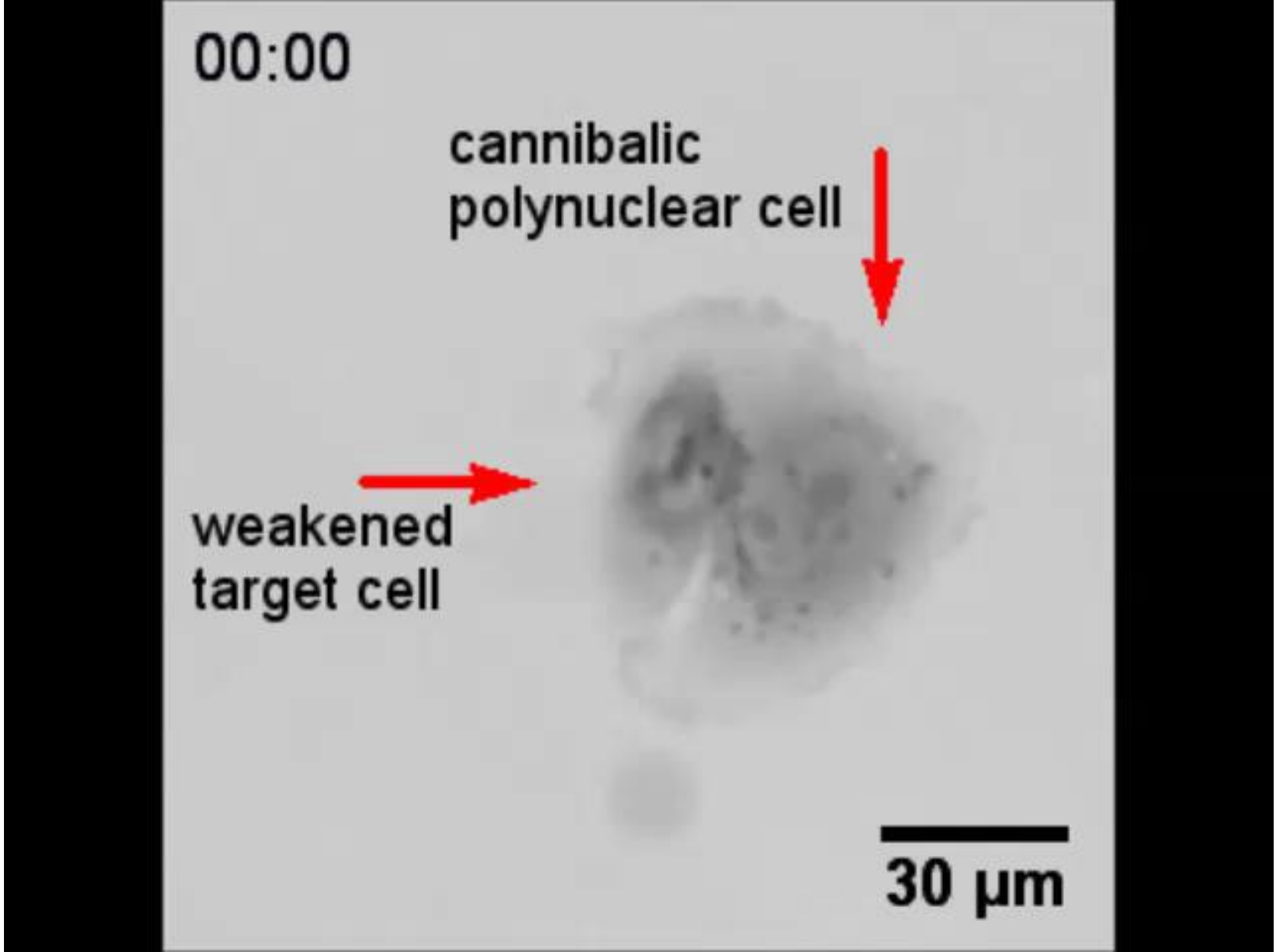
engulfed cell
cannibalic
polynuclear cell
30 µm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cannibalic
polynuclear cell
weakened
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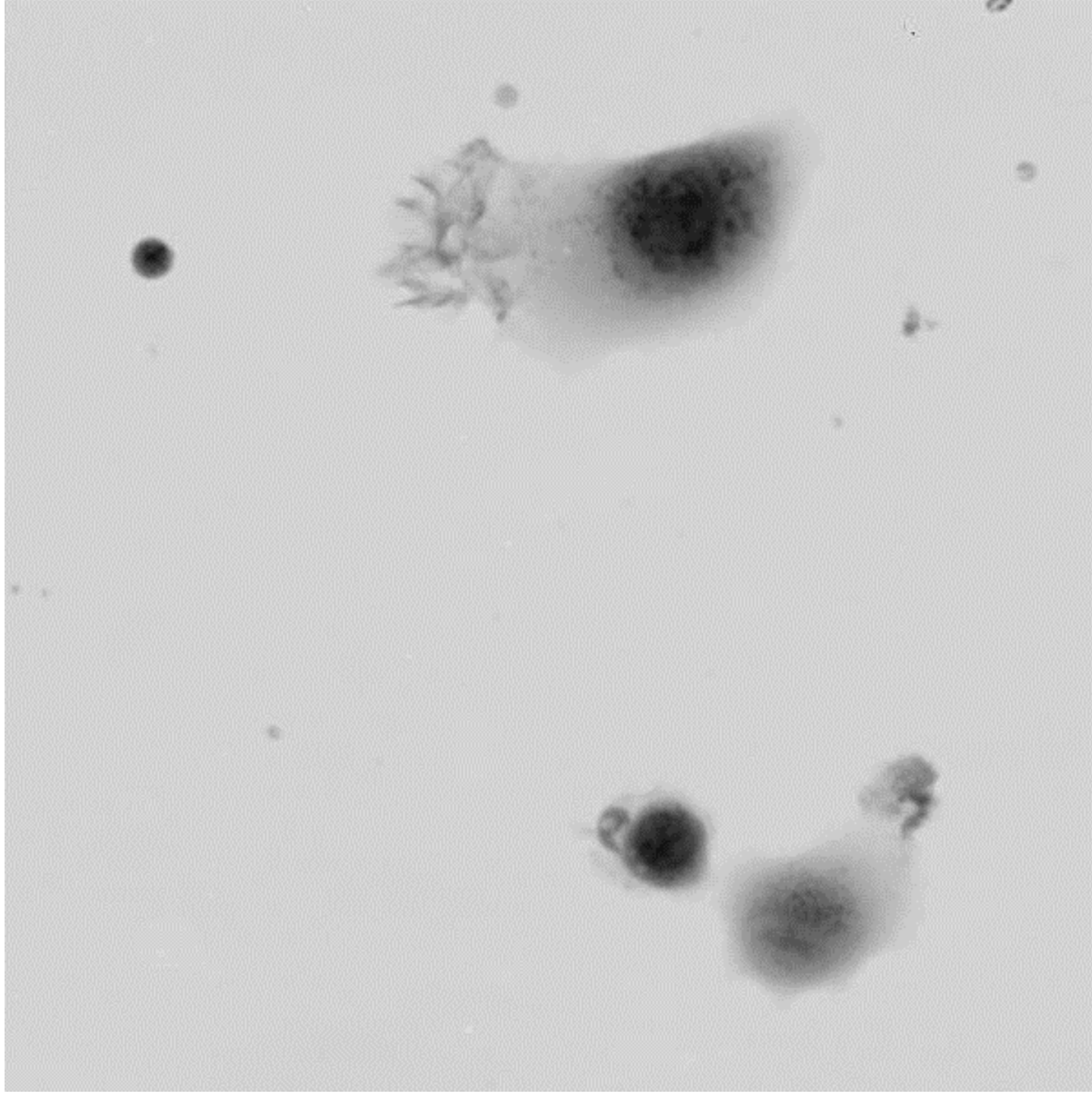
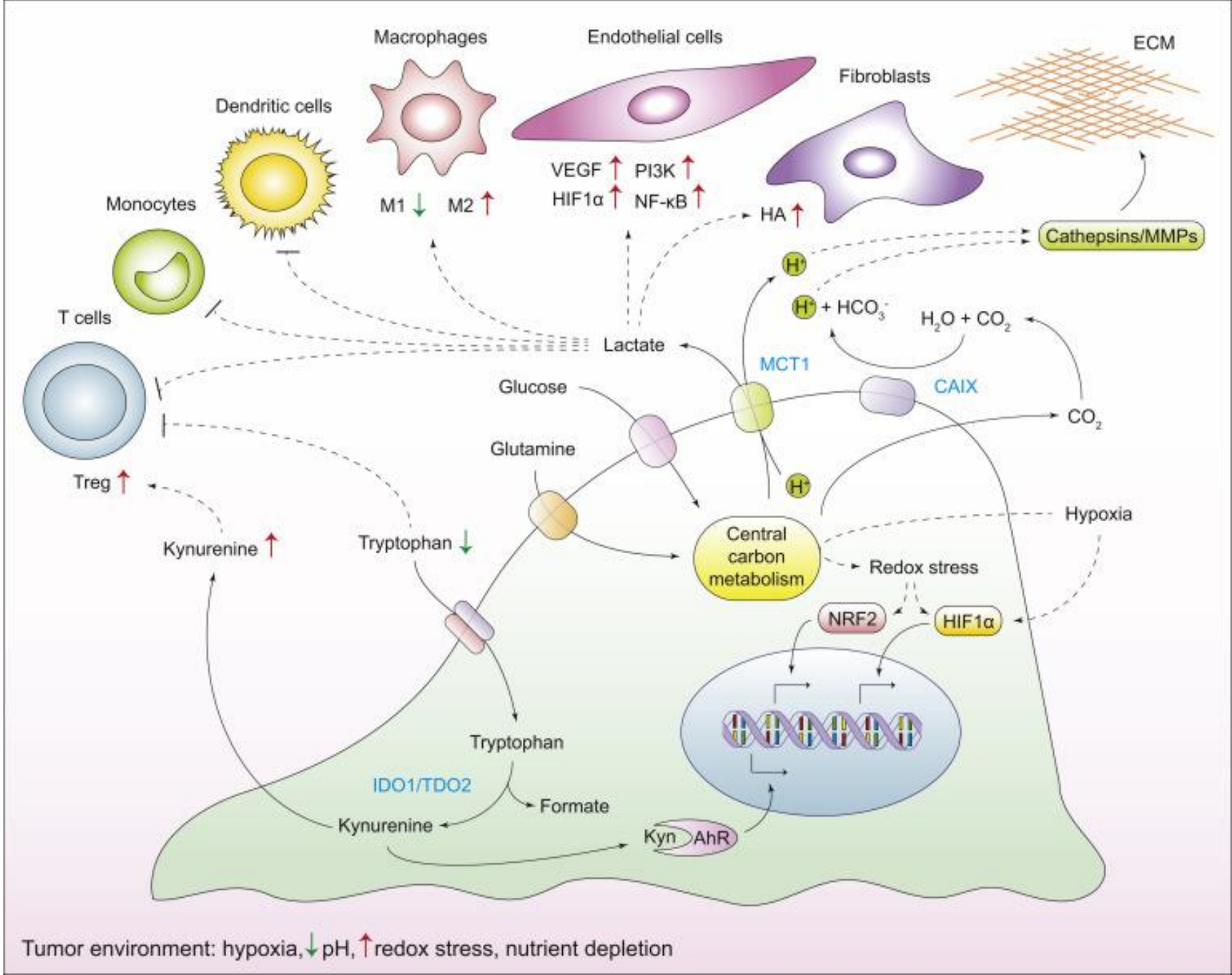


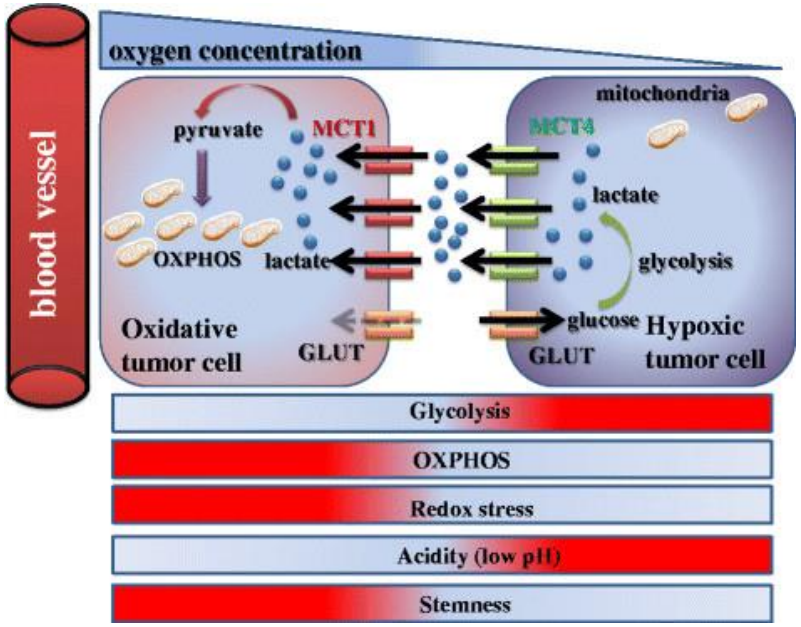
Metabolic interactions with the microenvironment

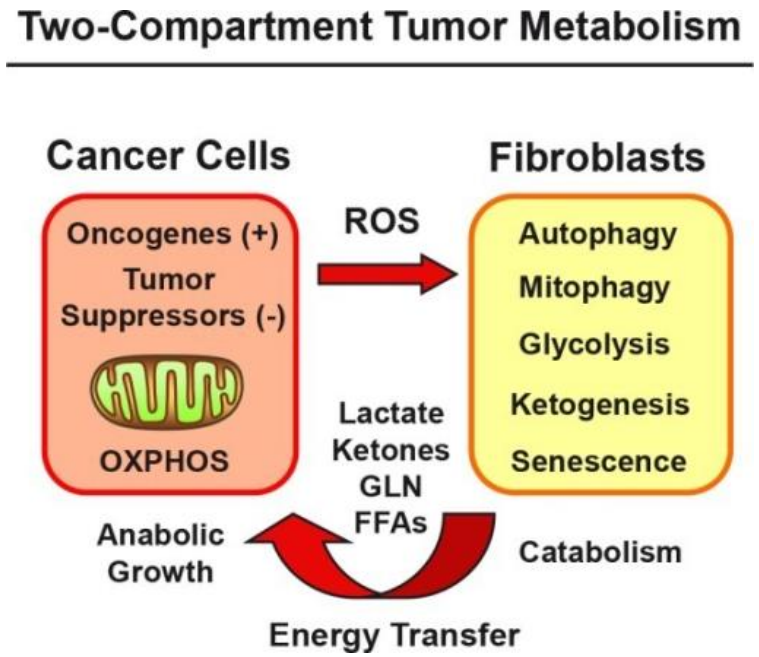
Cancer cells alter the chemical composition of the extracellular milieu, which exerts **pleiotropic effects** on the phenotypes of normal cells that reside in the vicinity of the tumor. Reciprocally, the microenvironment affects the metabolism and signaling responses of cancer cells. The high metabolic demand of cancer cells leads to an accumulation of H+ ions in tumor microenvironment – **acidosis**.



Metabolic symbiosis

Catabolic fibroblasts are rich source of energy and biomass for the growth and survival of anabolic cancer cells.
A linear path of clonal succession oversimplifies the reality of cancer; number of **genetically distinct subclones** of cells coexist within a single tumor mass: intra-tumor heterogenity - oxidative and glycolytic tumor cells in one tumor.





j.gumulec@med.muni.cz | @jarogumulec | www.med.muni.cz/masariklab