Metabolism of tumor cells

Teaching unit 15

Metabolism of tumor cells

- Tumor is a genetic disease that involves changes in the genome and consists of several complicated events.

- Loss of function of **tumor suppressor genes**

- Enabling function of **oncogene activation**

- Mutations that affect **gene stability.**

Main characteristics that every tumor cell desire

✓Unlimited replicative potential

✓Angiogenesis

✓Avoidance of apoptosis

✓Independent growth

✓Non-responsiveness to anti-growth signals

✓Tissue invasion

✓Metastasis

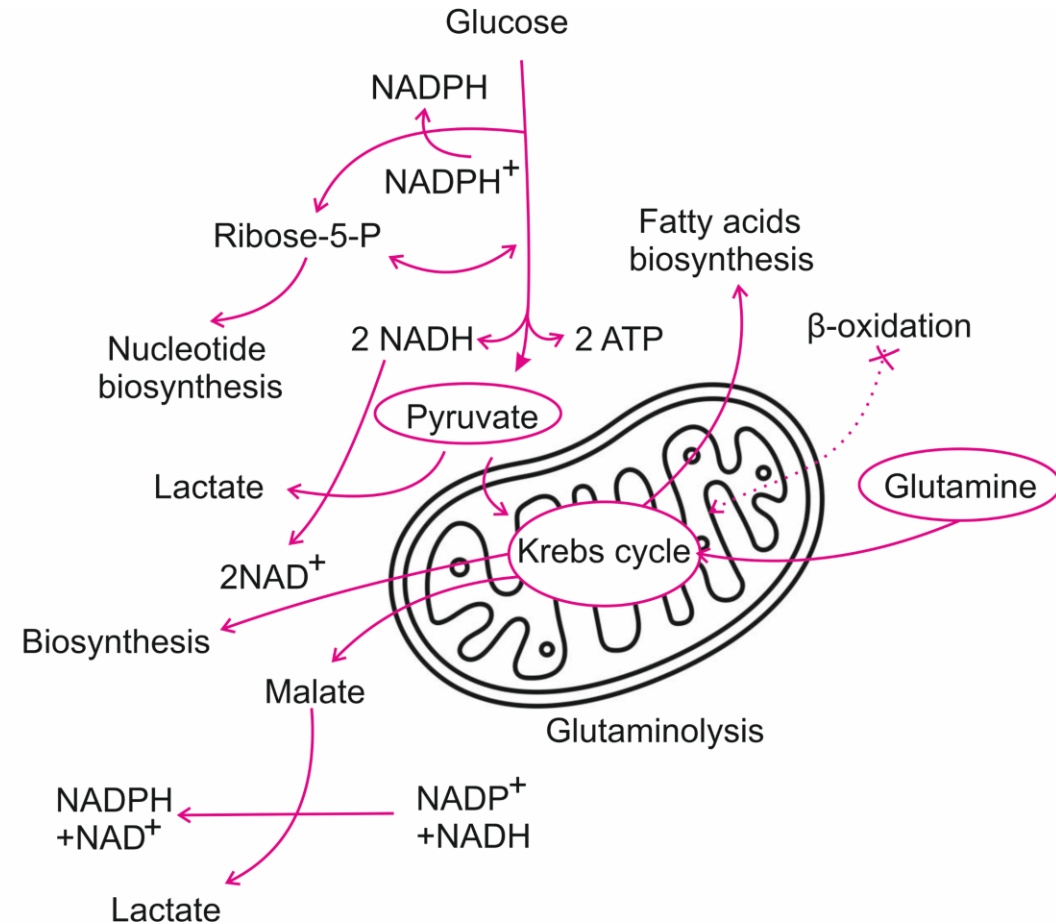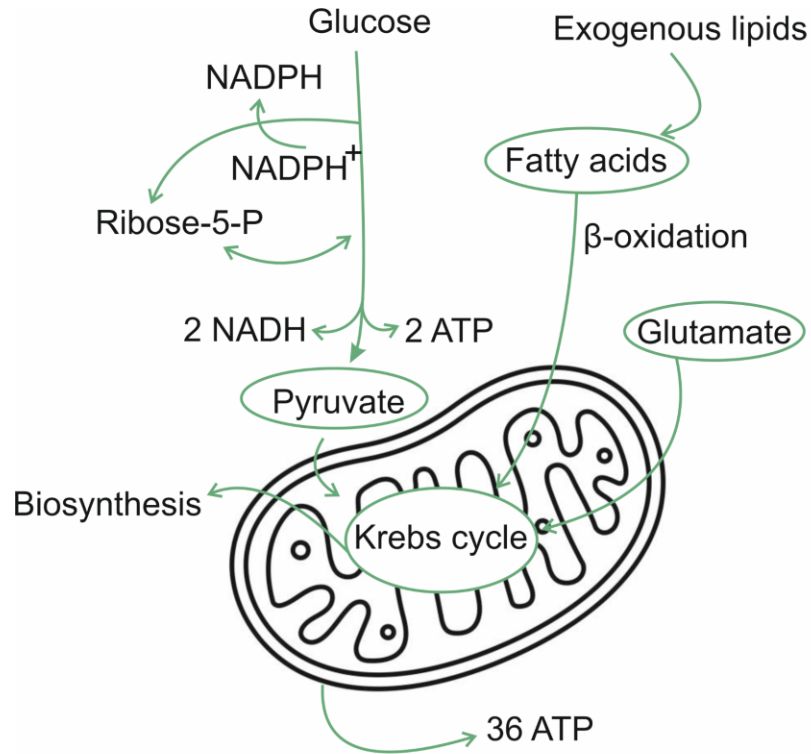# Main characteristics that every tumor cell desire

✓Unlimited replicative potential

✓Angiogenesis

✓Avoidance of apoptosis

✓Independent growth

✓Non-responsiveness to anti-growth signals

✓Tissue invasion

✓Metastasis

✓ Avoiding the immune system

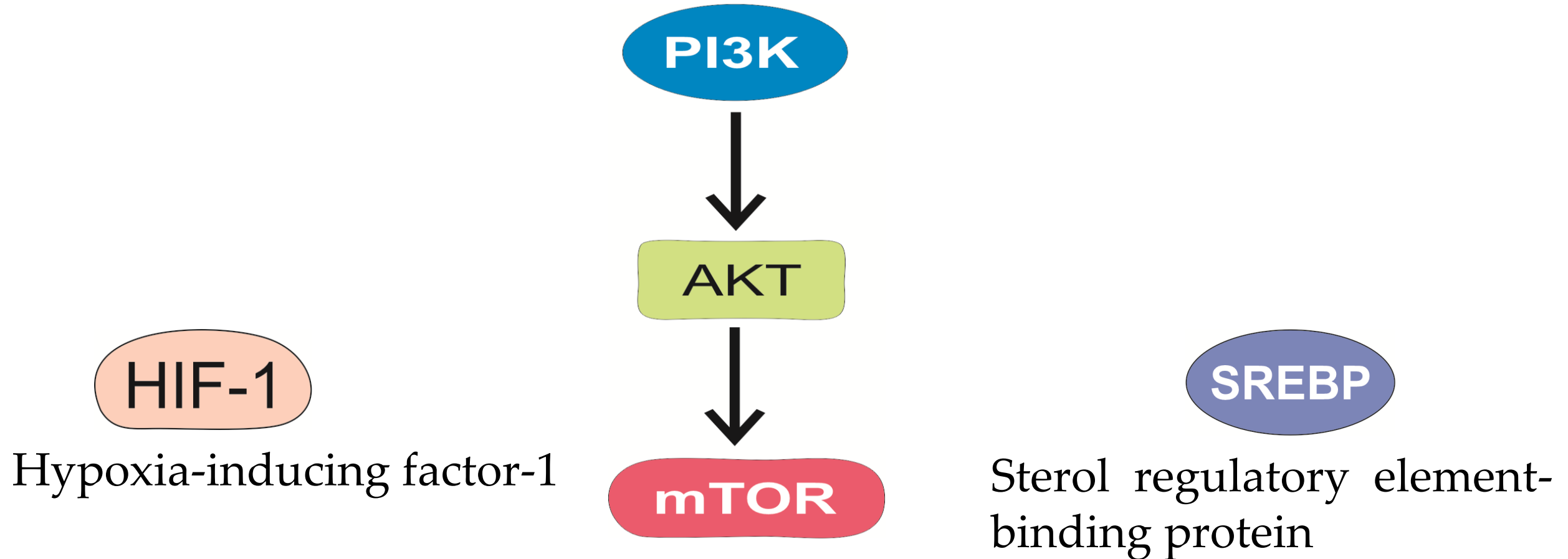✓ Reprogramming the energy metabolism

Increased proliferation = Reorganization of metabolic pathways

- Increased rates of glycolysis; high lactate production
- Tumor cells can reprogram their metabolism based on changes in the microenvironment
- Warburg effect or aerobic glycolysis
- Reaction to hypoxia in normal tissues is glycolysis
- Otto Warburg observed that tumor cells constitutively take up glucose and produce lactate, regardless of oxygen availability
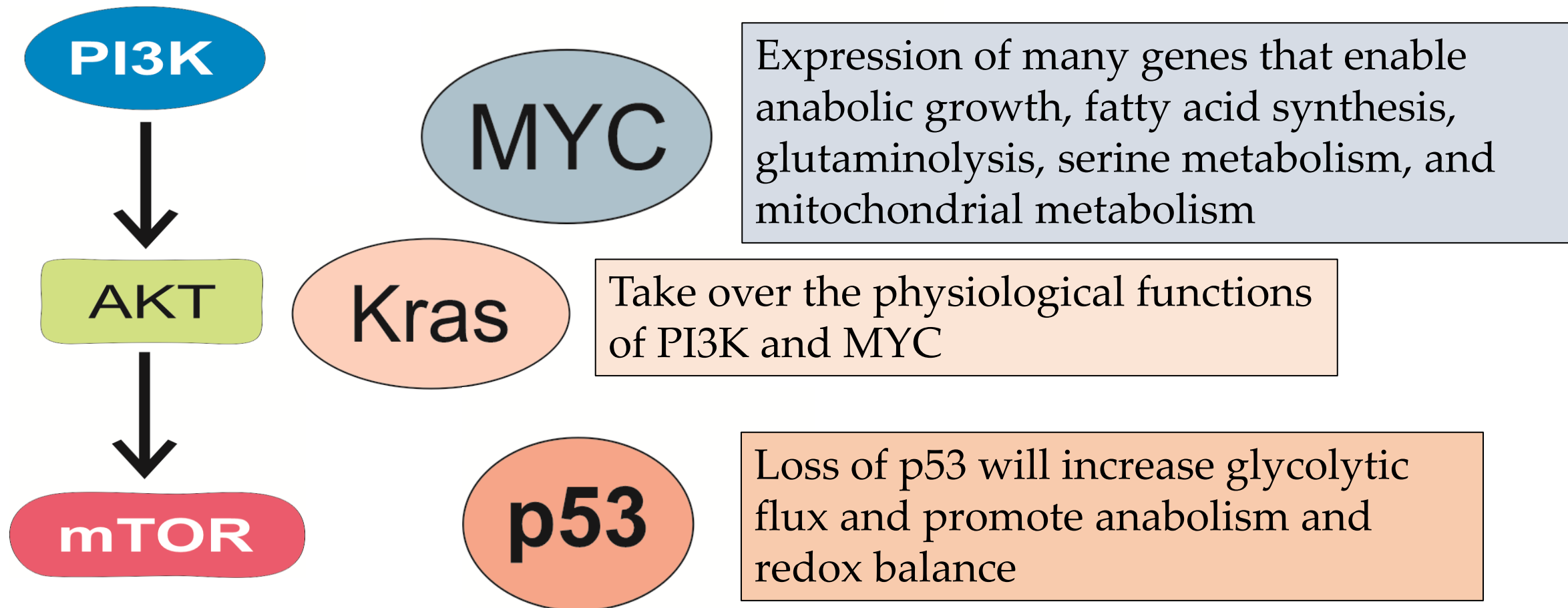
Metabolism of normal and tumor cells

Normal cells upon stimulation with growth factors, activate phosphatidyl-inositol 3-kinase (PI3K) consequently downstream AKT pathway and the mammalian target of rapamycin (mTOR)

Hypoxia-inducing factor-1

Sterol regulatory element-binding protein

Tumor cells often have mutations that enable strong activation of PI3K-AKT-mTOR signaling that is minimally dependent on growth factors

PI3K → AKT → mTOR

MYC

Expression of many genes that enable anabolic growth, fatty acid synthesis, glutaminolysis, serine metabolism, and mitochondrial metabolism

Kras

Take over the physiological functions of PI3K and MYC

p53

Loss of p53 will increase glycolytic flux and promote anabolism and redox balance

Activation of HIF-1 under hypoxia

Hyperactivation of mTORC1

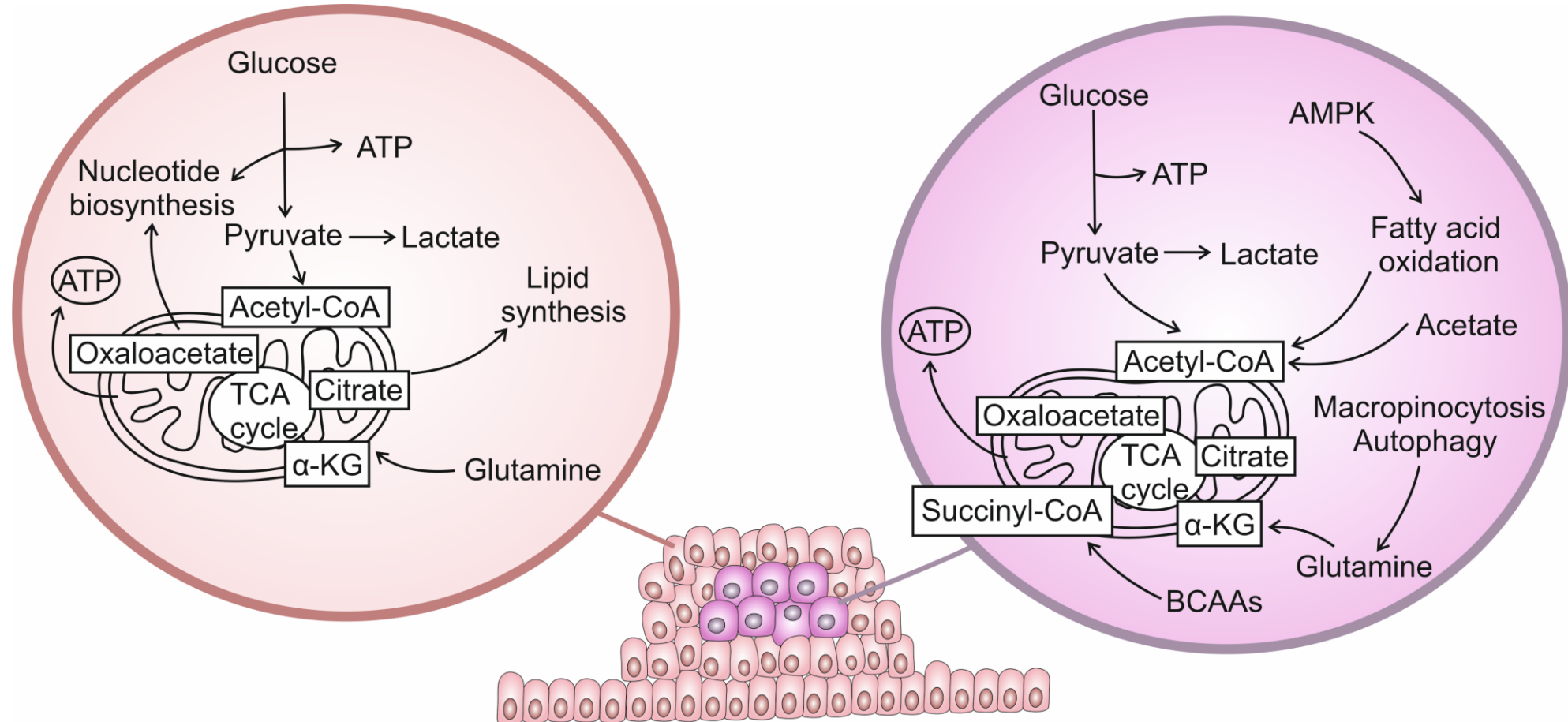Loss of VHL gene (Von Hippel–Lindau, tumor suppressor gene)

Accumulation of ROS

Accumulation of succinate and fumarate TCA cycle metabolites, caused by SDH (succinate dehydrogenase) and FH (fumarate hydratase) mutations.

Increased expression of phosphoglycerate dehydrogenase (PHGDH)

• Serine metabolism - nucleotide synthesis, methylation reactions, NADPH production

• Inhibition of serine biosynthesis – Inhibition PHGDH – growth suppression – PHGDH enzyme shows oncogenic properties

Metabolic pathways under nutrient-replete and nutrient-deprived conditions

mTOR kinase

- Inhibited when amino acid and oxygen levels ⬇

⬇ mTOR activity   autophagic flux ⬆

- Autophagy provides an intracellular glutamine supply to sustain mitochondrial function

mTOR kinase

- Protein biosynthesis is strictly regulated and requires access to essential and non-essential amino acids.

- Tumor cells and other cells under growth factor signaling express surface transporters that allow them to take up amino acids from the extracellular space.

- mTORC1 activates protein synthesis

- Tumor cells take up glutamine and convert it into glutamate $\Rightarrow$

synthesis of non-essential amino acids.

mTOR kinase

- Tumor cells rapidly produce fatty acids for membrane synthesis, lipidation reactions, and signaling.

- Fatty acid synthesis requires acetyl-CoA

- Transcription of genes involved in fatty acid synthesis is regulated by the transcription factor SREBP-1

- SREBP-1 regulates not only the enzymes needed to convert acetyl-CoA into fatty acids but also the enzymes of the PPP and pathways required to convert acetate and glutamine into acetyl-CoA

mTOR kinase
fatty acid synthesis

- mTORC1 signaling
- Effector S6 kinase (S6K)
- SREBP-1; SREBP-2
- mTORC1-mediated cell proliferation
- Fatty acids and lipids can also be obtained from the extracellular space, for membrane synthesis.
- PI3K signaling activates fatty acid uptake and suppresses fatty acid oxidation

Synthesis of RNA and DNA

- Purine and pyrimidine nucleotides

- Constructed from various nonessential amino acids and methyl groups donated from the one-carbon/folate pool

- Oxaloacetate ⟶ aspartate

- Conversion of ribonucleotides to deoxynucleotides by ribonucleotide reductase requires a source of NADPH

Redox balance

- ROS; oxygen; superoxide anion; hydrogen peroxide; hydroxyl radical

- mitochondria and cytosolic NADPH oxidases (NOXs) produce O_2^- from the one-electron reduction of oxygen. O_2^- is converted into H_2O_2 by the enzymatic activity of superoxide dismutase 1 or 2, which are localized to the cytosol or mitochondrial matrix, respectively. H_2O_2 is subsequently detoxified to water by the enzymatic activity of mitochondrial and cytosolic peroxiredoxins (PRXs), which, as a consequence, undergo H_2O_2-mediated oxidation of their active-site cysteines

Redox balance

- Thioredoxin (TXN), thioredoxin reductase (TrxR), and the reducing equivalent NADPH reduce oxidized PRXs to complete the catalytic cycle. Glutathione peroxidases (GPXs) can also convert H_2O_2 to water in the mitochondrial matrix and cytosol through H_2O_2-mediated oxidation of reduced glutathione (GSH). Glutathione reductase (GR) and NADPH reduce oxidized glutathione (GSSG) back to GSH.

Redox balance

- Catalase, an abundant antioxidant in peroxisomes, can detoxify H_2O_2 to water without any cofactors. However, in the presence of ferrous or cuprous ions, H_2O_2 can become OH· and quickly cause the oxidation of lipids, proteins, and DNA, resulting in cellular damage

- NADPH is required to maintain multiple antioxidant defense systems. The cytosol has multiple sources of NADPH generation, including the oxidative PPP, malic enzyme 1, IDH1, and one-carbon metabolism. NADPH generation in the mitochondria, in part, is controlled by one-carbon metabolism and IDH2.

Redox balance

- Low levels of ROS, H_2O_2, can reversibly oxidize the cysteine residues of proteins to positively regulate cell proliferation and cellular adaptation to metabolic stress
- As H_2O_2 levels increase, however, cell death signaling pathways are initiated, and H_2O_2 is converted to OH·, which can directly damage DNA, proteins, and lipids
- Activation of oncogenes, PI3K signaling pathway induction, and hypoxia stimulate the increased rate of ROS production from the mitochondria and NOXs in cancer cells
- Mitochondria-targeted antioxidants and NOX inhibitors can prevent cancer cell proliferation, hypoxic activation of HIF, tumorigenesis, and metastasis

Redox balance

- Cancer cells have higher levels of ROS scavenging enzymes than normal cells, preventing ROS-mediated activation of death-inducing pathways like c-Jun N-terminal kinase (JNK) and p38 MAPK and oxidation of lipids, proteins, and DNA, resulting in irreversible damage and cell death.

- One mechanism by which cancer cells increase their antioxidant capacity is by activating the transcription factor nuclear factor (erythroid derived 2)–related factor-2 (NRF2).

Redox balance

- NRF2 also regulates the serine biosynthesis pathway; NADPH in the mitochondria

- Inactivating NRF2 or disabling antioxidant proteins in cancer cells would allow for the accumulation of excessive amounts of ROS to levels that initiate toxicity and reduce tumorigenesis

Redox balance

Tumor initiates metabolic activity of cancer cells is increased. Increase in ROS production and activation of signaling pathways that support cancer cell proliferation, survival, and metabolic adaptation.

To prevent toxic levels of ROS, tumor cells increase their antioxidant capacity to allow cancer progression. Increases ROS levels due to hypoxia, and the low glucose levels limit flux through the cytosolic oxidative PPP, thus decreasing cytosolic NADPH levels.

Cells in these nutrient-deprived conditions activate AMPK to increase NADPH levels by stimulating PPP dependent NADPH and diminishing anabolic pathways, such as lipid synthesis, that require high levels of NADPH. ROS-dependent signaling and increased mitochondrial respiration are also necessary for tumor metastasis

Redox balance

Tumor cells detach from a matrix, they encounter high levels of ROS that incur cellular damage and require activation of adaptive ROS-mitigating pathways to survive and grow.

The ability to up-regulate antioxidant proteins and increase flux through NADPH-producing metabolic pathways enables distant metastasis to occur.

Perhaps disabling antioxidant capacity in cancer cells to raise ROS levels might be beneficial in preventing metastasis.

Therapy based on a tumor metabolism

- Metabolic enzymes inhibition = toxic
- Immune cells and stem cells in some cases = tumor metabolism
- Nucleotide and DNA synthesis can be targeted by antifolates
- Targeting multiple metabolic pathways simultaneously
- Targeting a particular metabolic pathway in combination with other ways of cancer therapy

Therapy based on a tumor metabolism

- Glycolysis
- LDH-A, a metabolic enzyme that converts pyruvate to lactate, first metabolic target of the oncogene MYC
- Inhibition of LDH-A diminish MYC-driven tumors in xenograft models
- LDH-A inhibition leads to the regression of established tumors in genetically engineered mouse models of NSCLC (Non-small cell lung cancer) without systemic toxicity.
- Genetic ablation of LDH-A delays the progression of myeloid leukemia

Therapy based on a tumor metabolism

- Many tumor cells overexpress HK2

- HK2 inhibition delays tumor progression.

- Lactate can inhibit cytotoxic T cells, so LDH-A inhibition may cooperate with immune checkpoint inhibitors to unleash host inflammatory T cells that will specifically attack tumor cells.

- Lactate can also reprogram macrophages to promote tumorigenesis.

Therapy based on a tumor metabolism

- Phosphoglycerate dehydrogenase; PHGDH; enzyme in the de novo serine synthesis pathway

- High levels of PHGDH; found in a subset of human melanoma and breast cancers

- In many cancer types, SHMT2 expression is elevated and correlates with a poor prognosis

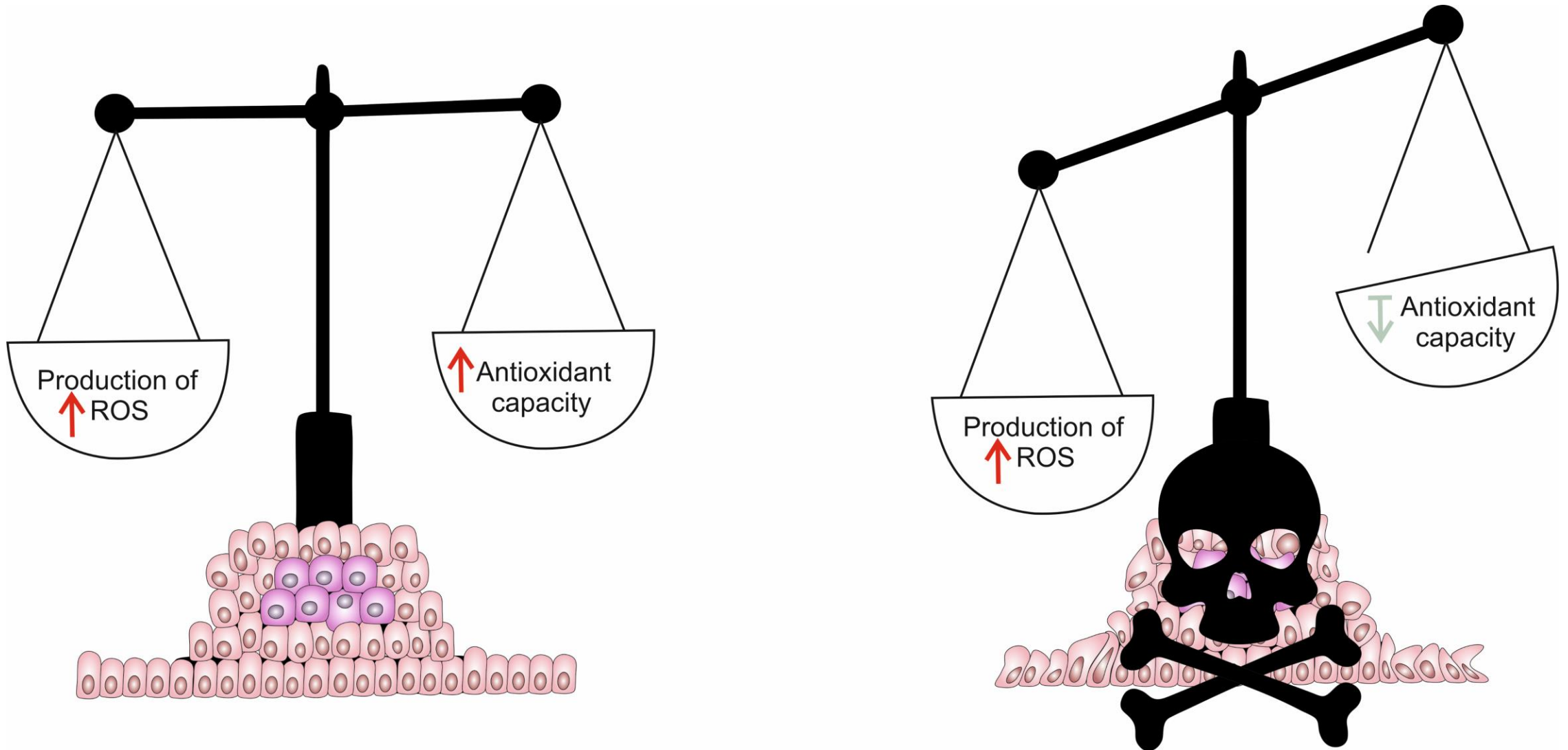- MYC and HIF induce SHMT2 under hypoxia to promote survival

Therapy based on a tumor metabolism

- Mitochondrial metabolism key target for tumor therapy
- Metformin
- Inhibits mitochondrial ATP production
- Inducing cancer cell death when glycolytic ATP levels diminish as a result of limited glucose availability
- Inhibits the biosynthetic capacity of the mitochondria to generate macromolecules
- Safety profile of metformin is due to its uptake by organic cation transporters (OCTs), which are only present in a few tissues, such as the liver and kidney.
- Identify the tumors with highest expression of OCTs

Therapy based on a tumor metabolism

- Use of autophagy or glutaminase inhibitors
- Autophagy provides amino acids, such as glutamine, that fuel the TCA cycle
- Target acetate metabolism
- Mitochondria provide acetyl-CoA to the cell, cancer cells can also use acetate to support cell growth and survival during metabolic stress
- Acetyl-CoA synthase 2; acetate to acetyl-CoA

Therapy based on a tumor metabolism

Therapy based on a tumor metabolism

- NADPH-generating systems; critical for cell survival
- ✓G6PDH; NADP+ to NADPH
- ✓Mitochondrial one-carbon metabolism protein;MTHFD2; generate NADPH
- Vitamin C; DHA
- NRF2; SOD1