Cancer cell metabolism

- Normal cells use the TCA cycle and undergo oxidative phosphorylation, produce 32~34 glucose per ATP
    - Warburg effect in cells, increase in glycolysis and oxidative glycolysis (increased lactic acid output even with sufficient oxygen). This is because oxidative phosphorylation produce more carbon-rich intermediates, provide carbon for biosynthesis, less metabolic ROS production.
    - As cancer cell stage progresses, resistance to oxidative stress increase/reliance on oxidative phosphoylation increase.

Variability in cancer cell metabolism

- Constant proliferation of cancer cells - rapid Darwinian selection model, increase in genetic variation.
- Spectrum of metabolic niche and differentiated states - between different tumour types
- Cancer types with more differentiated tumour cells (e.g. Renal, colon, pancreas) requires less glucose and oxygen
- Cancer types with more cancer stem cells (e.g. lung, ovarian, leukemia), requires higher O2 and glucose levels.
- Cancer adapt to metabolise unusual types of nutrients (e.g. ketone, acetate, ammonia)

Selection pressure: biosynthesis capacity—>cell-type specific metabolism (parental tissue or metastasis tissue), oxidative phosphorylation and treatment resistance in tumour after angiogenesis

Tumour metabolism influenced by intrinsic + extrinsic factors

- Patient metabolism: diet, metabolic diseases (diabetes)
- Tumour microenvironment: nutrient availability, mechanical structure
- Parental tissue: location in the body, epigenetic regulation, genetic regulatory network
- Intrinsic effect: effect of mutation, aberration in signalling pathway

Myc: regulator for biogenesis pathways (glucose metabolism, protein synthesis, nucleotide, lipid, amino acid synthesis)

HIF1α: Switch upregulating oxidative glycolysis

- Only active in hypoxic normal cells. Active in tumour cells regardless of O2 availability
- Usually hydroxylated, ubiqutinated by E3 ubiquitin ligase, and degraded, but activated in tumour cells due to hyperactive AKT-mTOR pathway.
- Promote neoangiogenesis, upregulate expression of VEGF
- Promote glucose intake, glucose metabolism
- Promote expression of lactate dehydrogenase and pyruvate dehydrogenase, shift metabolism from oxidative phosphorylation to oxidative glycolysis.

Angiogenesis:

- Initial tumour without blood vessels remain in hypoxic state, remains 1-3 mm^3 in size
- With blood supply, allow more biogenesis, more proliferation, acquisition of phenotype (invasive-metastasis, hypoxic-resistance).
- Tumour cells activate angiogenesis genes and secrete VEGF FGF Angiopoietin
- Various modes of angiogenesis:
    - Sprouting angiogenesis: new vessel branch from old vessel
    - Other mechanisms include Intussusception, vessel mimicry