The 6 features of cancer metabolic reprogramming

- Deregulated uptake of glucose and amino acids
- Use of opportunistic modes of nutrient acquisition
- Use of glycolysis/TCA cycle intermediates for biosynthesis and NADPH production
- Increased demand for nitrogen
- Alterations in metabolite driven gene regulation
- Metabolic interactions with the TME

The Warburg effect: Aerobic glycolysis

Vander Heiden et al, Science 2009
When non essential becomes essential: Glutamine

- Harry Eagle 1950s
  - Optimal growth of cultured HeLa cells requires 10 -100 fold molar excess of glutamine in culture medium relative to other amino acids (Eagle 1955)
- Glutamine found to be most rapidly consumed amino acid by Ehrlich ascites carcinomas as well as by a number of hepatomas and carcinosarcomas proliferating in vivo (Marquez et al 1989, Sauer et al 1982).
Why Glutamine?

- Contributes Carbon and nitrogen
  - Purine and pyrimidine nucleotides, glucose 6 phosphate, and nonessential aa
- Uptake of essential amino acids
  - Import of essential amino acid leucine is through the neutral amino acid antiporter LAT1 and this is coupled to simultaneous efflux of glutamine
  - In this manner, intracellular glutamine may facilitate the import of a broad range of LAT1 substrates, including leucine, isoleucine, valine, methionine, tyrosine, tryptophan and phenylalanine (Yanagida et al 2001).
- 18F-glutamine recently employed to provided tumor information where 18F-fluoroglucose is not feasible eg tumors located in sites of heavy glucose utilization such as the brain.

Genetic mutations

- AKT: GLUT1
- Ras: GLUT1
- MYC: ASCT2 and GLS1
- Xct: as glutamate accumulates it cannot exit through glutamine transport, and as it accumulates, promotes TCA cycle anaplerosis and stimulates uptake of cysteine by acting as an exchange substrate for the cysteine antiporter Xct.
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Extracellular protein scavenging

• MACROPINOCYTOSIS: bulk extracellular fluid is taken up into giant vesicles (Kerr and Teasdale, 2009).

Macropinocytosis

Schematic conceived and designed by C. Commissio
Entosis

- Engulfment and digestion of entire living cells
- KRAS mutant cells are more likely to perpetrate entosis than to be consumed in this process (Sun et al 2014)

Phagocytosis of apoptotic cellular corpses also supply amino acids to support cell survival and proliferation during conditions of amino acid deficits

Autophagy
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Use of glycolysis and TCA cycle intermediates for biosynthesis and NADPH production

WHY make less ATP?
Use of glycolysis and TCA cycle intermediates for biosynthesis and NADPH production
The Pentose Phosphate Pathway (PPP)

Protection from oxidative damage