Cancer Metabolism

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ONCOGENE and TUMOR SUPPRESSOR CENTRIC view of cancer
Hallmarks of cancer

(Hanahan and Weinberg 2000)

Tumor Suppression in the Absence of p53-Mediated Cell-Cycle Arrest, Apoptosis, and Senescence

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Retained ability to activate
1. Gls
2. Tigar
3. Glut3

Not cell cycle arrest
Not apoptosis
Not senescence
The somatic mutation profiles of 2,433 breast cancers refine their genomic and transcriptomic landscapes

Bernard Pereira1,2,3, Sue-Fung Chiu1,2,3, Oscar M. Roda1,2, Hans-Kristian Moen Vollan4,5, Elena Prenzhausen4,5, Helen A. Bardwell6, Michelle Pugh7, Linda Jones8,9, Robin Russell7, Stephen John Samuels10,11, Dana W. Taylor11, Bri L. Jones10, Sarah-Jane Dawson10, Joan Abraham10, Helen Norden10, John F. Ready10, Abhishek Mahesvaran10, Gábor Tóthfalvi10, Andrew R. Green12, Steve McKinney7, Arvata Choung7, Senthil Shan10, Nitza Roschetzky7, Leith Murphy7, David R. Bentley7, Ian O. Ellis7, Arne Furusatoth7, Sarah E. Poscle10, Anne-Lise Berreym-Dale8, Helena M. Earl8, Paul D. Mann7, Mark T. Ross7, Samuel Aparicio8,9,11 & Carlos Caldas12,13,14

"Using a custom pipeline (Methods), we identified 32,476 somatic mutations, with 13,084 predicted to affect protein sequence. These coding mutations included 11,006 SNVs (10,193 missense, 808 nonsense, 5 read-through) and 1,635 small insertions or deletions (indels: 1,315 frameshift, 320 in-frame). We also detected 443 variants (268 SNVs, 175 indels) predicted to affect canonical splice sites. Each tumour had an average of 13 mutations (5 coding), with 131 tumours harbouring at least 30 mutations and 38 tumours devoid of any mutation (76 devoid of coding mutations)."

All roads lead to metabolism?
Demosplasia in solid tumors

- Hypovascularity
- Collapsed blood vessel
- Limits nutrient availability

Hypoxia
Nutrient stress
METABOLIC ADAPTATIONS
CELLULAR METABOLISM: A RECAP
Metabolic inputs
**CELLULAR RESPIRATION**

Fructose 1,6 bisphosphate

Glyceroldehyde 3 phosphate

1,3- bisphosphoglycerate
Electron flow

- Significant fraction of metabolism concerns the flow of electrons (redox reactions)
- Respiration in general
- NAD+/NADH and NADP+/NADPH are the major carriers of reducing equivalents

The goals of remodeling cancer metabolism

- Affecting metabolite influx through conferring an increased ability to acquire the necessary nutrients
- Shaping the way the nutrients are preferentially assigned to metabolic pathways that contribute to cellular tumorigenic properties
- Exerting long ranging effects on cellular fate, among which are alterations in differentiation of cancer cells and cells of the TME
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