Cancer metabolism and therapy

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Cancer research has come a long way from earlier days' searching for the cause to nowadays' search for the cure of cancer; there have been many challenges, a lot of excitements, but never dull moments. Early efforts were largely directed toward how mutations of oncogenes or tumor suppressors led to the altered growth, survival and migration properties of the cancer cells; in recent years, metabolic reprogramming of cancer cells to cope with the requirement of rapid increase of cell mass and the nutrition and oxygen (hypoxia)- deprived tumor microenvironment have gained increasing attentions. While the root cause of cancer is genomic mutation and instability, metabolic adaptation is equally important in letting cancer cell survive and expand. Indeed, several oncogenes (e.g., myc) and tumor suppressors (e.g. p53) also regulate tumor metabolism and several metabolic genes (e.g., IDH1) are also mutated and considered to be oncogenes. From the therapy standpoint, conventional therapy focuses on genotoxic-stress based treatments to "poison" or "burn" cancer cells to death, the emerging concept is to preferentially "starve" cancer cells to death by metabolic-stress. The latter exploits the differential metabolic requirements of cancer cells versus normal cells. These two types of treatments may utilize different killing mechanisms and thus complement each other. In this lecture, I will illustrate this principle by describing how tumors cells transform a metabolic gene PKM2 (a pyruvate kinase) into a nuclear oncogene which activates HIF-1a, a key factor in hypoxia response, to reprogram tumor metabolism and how these processes are regulated by epigenetic factors including histone demethylases and long-noncoding RNA.

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COURSE OUTLINE

I. BACKGROUND

Cancer as a metabolic disease
- Metabolic adaptation and tumor progression
- Metabolic drugs and anticancer effects
- Metabolic genes as oncogenes

Cancer metabolism:
- Warburg effect
- glycolysis vs. oxidative phosphorylation

The gatekeeper of mitochondria activity
- Pyruvate and PKM2
- Mitochondrial functions and signaling

Cancer therapeutics:
- "poison", "burn" and "starve"
- Metabolic stress as an alternative therapeutic strategy
- 3 ways to die: apoptosis, autophagy and necroptosis

II. A SPECIFIC EXAMPLE: Arginine addiction and arginine deprivation therapy for prostate cancer

Arginine metabolism and the cancer connection
ASS1 silencing and arginine addiction in cancers
Arginine- deprivation and tumor specific killing
Mitochondria dysfunction and ROS generation
DNA damage and metabolite depletion
Epigenetic silencing of genes involved in mito-functions
ADI (arginine deiminase) therapy and translational potential.

GENERAL REFERENCES

Thomas N Seyfried and Laura M Shelton "Cancer as a Metabolic Disease" *Nutr Metab. 2010;7:7*

Hilary A. Coller "Is Cancer a Metabolic Disease" *Am J Pathol. 2014 Jan;184(1):4-17*