



Cancer Metabolism: a Hope for Curing Cancer

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There must be two questions in cancer biology. First, we can ask what causes cancer. It is fundamentally based upon genetic mutations and multiple carcinogenic progress (Vogelstein and Kinzler, 1993; Weinberg, 1989). The question is answered by a series of mechanism studies against a selected targets in cancer biology, which lead to a discovery of new mechanisms to understand cancer physiology as well as response against anti-cancer treatment. However, discovery of a new target and revealing a novel molecular mechanism of cancer is helpless to suggest therapeutic approach because tumor is composed of cancer cells containing infinite target variant mutation combination (Greaves and Maley, 2012). Some thoughtful scientists cautioned that discoveries by genomic approach is wrong way of developing cancer therapeutics due to genomic instability in cancer (Gabor Miklos, 2005).

Second one is that we can ask how to cure cancer. It is answered by screening based on anti-cancer efficacy through targeting simply tumor growth such as 5-fluorouracil (Heidelberg *et al.*, 1957) or targeting specific molecular targets such as imatinib against BCR-ABL fusion gene (Druker *et al.*, 1996). The question resulted in FDA approved anti-cancer drugs as cytotoxic drugs including alkylating agents, anti-mitotic agents, topoisomerase inhibitor, and DNA/RNA anti-metabolites, or as targeted drugs including inhibitors of tyrosine receptor kinases, Wnt signaling, RAS signaling, and mTOR signaling. During last two decades, every efforts on cancer therapy was focused on abrogating biomolecule synthesis by targeting growth signaling such as receptor tyrosine kinases including EGFR, VEGFR, PDGFR, and downstream kinases of them including PI3K, AKT, ERK, and final downstream signaling of biomolecule synthesis such as mTOR (Engelman *et al.*, 2006). However, blocking a signaling pathway always makes cancer cell opening alternative signaling detours to transfer growth signal. Finally, when we blocked the translation master mTOR, cancer cells evade shortage of biomolecule supply through autophagy (Janku *et al.*, 2011) or alternative signaling activation through mTORC2 activation (Harada *et al.*, 2013).

These phenomena often observed in the clinic as recurrent cancer or drug resistance cancer, which resulted in a therapeutic limit. Therefore, an alternative therapeutic approach is needed beyond blocking translation signal. Regulating cancer metabolism is perfectly fit to this demand and co-operative with current drug development, because it is totally different domain of cancer regulation to compare to the conventional strategy (Kim, 2015a, 2015b). Historically, it has been suggested that molecular and cellular mechanisms of many anti-cancer drugs are associated with metabolic regulation (Table 1). People disappointed with the limit of therapeutic response by metabolic regulation. But it can be overcome soon because the metabolic bypath was not counted in cancer. Once we identify correct target as well as bypath in a certain type of cancer, it will be very easy to control cancer without any harm to normal cell. It is demonstrated that a simple combination of low glucose supply and inhibition of lactate uptake made a critical damage to cancer growth (Sonveaux *et al.*, 2008).

We need to find effective targets responsible for cancer supply as well as develop effective inhibitors against them. Increasing number of promising targets for regulating cancer metabolism have been reported (Galluzzi *et al.*, 2013). The most veiled part of understanding is that the metabolic switch of cancer cells is different from destined metabolic profiles in normal cells. Current studies of regulating cancer metabolism reveal shapes of therapeutic directions, which suggests drugs against metabolism. More evidences and more clever combinations will be available for cancer therapy in the very near future with powerful arsenals from medicines of metabolic diseases (Kim, 2015a, 2015b).

In this special review, we have five parts of cancer metabolism including a general introduction, an anabolic metabolism, a catabolic metabolism, a metabolic regulation, and a imaging metabolism. A general trend in cancer metabolism research was reviewed by Dang and Kim (2018), which includes cancer specific metabolism as well as metabolic adaptation in tumor microenvironment including immunity. A recent update of

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Table 1. Anti-cancer therapeutics to modulate cancer metabolism

| Metabolic targets | Metabolic pathways | Drugs | Application | Reference |
|--|---------------------------|---|---|-----------------------------------|
| CPT1 (Carnitine O-palmitoyl-transferase1) | β-oxidation | Etomoxir Oxfenicine | | (Samudio <i>et al.</i> , 2010) |
| Mitochondrial Complex I | Oxidative phosphorylation | Metformin Phenformin | Phenformin is not available, and metformin is drug for type II diabetes | (El-Mir <i>et al.</i> , 2000) |
| Hexokinases | Glycolysis | 2-deoxyglucose 3-bromopyruvate Lonidamine | Clinical trial of these drugs has been discontinued | (Galluzzi <i>et al.</i> , 2013) |
| PDK1 (Pyruvate dehydrogenase kinase1) | TCA cycle | Dichloroacetate | DCA is an approved drug for lactic acidosis | (Michelakis <i>et al.</i> , 2008) |
| HMGCR (3-hydroxy-methylglutaryl-CoA reductase) | Mevalonate pathway | Statins | Statins are drug for hypercholesterolaemia | (Cao <i>et al.</i> , 2011) |
| mTOR (Mechanistic target of rapamycin) | Cell growth | Rapalogues Torins | Rapalogues are drug for graft rejection too. | (Sabatini, 2006) |
| Cyclooxygenase 2 | Cell growth | Aspirin | It is an anti-inflammatory drug. | (Hawley <i>et al.</i> , 2012) |

heterogeneous anabolic metabolism including glycolysis, glutaminolysis, and pentose phosphate pathway in cancer were reviewed by Neugent *et al.* (2018), Choi and Park (2018), and Cho *et al.* (2018), respectively. A catabolic metabolism especially in cancer energy metabolism was reviewed by Kim (2018) although main pathway of catabolic energy metabolism in cancer remains to be clarified. A metabolic regulation focused on epigenetic modifications was reviewed by Kim and Yeom (2018) that is an important non-genetic factor for tumor progression. A metabolic regulation mediated by transcription factor of NRF2 was reviewed by Jung *et al.* (2018) that is an important genetic factor for tumor progression. Oncogene-driven metabolic regulation such as RAS, MYC and EGFR was also reviewed by Min and Lee (2018). A recent technical advance of imaging cancer metabolism including multi-modality imaging was reviewed by Momcilovic and Shackelford (2018), which suggests clinical approaches for the ultimate goal of improving detection, diagnosis and treatment of cancer patients.

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