Novel strategies for cancer therapy

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In this Special Issue of the *Journal of Molecular Medicine*, we are privileged to publish review articles from three leading laboratories in the field of cancer research summarizing their efforts to translate advances in cancer biology to improvements in cancer therapy.

It has been 32 years since the laboratory of Mariano Barbacid first reported activating mutations of the *KRAS* oncogene in lung cancer [1], but efforts to target this critical signaling protein have not led to increased survival of cancer patients. Drosten and Barbacid summarize elegant and comprehensive studies constructing genetically engineered mouse models of lung cancer, in which *KRAS* gain-of-function is combined with loss-of-function of various other signaling proteins, to screen for combinations that result in synthetic lethality, thereby identifying novel therapeutic targets for the treatment of *KRAS*-mutant lung cancer [2].

The critical role of metabolic reprogramming in cancer progression has become increasingly appreciated over the last decade. The laboratory of Adrian Harris has made a major contribution to the field of cancer metabolism by

demonstrating the importance of glycogen metabolism for cancer cell survival in the hypoxic tumor microenvironment. In their review article, Zois and Harris summarize the biochemistry of glycogen metabolism, what is known about the role of glycogen metabolism in cancer biology, and the effect of small molecule inhibitors of glycogen metabolic enzymes on tumor growth and cancer cell survival [3].

Otto Warburg's pioneering studies reporting increased conversion of glucose to lactate in liver cancer cells initiated the field of cancer metabolism a century ago [4]. Over the last several decades, the laboratory of Jacques Pouyssegur has focused on the importance of lactate and H^+ export, which is mediated by the monocarboxylate transporters MCT1 and MCT4, along with the chaperone protein Basigin (also known as CD147 or EMMPRIN), for cancer cell survival, particularly in the hypoxic tumor microenvironment, and this work is summarized in the comprehensive review article by Marchiq and Pouyssegur [5]. Small molecule inhibitors of MCT4 and Basigin have been identified and shown to have anti-cancer effects on cancer cell lines in tissue culture and in mouse tumor xenograft models.

Taken together, these three outstanding review articles highlight the increasingly sophisticated approach to cancer therapy, which recognizes the potential therapeutic benefit of targeting multiple pathways in an individualized manner as well as the importance of targeting pathways that are not activated by mutation but in response to metabolic demands exerted on cancer cells by the tumor microenvironment. Combining these two approaches may be necessary to achieve the goal of preventing or treating metastatic disease and thereby extending the survival of cancer patients.

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References

1. Santos E, Martin-Zanca D, Reddy EP, Pierotti MA, Della Porta G, Barbacid M (1984) Malignant activation of a K-ras oncogene in lung carcinoma but not in normal tissue of the same patient. *Science* 223: 661–664
2. Drosten M, Barbacid M (2016) Modeling K-Ras-driven lung adenocarcinoma in mice: preclinical validation of therapeutic targets. *J Mol Med*. doi:[10.1007/s00109-015-1360-5](https://doi.org/10.1007/s00109-015-1360-5)
3. Zois C, Harris AL (2016) Glycogen metabolism has a key role in the cancer microenvironment and provides new targets for cancer therapy. *J Mol Med*. doi:[10.1007/s00109-015-1377-9](https://doi.org/10.1007/s00109-015-1377-9)
4. Koppenol WH, Bounds PL, Dang CV (2011) Otto Warburg's contributions to current concepts of cancer metabolism. *Nat Rev Cancer* 11:325–337
5. Marchiq I, Pouyssegur J (2016) Hypoxia, cancer metabolism and the therapeutic benefit of targeting lactate/H⁺ symporters. *J Mol Med*. doi:[10.1007/s00109-015-1307-x](https://doi.org/10.1007/s00109-015-1307-x)