



## In Focus

## Is Cancer a Genetic Disease or a Metabolic Disease?



David S. Wishart

Department of Biological Science, University of Alberta, Edmonton, AB T6G 2E9, Canada

Department of Computing Science, University of Alberta, Edmonton, AB T6G 2E8, Canada

National Institute of Nanotechnology, National Research Council, Edmonton, AB T6G 2M9, Canada

Cancer is already the leading cause of death in Canada, the UK, Australia, New Zealand, and Denmark. In the US it is projected that cancer will surpass heart disease as the nation's leading killer by 2030. In 2015 more than 1.65 million Americans will be diagnosed with cancer and 590,000 will die from it (SEER, 2015). Currently nearly 15 million people in the US are either living with cancer or are cancer survivors. Because cancer is such a widespread, pernicious disease that requires significant, long-term medical intervention, the economic costs are considerable. Current estimates of the cost of cancer care in the US are pegged at \$150 billion/year and are expected to rise to nearly \$173 billion/year by 2020.

Since 1971, global spending on cancer research has exceeded \$200 billion, with the US accounting for nearly 60% of that figure. Thanks to this investment, 5-year cancer survival rates in the US have improved from 48.9% in 1975 to 68.7% in 2015 (SEER, 2015). However, most of these improvements in survival have been attributed to improved screening and better detection techniques rather than improved treatment. Screening allows cancer to be detected at its earliest stages where intervention is most effective. Survival rates for most forms of metastatic or late stage (stage 3 or 4) disease have remained largely unchanged for the past 40 years (Kolata, 2009). Furthermore, the US cancer death rate, adjusted for population age and size, has decreased by just 5% since 1950. This is in marked contrast to death rates from stroke and heart disease, which have dropped by 70% over the same period (Kolata, 2009). These same disheartening trends in cancer outcomes have been mirrored in many other industrialized countries.

Why has progress been so slow? The short answer is that cancer is a very complex disease. Decades of detailed genetic analysis have revealed that there are nearly 1000 known cancer-associated genes in humans (~250 oncogenes, ~700 tumor suppressors). Given that cells typically need 2 or more mutations in these cancer-associated genes to become carcinogenic, simple mathematics indicates that there could be >1 million different cancer genotypes. How can anyone hope to treat a million different diseases? Recent genetic data is even more discouraging. Comprehensive sequence analysis of nearly 1 million tumor samples over the past decade has identified >2 million coding point mutations, >6 million noncoding mutations, >10,000 gene fusions, ~61,000 genome rearrangements, ~700,000 abnormal copy

number segments and >60 million abnormal expression variants (Forbes et al., 2015). Whole genome sequencing of tumor samples in one study showed between 10,000–50,000 different single nucleotide variants in tumor cells compared to adjacent normal tissue (Lee et al., 2010). In simple terms, tumor cells are a genetic “train wreck”. Using genetic fingerprinting of tumors in order to design custom, tumor-specific drugs appears to be a daunting challenge.

However, a glimmer of hope is now on the horizon. Detailed analysis of the function of most oncogenes and tumor suppressors suggested that many play a key role in cellular metabolism (Boroughs and DeBerardinis, 2015). Indeed, it appears that many of the seemingly infinite number of cancer mutations and cancer genes in humans seem to affect three major metabolic pathways: 1) aerobic glycolysis; 2) glutaminolysis; and 3) one-carbon metabolism. These pathways allow cancer cells to shift from simply producing ATP (energy) to generating large quantities of amino acids, nucleotides, fatty acids and other intermediates needed for rapid cell growth and division. Could it be that cancer is essentially a metabolic disease? Interestingly, prior to 1970, most cancer researchers thought of cancer as a metabolic disorder. In 1927 Otto Warburg noticed that cancer cells exhibited a distinct metabolic phenotype, consuming up to 200× more glucose than normal cells (the “Warburg effect”). Indeed, based on Warburg's influence, most cancer drugs discovered in the 1950s and 1960s were called “antimetabolites”. However, with Warburg's death in 1970 and the discovery of oncogenes in 1971, most cancer researchers shifted their thinking to view cancer as a genetic disease rather than a metabolic disease. The “re-discovery” of cancer as a metabolic disorder largely occurred in the last five years. This shift in thinking has mostly been due to the increased accessibility of metabolomics and the discovery, via metabolomics, of “oncometabolites”. Oncometabolites are endogenous metabolites whose accumulation initiates or sustains tumor growth and metastasis. The first oncometabolite to be discovered was 2-hydroxyglutarate, a relatively rare metabolite that is found in high concentrations in gliomas (Ward et al., 2010). This compound appears to (indirectly) alter histone methylation patterns that ultimately lead to carcinogenesis. Since the discovery of 2-hydroxyglutarate many other oncometabolites have been identified or subsequently “reclassified”. These include: fumarate (renal cell carcinoma), succinate (paraganglioma), sarcosine (prostate cancer), glycine (breast cancer), glucose (most cancers), glutamine (myc-dependent cancers), serine (most cancers), asparagine (leukemia), choline (prostate, brain, breast cancer), lactate (most cancers) and polyamines (most cancers). Almost all of these oncometabolites

E-mail address: [dwishart@ualberta.ca](mailto:dwishart@ualberta.ca).

arise from, or are needed for, aerobic glycolysis, glutaminolysis or one-carbon metabolism.

What does this mean for cancer diagnosis and treatment? For one, it suggests that early stage cancer may be detectable by looking for simple metabolic changes such as increased levels of acetate, lactate, serine, sarcosine, asparagine, dimethylspermine, betaine or choline in blood, saliva, breath or urine. Indeed recent publications have demonstrated impressive results for colonic polyps and early stage pancreatic cancer and suggest that more cancer metabolite biomarkers may be on the way (Wang et al., 2014; Xie et al., 2015). Given that more than 95% of cancers are of somatic origin and cannot be detected via genetic screening, metabolite screening could be a fast, cost-efficient way of identifying early stage cancers or pre-cancers. As noted above, early cancer detection is still the best route to ensure optimal treatment outcomes. A second opportunity lies in the ability to metabolically phenotype cancers using metabolomic blood tests, PET imaging or magnetic resonance spectroscopy (Qu et al., 2012). Some cancers appear to prefer aerobic glycolysis, while others depend more on glutaminolysis while still others use a combination of two or more of these pathways. Using non-invasive methods to identify which of the seven different “metabotypes” a given tumor might belong to, or which oncometabolites it is accumulating, would allow for better customization or informed adjustment of cancer therapies. The third opportunity lies in the relative ease of developing or repurposing drugs for well-studied metabolic enzymes. Some existing drugs are already showing impressive results as anticancer therapies, including metformin (a diabetic biguanide that inhibits hexokinase II), dichloroacetate (a lactic acidosis drug that inhibits pyruvate dehydrogenase kinase), ritonavir (an antiviral drug that also inhibits glucose transporters) and orlistat (an anti-obesity drug that blocks fatty acid synthase). Likewise diets or medical foods that significantly reduce the amount of glucose (ketogenic diets) or the amount of non-essential amino acids have shown good promise in stopping or reducing tumor growth in animal models and even humans (Seyfried, 2012).

As with all new discoveries and emerging fields, the excitement over metabolism and cancer needs to be tempered with some caution. However, the bottom line is that while cancer as a genetic disease looks to be

impossibly complex, cancer as a metabolic disease appears to be remarkably simple.

## Conflicts of Interest

None.

## References

- Boroughs, L.K., DeBerardinis, R.J., 2015. Metabolic pathways promoting cancer cell survival and growth. *Nat. Cell Biol.* 17, 351–359.
- Forbes, S.A., Beare, D., Gunasekaran, P., Leung, K., Bindal, N., Boutselakis, H., Ding, M., Bamford, S., Cole, C., Ward, S., Kok, C.Y., Jia, M., De, T., Teague, J.W., Stratton, M.R., McDermott, U., Campbell, P.J., 2015. COSMIC: exploring the world's knowledge of somatic mutations in human cancer. *Nucleic Acids Res.* 43, D805–D811 (Database issue).
- Kolata, G., 2009. In long drive to cure cancer, advances have been elusive. *The New York Times*, April 23.
- Lee, W., Jiang, Z., Liu, J., Haverty, P.M., Guan, Y., Stinson, J., Yue, P., Zhang, Y., Pant, K.P., Bhatt, D., Ha, C., Johnson, S., Kennemer, M.L., Mohan, S., Nazarenko, I., Watanabe, C., Sparks, A.B., Shames, D.S., Gentleman, R., de Sauvage, F.J., Stern, H., Pandita, A., Ballinger, D.G., Drmanac, R., Modrusan, Z., Seshagiri, S., Zhang, Z., 2010. The mutation spectrum revealed by paired genome sequences from a lung cancer patient. *Nature* 465, 473–477.
- Qu, W., Oya, S., Lieberman, B.P., Ploessl, K., Wang, L., Wise, D.R., Divgi, C.R., Chodosh, L.A., Thompson, C.B., Kung, H.F., 2012. Preparation and characterization of D-[5-<sup>11</sup>C]-glutamine for metabolic imaging of tumors. *J. Nucl. Med.* 53, 98–105.
- Surveillance, Epidemiology, and End Results (SEER) Program ([www.seer.cancer.gov](http://www.seer.cancer.gov)) Research Data, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2015.
- Seyfried, T., 2012. *Cancer as metabolic disease: on the origin, management, and prevention of cancer*. Wiley, Hoboken NJ (438 pp.).
- Wang, H., Tso, V., Wong, C., Sadowski, D., Fedorak, R.N., 2014. Development and validation of a highly sensitive urine-based test to identify patients with colonic adenomatous polyps. *Clin. Transl. Gastroenterol.* 5, e54.
- Ward, P.S., Patel, J., Wise, D.R., Abdel-Wahab, O., Bennett, B.D., Collier, H.A., Cross, J.R., Fantin, V.R., Hedvat, C.V., Perl, A.E., Rabinowitz, J.D., Carroll, M., Su, S.M., Sharp, K.A., Levine, R.L., Thompson, C.B., 2010. The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. *Cancer Cell* 17, 225–234.
- Xie, G., Lu, L., Qiu, Y., Ni, Q., Zhang, W., Gao, Y.T., Risch, H.A., Yu, H., Jia, W., 2015. Plasma metabolite biomarkers for the detection of pancreatic cancer. *J. Proteome Res.* 14, 1195–1202.