Citation: Cell Death and Disease (2012) 3, e303; doi:10.1038/cddis.2012.41
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Meeting Report

Emerging concepts: linking hypoxic signaling and cancer metabolism

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Cell Death and Disease (2012) **3,** e303; doi:10.1038/cddis.2012.41; published online 3 May 2012

Subject Category: Cancer Metabolism

Keystone Symposium: Banff Springs, Canada, February 2012

The Joint Keystone Symposia on *Cancer and Metabolism* and *Advances in Hypoxic Signaling: From Bench to Bedside* were held in Banff, Alberta, Canada from 12 to 17 February 2012. Drs. Reuben Shaw and David Sabatini organized the *Cancer and Metabolism* section, and Drs. Volker Haase, Cormac Taylor, Johanna Myllyharju and Paul Schumacker organized the *Advances in Hypoxic Signaling* section. Accumulating data illustrate that both hypoxia and rewired metabolism influence cancer biology. Indeed, these phenomena are tightly coupled, and a joint meeting was held to foster interdisciplinary interactions and enhance our understanding of these two processes in neoplastic disease. In this report, we highlight the major themes of the conference paying particular attention to areas of intersection between hypoxia and metabolism in cancer.

One opening keynote address was delivered by Craig Thompson (Memorial Sloan-Kettering, USA), in which he provided a comprehensive perspective on the current thinking around how altered metabolism supports cancer cell growth and survival, and discussed areas likely to be important for future discovery. In particular, Thompson highlighted the essential roles of glucose and glutamine in cell growth, how glucose- and glutamine-consuming processes are rewired in cancer and how this rewiring facilitates anabolic metabolism. These topics were at the core of many of the metabolism presentations that described in detail how some metabolic alterations contribute to the properties of transformed cells.

The other keynote address was delivered by Peter Ratcliffe (University of Oxford, UK), in which he provided a historical perspective on the progress of how signaling events sense oxygen. Mammals have evolved multiple acute and long-term adaptive responses to low oxygen levels (hypoxia). This response prevents a disparity in ATP utilization and production that would otherwise result in a bioenergetic collapse when oxygen level is low. Multiple effectors have been proposed to mediate the response to hypoxia including prolyl hydroxylases, AMPK, NADPH oxidases and the mitochondrial complex III. Currently, however, the precise mechanism by which oxygen is sensed in various physiological contexts remains unknown. Indeed, this was an active point of debate, with Peter Ratcliffe favoring the prolyl hydroxylase PHD2 as the primary cellular oxygen sensor.

Cancer and Metabolism

Anabolic glucose metabolism and the Warburg effect. Nearly a century ago, Warburg noted that cancer tissues take up glucose in excess than most normal tissues and secrete much of the carbon as lactate. Recently, headway has been made toward determining how the enhanced glucose conversion to lactate occurs and contributes to cell proliferation and survival. Heather Christofk (University of California, Los Angeles, USA) and John Cleveland (the Scripps Research Institute, USA) described a role for the lactate/pyruvate transporter MCT-1 in carbon secretion, and suggested that blocking lactate or pyruvate transport may be a strategy to target glucose metabolism in cancer cells. Kun-Liang Guan (University of California, San Diego, USA) described a novel feedback loop to control glucose metabolism in highly glycolytic cells. Specifically, he discussed how glucose-derived acetyl-CoA can be used as a substrate to modify two enzymes involved in glucose metabolism, pyruvate kinase M2 (PKM2) and phosphoenolpyruvate carboxylase (PEPCK). In both cases, acetylation leads to protein degradation and decreased glycolysis and gluconeogenesis, respectively. Data presented from Matthew Vander Heiden's laboratory (Koch Institute/MIT, USA) illustrated that loss of pyruvate kinase activity can accelerate tumor growth, suggesting that the regulation of glycolysis may be more complex than previously appreciated. Almut Schulze (London Research Institute, UK) discussed a novel

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regulatory role for phosphofructokinase in controlling glucose metabolism and Jeffrey Rathmell (Duke University, USA) discussed parallels between glucose metabolism in cancer cells and lymphocytes that suggest many of these phenotypes could be a feature of rapidly dividing cells.

Glutamine addiction. Cancer cells also consume glutamine to support proliferation and survival. Alfredo Csibi (Harvard Medical School, USA) described how mTORC1 promotes glutamine utilization by indirectly regulating the activity of glutamate dehydrogenase. This work united two major themes at the meeting, mTOR signaling and glutamine metabolism, highlighting the interconnectedness of signal transduction and metabolic regulation. Richard Cerione (Cornell University, USA) described a small molecule inhibitor of glutaminase that can be used to target glutamine-addicted cancer cells. Christian Metallo (University of California, San Diego, USA), Andrew Mullen (University of Texas Southwestern Medical School, USA) and Patrick Ward (Memorial Sloan-Kettering, USA) presented data demonstrating that the carbon skeleton of glutamine can be incorporated into newly synthesized lipids. This contribution of glutamine to lipid synthesis was most pronounced in hypoxia or when the mitochondrial electron transport chain was compromised.

Signal transduction and metabolism. The protein kinases AMPK and mTOR can function as sensors of metabolic impairment, whose activation by energy stress controls multiple cellular functions. Grahame Hardie (University of Dundee, UK) and Reuben Shaw (Salk Institute, USA) highlighted novel roles for AMPK, including inhibition of viral replication, and the control of histone acetylation via phosphorylation of class IIa HDACs, respectively. Brandon Faubert (McGill University, USA) reported on an AMPK-dependent effect on glucose metabolism in unstressed cells. Brendan Manning (Harvard Medical School, USA) found that chronic activation of mTOR in the mouse liver, due to genetic ablation of this complex, promotes the development of liver cancer. Kevin Williams (University of California, Los Angeles, USA) discussed how growth signaling can control both lipid and glucose metabolism by impinging on SREBP-1, a transcription factor downstream of mTOR. AMPK-independent control of mTOR was addressed by John Blenis (Harvard Medical School, USA), who discussed the possible role of mTOR stabilizing proteins as mediators of mTOR inactivation upon energetic stress. David Sabatini (Whitehead Institute/MIT, USA) discussed several aspects of amino-acid sensing by Rag GTPases and showed that constitutive activation of the Rag GTPases leads to metabolic defects in mice.

One of the outcomes of AMPK activation and mTOR inhibition is autophagy, which can provide amino acids and fatty acids to nutrient-deprived cells. Ana Maria Cuervo (Albert Einstein College of Medicine, USA) and Eileen White (Rutgers University, USA) illuminated the role of chaperone-mediated autophagy (CMA) and macroautophagy, respectively, in tumor survival. White described a role for macroautophagy in the regulation of mitochondrial fitness, maintenance of TCA cycle and tumorigenesis induced by oncogenic Ras. Cuervo described how CMA is consistently elevated in tumor cells, and how its inactivation leads to metabolic impairment via p53-mediated downregulation of glycolytic enzymes.

Oncogene-specific changes to metabolism. Lewis Cantley (Harvard Medical School, USA) described a metabolic role for oncogenic Kras in the rewiring of glucose metabolism in pancreatic cancer. Specifically, Myc-mediated transcription (downstream of MEK-ERK signaling) both enhances glucose uptake and diverts glucose carbon into the nonoxidative pentose phosphate pathway to facilitate nucleotide biosynthesis. Alejandro Sweet-Cordero (Stanford University, USA) described how oncogenic Kras increases glycolysis and represses mitochondrial respiration (via decreased pyruvate dehydrogenase phosphatase 1 (PDP1) expression) in colon cancer. While these studies indicate that hyperstimulation of the Erk pathway suppresses PDH flux through suppression of PDP1, Joan Brugge (Harvard Medical School, USA) described studies showing that reduction of Erk signaling in normal epithelial cells also causes suppression of PDH flux, in this case through loss of repression of PDK4. The seemingly contradictory nature of these results highlighted an important theme emphasized throughout the week-long conference—that cellular context has an important role in shaping how oncogenic mutations or pathway activation rewires metabolism.

Targeting cancer metabolism. There was extensive discussion around targeting metabolism for cancer therapy. Metformin and phenformin, which act in part by mitochondrial complex I inhibition, can activate AMPK and influence cancer cell metabolism. Kevin Struhl (Harvard Medical School, USA) described how metformin can selectively target cancer stem cells, whereas Jessica Howell (Harvard Medical School, USA) described how the therapeutic activity of metformin relies on both AMPK and mTOR signaling to mediate its effect. Similarly, David Shackelford (University of California, Los Angeles, USA) demonstrated efficacy for phenformin in LKB1-deficient mouse models.

Several presentations, including those by Taru Muranen (Harvard Medical School, USA), Karen Vousden and Eyal Gottlieb (both from the Beatson Institute for Cancer Research, UK), provided insight into genetic control mechanisms that cancer cells use to promote survival under conditions of increased biosynthesis. As an example, Vousden illustrated how p53 loss can make cancer cells more dependent on exogenous serine. Several additional presentations, including those by Gottlieb, Richard Possemato (Whitehead Institute/MIT, USA), Michael Pollak (McGill University, USA) and Kevin Marks (Agios Pharmaceuticals, USA), also included data highlighting the important role of serine biosynthesis and metabolism in cancer growth. Collectively, these data highlight a metabolic addiction that may be therapeutically exploitable. Similarly, Cristina Muñoz-Pinedo (Institut d'Investigació Biomèdica, Spain) described how mimicking glucose deprivation with 2-deoxyglucose can cause programmed cell death and may be an effective cancer treatment.

Advances in Hypoxic Signaling: from Bench to Bedside

Regulation of hypoxic responses. Peter Carmeliet (University of Leuven, Belgium) highlighted the mechanisms of resistance against VEGF-targeted therapies. Roland Wenger (University of Zurich, Switzerland) discussed the oxygen-responsive transcriptional networks and, in particular, the difference between the transcription factors HIF-1α and HIF-2α. Importantly, he demonstrated a rapid role for HIF-1α, and a later and more persistent response for HIF-2α. These results were central to a recurrent theme calling for the distinction of HIF-1α and HIF-2α target genes and how these responses mediate divergent hypoxic adaptations.

Advances in hypoxic signaling. Brooke Emerling (Harvard Medical School, USA) introduced CUB domain-containing protein 1 (CDCP1) and showed persuasive data on CDCP1 being a HIF-2α target gene involved in cell migration and metastasis, and suggested CDCP1 regulation as an attractive therapeutic target. Johannes Schodel (University of Oxford, UK) described an elegant HIF-ChIP-Seq methodology to define direct transcriptional targets of HIF in renal cancer.

Randall Johnson (University of Cambridge, UK) emphasized that loss of HIF-1α results in decreased lung metastasis. Lorenz Poellinger (Karolinska Institutet, Sweden) focused on how hypoxia can alter the epigenetic landscape of cells, and furthermore, how the disruption of the histone demethylase JMJD1A and/or the H3K9 methyltransferase G9a has opposing effects on tumor growth and HIF target gene expression.

Paul Schumacker (Northwestern University, USA) further emphasized the importance of mitochondrial ROS signaling under hypoxic conditions showing that ROS could be detected in the inter-membrane space of the mitochondria before activating signaling cascades in the cytosol. He also presented evidence for mitochondria as a site of oxygen sensing in diverse cell types. Similarly, Margaret Ashcroft (University College London, UK) argued for a critical role of mitochondria in hypoxic signaling. She presented on a family of mitochondrial proteins (CHCHD4) that influence hypoxic signaling and tumorigenesis and suggested that CHCHD4 is important for HIF and tumor progression.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements. We apologize to colleagues whose work was not discussed due to space limitations. CAL is the Amgen fellow of the Damon Runyon Cancer Research Foundation (DRG-2056-10). MGVH is supported by the Burrough's Wellcome Fund, the Damon Runyon Cancer Research Foundation, the Lustgarten Foundation, the Smith family and the Stern family. CMP is supported by La Marató-TV3 and ISCIII. BME is supported by the Dana Farber/Harvard Career Development Award.

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