Better cancer therapy from redox biology

Banbury Center, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA
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Organizers:
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BACKGROUND
An unanswered question in human health is whether anti-oxidation prevents or promotes cancer. Anti-oxidation has historically been viewed as chemo-preventive but emerging evidence suggests that antioxidants may be supportive of neoplasia. To leverage cellular redox changes towards the development of a safe and effective therapeutic strategy necessitates experimental delineation of specific redox signaling pathways that are uniquely required by cancer cells to grow and to survive.

This Banbury meeting on redox biology centered on the complexity of redox regulation in the context of cancer biochemistry and therapy. Specifically, the meeting aimed to explore ROS genesis and metabolism in cancer cells, as well as the “productive” and “destructive” signal transduction by free radicals through the oxidation of intermediates such as protein encoded cysteine and methionine residues.
DETAIL

Redox chemical reactions represent a principle constituent of all life. Despite this, our current understanding of redox biochemistry inside living cells remains surprisingly elusive in both physiological and pathological settings. In the context of tumorigenesis, there is much excitement over the possibility of harnessing differences in cellular redox states to develop novel therapeutic strategies. To date, most effort has been invested in defining the role of reactive oxygen species (ROS) as a tumor promoting or a tumor-suppressing agent, with abundant evidence supporting either argument. ROS on the one hand, can suppress cell growth through genotoxic stress and mRNA translational arrest; and on the other hand, can promote cell growth through activation of mitogenic signaling cascades. The role of ROS in cellular outcome is clearly more diverse than anticipated. Cellular responses to ROS reflect a complex integration of ROS type, location and levels. This presents a conundrum on how we should approach ROS therapy in cancer.

Participants in the April 2017 Banbury Center meeting on Better Cancer Therapy from Redox Biology explored the complexity of redox regulation in the context of cancer biochemistry and therapy. The goal is to synthesize this information to inform the design of therapeutic strategies to selectively target neoplastic cells. Specifically, the group explored the selective role of different ROS-generating mitochondrial components in physiology and development, as well as the application of genomic screens to identify pharmacologically actionable liabilities that are created in cancer cells. The intricacy of redox biology is highlighted by the cell compartment-specific functions of different free radicals, their interaction with metals and also target selectivity. Indeed, ROS involvement in cancer is not confined to indiscriminate macromolecular damage. The regulation of ROS is both topological and temporal. Given this, the potential number of ROS-specific effectors is predicted to be massive and underexplored.

Cancer is a complex entity that co-evolves with a microenvironment comprised of an extracellular matrix, fibroblasts and immune cells, all of which dynamically communicate in paracrine and juxtacrine manners. As such, the role of redox homeostasis extends beyond tumor cell intrinsic properties and is involved in mediating organ-specific tumor development, metastatic properties, as well as immune cell activation and function.

Emerging technologies that identify ROS, including protein- and chemical-based probes to track and quantify free radical species in both space and time, were discussed during this meeting. The application of these new technologies will be invaluable to deciphering the selective role of different reactive oxygen species in specific cell types and cell compartments within the tumor mass and will inform the design of more effective therapeutic strategies against cancer.

Christine Chio & David Tuveson
April 2017
MEETING SESSIONS

Session I: Free radicals and antioxidants in physiological functions
Chair: Arne Holmgren, Karolinska Institute, Stockholm, Sweden

James Watson, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA
To Overcome Chemo-Resistant Cancers, Use Natural Product Quinones

Christine Winterbourn, University of Otago, Christchurch, New Zealand
Cellular mechanisms for regulating hydrogen peroxide metabolism and oxidative stress

Ursula Jakob, University of Michigan, Ann Arbor, Michigan, USA
Role of polyphosphate in oxidative stress defense

Nicholas Tonks, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA
Redox regulation of Protein Tyrosine Phosphatases for therapeutic development

Navdeep Chandel, Northwestern University, Chicago, Illinois, USA
Functional genomic screens to uncover redox biology

Paul Schumacker, Northwestern University, Chicago, Illinois, USA
Mitochondrial regulation of cell proliferation

Session II: Free radicals and antioxidants in cancer
Chairs: Arne Ostman, Karolinska Institute, Stockholm, Sweden, and Karen Liby, Michigan State University, East Lansing, Michigan, USA

Karen Vousden, Francis Crick Institute, London, United Kingdom
Modulating TIGAR to probe ROS functions in tumour development and metastasis

Tak Mak, University of Toronto, Ontario, Canada
Modulation of oxidative stress as an anticancer strategy

Edward Schmidt, Montana State University, Bozeman, Montana, USA
Endogenous oxidants and cellular antioxidant systems in liver cancer

Martin Bergo, Karolinska Institutet, Huddinge, Sweden
Antioxidants cause long-term programming of lung cancer cells into a metastatic phenotype

Nissim Hay, University of Illinois, Chicago, Illinois, USA
Akt, hexokinase 2, ROS, and cancer therapy

Session III: NRF2 in redox homeostasis and metabolism
Chair: Michael Espey, National Cancer Institute, Rockville, Maryland, USA

John Hayes, University of Dundee, Dundee, United Kingdom
The mechanisms of repression of transcription factor Nrf2 and its crosstalk with lipid metabolism

Christine Chio, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA
Nrf2 promotes mRNA translation in pancreatic cancer

Masayuki Yamamoto, Tohoku University, Sendai, Japan
Molecular basis of Keap1-Nrf2 system and Cancer

Thales Papagiannokopolus, New York University Medical School, New York, USA
Pro-tumorigenic NRF2 antioxidant program causes defects in central carbon metabolism
Gina DeNicola, Moffitt Cancer Center, Tampa, Florida, USA

Compartmentalization of ROS production and metabolism
Donna Zhang, University of Arizona, Tucson, Arizona, USA

NRF2: an integrator of cellular iron and redox signaling
Session IV: Redox imaging
Chair: Tobias Dick, German Cancer Research Center, Heidelberg, Germany

Vsevolod Belousov, Russian Academy of Sciences, Moscow, Russia
Metabolic engineering tools and fluorescent probes for redox biology

Kevin Brindle, University of Cambridge, Cambridge, United Kingdom
Imaging oxidative stress in vivo

Christopher Chang, University of California, Berkeley, California, USA
Chemical Imaging and Proteomics Probes for Studying Redox Biology

Tobias Dick, German Cancer Research Center, Heidelberg, Germany
Understanding the ‘anti-oxidant’ N-acetyl cysteine

Yi Yang, East China University of Science and Technology, Shanghai, China
Genetically encoded sensors for redox biology and their applications in drug screening

Michael Murphy, MRC Mitochondrial Biology Unit, Cambridge, United Kingdom
Therapeutic alteration to the mitochondrial redox environment

Session V: Therapeutics
Chair: Thomas Miller, IC-MedTech, Las Vegas, Nevada, USA

David Boothman, University of Texas Southwestern Medical Center, Dallas, Texas, USA
Leveraging NQO1 bioactivatable drugs for tumor-selective ROS production and anti-tumor activity

Garry Buettner, University of Iowa, Iowa City, Iowa, USA
Using science to guide clinics trials for cancer treatment where redox biology is at the center

Douglas Spitz, University of Iowa, Iowa City, Iowa, USA
O$_2^-$ and H$_2$O$_2$-Mediated Disruption of Fe Metabolism Causes the Differential Susceptibility of NSCLC and GBM Cancer Cells to Pharmacological Ascorbate

Sean Morrison, University of Texas Southwestern Medical Center, Dallas, Texas, USA
Distant metastasis requires cancer cells to adapt to cope with oxidative stress

Elizabeth Parkinson, University of Illinois, Urbana, Illinois, USA
Deoxynyboquinones as NQO1-targeted anticancer compounds

Session VI: Wrap-Up and Next Steps (David Tuveson and James Watson)
MEETING PARTICIPANTS

Vsevolod Belousov, Russian Academy of Sciences, Russia
Martin Bergo, Karolinska Institutet, Sweden
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