Nathan A. Berger: aging-cancer and obesity-cancer research require new mechanistic understandings

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Editor's note

Aging has been found to be a major risk factor for cancer development. The World Health Organization (WHO) statistics have shown that life expectancy in most developed countries is now exceeding 80 years. Aging population is highly associated with greater health burden, especially in the development of various types of cancers. According to the US National Cancer Institute's Surveillance Epidemiology and End Results Database, 43% of men and 38% of women will develop an invasive cancer over a lifetime, and more than half of cancers occur in individuals older than 70 (1).

Another fact of life that we must face is the close-knit relationship between obesity and cancer. Obesity has been found to heighten the risk of cancer development. Commonly observed cancer types associated with obesity include endometrial, esophageal adenocarcinoma, colorectal, postmenopausal breast, thyroid, hepatocellular, renal and myeloma (2). About 20% of all cancers are caused by excess weight, as suggested by recent research (3).

As a Who's Who in the World and one of the Best Doctors in America, Prof. Nathan A. Berger from Case Western Reserve University, School of Medicine has been focusing on the study of aging, energy balance, obesity and cancer in recent years. The following interview will highlight the most updated cellular, biochemical and molecular understandings of aging cancer and energy balance and cancer, the latest techniques involved and the research he is currently working on.

Expert's introduction

Nathan A. Berger, MD, currently serves as the Hanna-Payne Professor of Experimental Medicine, Director of the Center for Science, Health and Society and a Professor of Medicine, Biochemistry, Oncology, Genetics and Genome Sciences at Case Western Reserve University, School of Medicine (*Figure 1*).

Figure 1 Prof. Nathan A. Berger.

Commencing in the field of DNA Damage and Repair, Prof. Berger has gradually shifted his research focus to Aging, Energy Balance and Cancer. His laboratory focuses on poly (AdenosineDiPhospho-Ribose) Polymerase (PARP), DNA repair, stress proteins, developmental therapeutics and murine models to interrogate impact of energy balance on cancer. He was the Principal Investigator on two major grants funded by the National Cancer Institute: CASE Center for Transdisciplinary Research on Energetics and Cancer, and Aging-Cancer Research Program Development and currently is a Multi Principal Investigator on an NCI funded Cancer Disparities Specialized Program on Research Excellence. He is also the co-director of the Aging and Cancer Research Program at the Case Comprehensive Cancer Center.

Prof. Berger is actively involved in a variety of academic activities. He is the author of over 200 papers, reviews and book chapters in the field of DNA damage and repair and developmental therapeutics. He is or was an Editorial Board member of numerous renowned journals including Blood, the *Journal of Clinical Investigation* and the *Journal of Biological Chemistry*. He is Founding and Series Editor for the Energy Balance and Cancer Book Series. He received a number of honorable titles such as Leukemia Society of America Scholar "Million Dollar Professor"

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and Distinguished University Professor at Case Western Reserve University School of Medicine, and was listed in Who's Who in America, Who's Who in Medicine and Healthcare, Who's Who in the World as well as Best Doctors in America.

Interview

TCR: After starting in the field of DNA Damage and Repair, what led you to shift your focus to Aging, Energy Balance and Cancer?

Prof. Berger: I actually began my research activities as a Fellow at the National Institutes of Health (NIH) focused on inorganic biochemistry, applying nuclear magnetic resonance to study the interactions of metal ions with nucleic acids. Seeking to extend these studies to more biological aspects of this fundamental and rigorous approach, I investigated the role of metal ions in the processes of DNA replication and repair and their contribution to carcinogenesis and cancer therapy. These studies quickly focused on poly (AdenosineDiPhospho-Ribose) Polymerase (PARP), its regulatory role in the DNA Damage Response, and its contribution to modulation of energy metabolism by controlling Nicotinamide Adenine Dinucleotide (NAD) and adenosine triphosphate (ATP) levels. This focus led to the early proposal for use of PARP inhibitors to potentiate chemotherapy and to transdisciplinary studies on energy, aging balance and cancer.

The shift in focus to aging and cancer was motivated by the increase in cancer predicted to accompany aging of the population, while the focus on energy balance and cancer was promoted by expansion of the obesity pandemic and its association with both increased incidence and worse prognosis for patients with cancer. The linkages between energy balance, aging, obesity and cancer provided exciting and challenging opportunities for translational science including the possibility for interrogation at the laboratory level with extension to human interventions. The critical issues right now in the aging-cancer field are to better understand the mechanisms involved in aging and senescence, their associated comorbidities and how to molecularly intervene, regulate and overcome them in cancer prevention and control. Similarly, the critical issues in obesity-cancer research include better understanding of the mechanisms by which obesity and obesigenic diets accelerate cancer, how to prevent and correct obesity, how to molecularly prevent and disrupt the obesity impact on cancer incidence and its prognosis. An equally important aspect of this area of cancer research is the need to increase public awareness of the obesity-cancer linkage and the understanding that the obesity effect may occur after long latent periods indicating the need to maintain healthy weight on a life-long basis and the need to normalize weight as early as possible for obese individuals.

TCR: Throughout the past few decades, how have our understandings about cellular, biochemical and molecular aspects of aging cancer and energy balance and cancer been enhanced? What are the latest techniques associated with these studies?

Prof. Berger: Both the fields of aging-cancer and obesity-cancer research started with epidemiologic observations in retrospective cohort analyses leading to clinical trials, to studies of biomarkers of each process and the possibility that some of the biomarkers may actually be mediators of the linkage between aging and/or obesity and cancer. For example, decreasing adiponectin and increasing leptin, insulin and insulin-like growth factor (IGF) have all been identified as biomarkers of obesity and each has been investigated for its contribution to promoting the carcinogenic process. Little, however, has been, but needs to be done, to modulate these factors in trying to control cancerous processes. More recent research on translational aspects of these processes are focusing on adipocyte-cancer cross-talk including communications through exosomes and micro RNAs and on the contribution of epigenetics to carcinogenesis in response to aging, obesity, metabolism and stress. Studies in the latter now circle back to the reciprocal role of cell metabolism, energy balance and their impact on epigenetic control mechanisms involving protein and chromatin modifications mediated by NAD, acetylation, methylation and others.

TCR: How can these understandings help modulate or enhance therapeutic strategies?

Prof. Berger: At the clinical level, studies are in progress to critically evaluate the contribution of diet and exercise to regulate aging, prevent cancer, improve its response to therapy and prevent disease recurrence. For these goals, it would be useful to develop molecular markers to monitor mechanisms and efficacy of these interventions. Other studies focus on use of agents such as Metformin to control insulin and aspects of their metabolism as promoters of cancer growth. In addition, recent studies have begun to

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focus on the use of epigenetic modifiers to prevent and disrupt the aging-obesity-cancer linkage.

TCR: In your recently published article in TCR, you reviewed the conundrum of pancreatic cysts. What is the current level of and challenges in the management of pancreatic cysts?

Prof. Berger: Pancreatic cancer which in the past was most common in the over age 65 group, now has been identified as an obesity-associated cancer with increased incidence at younger ages. Incidental radiographically identified pancreatic cysts in a younger patient cannot simply be ignored, especially if that individual is obese. While the population-based articles did provide follow-up recommendations, they did not indicate obesity levels in the study populations. Accordingly, evidence-based guidelines need to be developed for obese individuals who are at greater risk for pancreatic cancer, and until such time as guidelines are available, follow-up for obese individuals should be more intensive than for those at average risk.

TCR: You have been the Principal Investigator on two major grants funded by NCI: Case Center for Transdisciplinary Research on Energetics and Cancer, and Aging Cancer Research Program Development. Will you briefly introduce us to both projects?

Prof. Berger: The objectives of the two NCI funded grants were to stimulate research at CWRU focused on Aging and Cancer and on Obesity-Cancer with the overall goal of reducing some of the comorbidities that accompany the aging process and disrupting the linkage between age, obesity and cancer. The Aging Cancer research grant led to fundamental discoveries in the nematode Caenorhabditis elegans and in mice demonstrating a critical role for PhosphEnolPyruvateCarboxy Kinase (PEPCK) and PhosphoFructoKinase (PFK) promotion of a metabolic shift that facilitates aging. These studies demonstrated that genetic manipulation of these enzymes could retard both the aging and carcinogenic processes. At the clinical level, these programs have been translated to ongoing trials led by our collaborators to investigate the effects of exercise and diet intervention to reduce functional decline in older women who have completed breast cancer therapy and to further investigate these effects on biomarkers and mediators. Studies in the planning phase include clinical trials to facilitate optimization of chemotherapy in older women undergoing adjuvant chemotherapy for breast cancer.

The objective of the TREC program was to bring a transdisciplinary approach to obesity-cancer problems, with the expectation that such an approach might be more likely to contribute to progress in the field compared to previous multi or interdisciplinary approaches. For this endeavor, we focused on GI Tract malignancies bringing together faculty and trainees with expertise in obesity, epidemiology, genetics, metabolism, biostatistics, metabolic syndrome, sleep physiology, exercise and GI malignancies, especially, esophageal adenocarcinoma and colon cancer. This project was remarkably successful, resulting in multiple important observations including the first demonstration of the relation of short sleep to increased incidence of colon adenomas and the demonstration that the carcinogenic effects of obesity are highly dependent on inflammation and the type of fat in the obesigenic diet. This work continues to be supported by multiple NIH grants to our collaborators including R01's, a U54 focused on Barrett's Esophagus, a P50 Specialized Program on Research Excellence (SPORE) in GI Malignancies and another P20 SPORE on Cancer Health Disparities.

TCR: During your 7-year term as Dean of the CWRU School of Medicine, you stimulated expansion of basic and translational research programs at the school of medicine. What were the challenges encountered during that time? Were there any memorable cases that you would like to share with us?

Prof. Berger: Our motivation to stimulate translational and transdisciplinary research was multifactorial. First and foremost was the concept to bring basic and clinical scientists together to provide new insights and approaches focused on solution of intractable problems. Clearly, another goal was to have these investigators collaborate to develop unique, innovative approaches that would increase their likelihood of obtaining peer-reviewed funding and ultimately solving problems. The biggest challenges in getting faculty to venture out of their departmental silos and really engage in translational and transdisciplinary research was to get them to trust each other, to understand each other's language and approach, and to work together to develop and test their research strategies. A positive motivator for these efforts was the ability to provide NIH and institutional grant funded support for developmental-pilot research projects, many of which went on to become full NIH funded grants.

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Another challenge to development of translational and transdisciplinary teams was institutional policies recognizing only individual scholarship for promotion and tenure. However, change in institutional policy, recognizing scholarly contributions to team science and funding, provided strong impetus for participation in developing translational and transdisciplinary research projects.

TCR: As a well-reputed expert in your field, what would be your advice to young researchers who would like to develop in your field?

Prof. Berger: Develop your own expertise and become recognized for your unique approach, but be alert, seek out and say yes to participation in transdisciplinary and translational opportunities. Participate in seminars and conferences that focus on your interests, but be sure to participate also in programs where you lack expertise. When you develop an exciting concept, do the experiment before you rationalize it away. Future progress in aging and obesity cancer research will require new understanding and approaches to markers and mediators, in order to disrupt cross-talk between adipocyte and tumor tissues and novel insights and interventions targeted at epigenetic effects of metabolic perturbations and their neoplastic consequences.

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