A NanoBioLab Symposium 2021 Webinar

Prof. Rakesh Jain, Massachusetts General Hospital, USA

NORMALIZING THE TUMOR MICROENVIRONMENT TO IMPROVE CANCER TREATMENT: FROM MATH MODELING TO MICE TO PATIENTS AND BACK

Wednesday, March 3, 2021
9:00 - 10:00 am SGT
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Prof. Rakesh Jain

A.W. Cook Professor of Radiation Oncology (Tumor Biology)
Director, E.L. Steele Laboratories
Department of Radiation Oncology
Harvard Medical School and Massachusetts General Hospital

ABSTRACT

For four decades, my research has focused on one challenge: improving the delivery and efficacy of anti-cancer therapeutics by normalizing the tumor microenvironment. Working on the hypothesis that the abnormal tumor microenvironment fuels tumor growth and treatment resistance, we developed an array of sophisticated imaging technologies and animal models as well as mathematical models to unravel the complex biology of tumors. Using these tools, we demonstrated that the blood and lymphatic vasculature, fibroblasts, immune cells and the extracellular matrix associated with tumors are abnormal, and these collaborate together to create a hostile tumor microenvironment characterized by low oxygen levels (hypoxia), low pH and high interstitial fluid pressure and solid stress.

We next hypothesized that agents that induce "normalization" of the microenvironment can improve the treatment outcome. Indeed, we demonstrated that judicious use of antiangiogenic agents—originally designed to starve tumors—could transiently "normalize" tumor vasculature, alleviate hypoxia, increase delivery of drugs and anti-tumor immune cells, and improve the outcome of various therapies, including immunotherapy. In parallel, we provided compelling evidence for vascular normalization in cancer patients treated with antiangiogenic agents. In fact, vascular normalization and the resultant improvement in tumor perfusion and oxygenation associated with longer survival in patients (J Clinical Oncology 2013; Cancer Cell 2014; PNAS 2015). Our preclinical finding that vascular normalization can improve immunotherapy (PNAS 2012) was confirmed by others in randomized phase III trials on combining antiangiogenic therapy with immune-checkpoint inhibitors for metastatic lung, liver, endometrial and kidney cancers (New England J Medicine 2018, 2019, 2020), and led to the FDA approval 5 such combinations for these cancers in the past 2 years.

The normalization hypothesis also opened doors to treating various non-malignant diseases characterized by abnormal vasculature that afflict >500 million people worldwide, such as, tuberculosis (PNAS 2015) and neurofibromatosis-2 (NF2) (New England J. Medicine 2009). Based on our findings, bevacizumab was approved for NF2-schwannoma patients in UK in 2014.

In parallel, by imaging collagen and measuring diffusion and perfusion in tumors in vivo, we discovered that the tumor cells and the extracellular matrix compress blood vessels and impede drug delivery in matrix-rich tumors (e.g., pancreatic cancer, triple negative breast cancers and ovarian cancer) (Science 2020). We subsequently discovered that angiotensin blockers – widely prescribed to control hypertension – are capable of "normalizing" the extracellular matrix, opening compressed tumor vessels, and improving the delivery and efficacy of molecular and nano-therapeutics. This finding offers new hope for improving treatment of highly fibrotic tumors and led to a successful phase II clinical trial at MGH on losartan and chemo-radiation therapy in pancreatic ductal adenocarcinomas (PDAC) (NCT01821729) (JAMA Oncology 2019). This trial demonstrated that the addition of losartan to the standard of care led to an unprecedented R0 resection rate of 61% in locally advanced PDAC and significantly improved survival of these PDAC patients. This finding has led to a multi-institutional randomized trial (NCT03563248). In my presentation I'll also discuss how these two broad strategies – "vascular normalization" and "matrix normalization" – can improve the delivery and efficacy of various cancer therapies, including immunotherapy (PNAS 2020).

ABOUT THE SPEAKER

Dr. Rakesh K. Jain is the Andrew Werk Cook Professor of Radiation Oncology (Tumor Biology) at Harvard Medical School, and Director of the Edwin L. Steele Laboratories at Massachusetts General Hospital. He is widely known for revealing how the abnormal tumor microenvironment fuels tumor progression and confers treatment resistance; developing innovative strategies to "normalize" the microenvironment; and then translating these strategies from bench to bedside. He has mentored more than 220 doctoral and postdoctoral students and authored of more than 750 publications. He is among the top 1% cited researchers. A recipient of more than 90 awards, Dr. Jain has the rare distinction of being a member of all three US National Academies –Sciences, Engineering and Medicine – as well as the National Academy of Inventors and the American Academy of Arts and Sciences. He received the 2013 US National Medal of Science (for biological sciences) from President Obama "For pioneering research at the interface of engineering and oncology, including tumor microenvironment, drug delivery, and imaging; and for discovering groundbreaking principles guiding the development and novel use of drugs for cancer and non-cancerous diseases."

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For enquiries, please contact nidyah@nbl.a-star.edu.sg