Executive Summary of the Immune Privilege of Stem Cells and Cancer Immunotherapy Workshop

Date of Workshop: May 1, 2023

The Division of Cancer Biology (DCB) of the National Cancer Institute hosted the workshop on the topic of *"Immune Privilege of Stem Cells and Cancer Immunotherapy"* with a group of tissue stem cell biologists, cancer cell biologists and tumor immunologists, to discuss how research into tissue stem cell immune privilege can inform improvements in developing more effective and safer cancer immunotherapies.

Background

Cancer immunotherapies, such as checkpoint blockade and adoptive cell transfer, have achieved unprecedented clinical responses in some patients, however there is still a long way to go to extend the success from a small fraction to all cancer patients. Immune evasion and immune suppression are central issues in innate and acquired resistance to cancer immunotherapies. It is known that tissue stem cells have certain "immune privileges" which are important to avoiding immune destruction and maintaining tissue homeostasis. It is also known that the mechanisms of stem cell immune privilege can be hijacked by tumor cells to evade immune destruction. However, whether and how the mechanisms of stem cell immune privilege are connected to the immune suppressive tumor microenvironment and resistance to immunotherapy is not clear. Lastly, in overcoming the immune evasive and immune suppressive attributes of cancer cells, next generation immunotherapies will need to avoid breaching the immune privileges of normal tissues so as not to trigger autoimmune or other adverse events.

Workshop goals

To evaluate the current state of the science and future directions of cancer immunotherapy requires a multi-disciplinary approach. This workshop, *"Immune Privilege of Stem Cells and Cancer Immunotherapy"* brings together a team of tissue stem cell biologists, cancer cell biologists, and tumor immunologists with the goal to:

1. Assess the current research on the mechanisms of stem cell immune privilege, including both tissue stem cells and cancer stem cells.
2. Evaluate whether those mechanisms might be related to immune evasion and the immune suppressive microenvironment in tumors.
3. Discuss the gaps in our current knowledge and the challenges and opportunities for improving cancer immunotherapy.

Workshop participants

A panel of fifteen experts with diverse research background in tissue stem cell biology, cancer cell biology and anti-tumor immunity participated in the workshop. An organizing committee consisting of workshop co-chairs and the NCI staff organized and coordinated the workshop. The workshop was also facilitated by DCB, NCI leadership and other staff members.

Summary of the workshop

Drs. Elaine Fuchs from the Rockefeller University and Justin Lathia from the Cleveland Clinic co-chaired the workshop. The workshop was held in person at the NCI Shady Grove Campus in a one-day meeting consisting of four sessions: 1) Immune Evasion Mechanisms of Stem Cells; 2) Signaling Networks, Transcriptional and Epigenetic Regulations Underlying Cancer Stem Cell Immune Evasion; 3) Stem Cells, Niche Microenvironment and Immune Homeostasis; 4) Stemness, Plasticity in Immune Evasion and Immunotherapy. A roundtable discussion was held at the end of the workshop, in which the participants shared their research experience and insights on related topics and discussed how the field of cancer immunotherapy might be informed by stem cell immune privilege research.

Key topics discussed at the workshop

Over the past decade, the development of immune checkpoint blockade (ICB)-based immune therapies has made remarkable progress in treating certain types of cancer, including non-small cell lung cancer, renal cancer, and melanoma. However, not all types of cancer respond to immune therapy with the same efficacy and some responders relapse eventually due to intrinsic and acquired immune evasion mechanisms. Understanding the mechanisms of immune evasion is fundamentally important for designing improved cancer immunotherapy strategies. Adult stem cells play an essential role in tissue homeostasis and regeneration. Stem cells possess self-renewing ability and can accumulate mutations over time, which potentially can mark the stem cells as targets for cytotoxic T cell elimination. However, it is known that tissue stem cells have certain “immune privileges”, which are important to avoid immune destruction and help maintain tissue homeostasis. It is believed that cancer stem cells can hijack the mechanisms of stem cell immune privilege, leading to immune evasion and/or immune suppression.

The immune evasion mechanism of stem cells and the various ways cancer stem cells adopt those mechanism to evade immune destruction were important topics discussed at the workshop. The signaling networks, transcriptional and epigenetic regulators that govern those immune evasion mechanisms were also discussed. Participants shared their research in various tumor models including breast cancer, glioblastoma, colon cancer, lung cancer, hepatocellular carcinoma, squamous cell carcinoma and leukemia. Further, a better understanding of immune surveillance of dormant metastatic tumors may contribute to our understanding of the mechanisms of immune privilege. The role of cancer stem cell and immune cell interactions, cytokine mediators and their impact on tumor immune microenvironment were also examined.

In a broader context of tissue homeostasis, while overcoming mechanisms of immune privilege can lead to tumor elimination such approaches can also lead to tissue inflammation and autoimmunity - immune-related adverse events (irAEs) that interfere with the application of effective immunotherapies. irAEs are autoimmune or inflammatory reactions in normal tissues caused by cancer immunotherapy, most often ICB. Checkpoints are “brakes” built in the immune system, the inhibition of which by ICB will shift the balance from tolerance/immune evasion towards enhanced anti-tumor immunity but also irAEs. Whether anti-tumor immunity and irAEs are distinct processes caused by ICB and how they can be separated are critical topics in the field of cancer immunotherapy research.

Cancer cell stemness and plasticity play important roles in immune evasion. How do stemness and plasticity of cancer cells contribute to a protective niche microenvironment and lead to immune evasion was another focus of the workshop, including various regulatory mechanisms underlying those complex interactions. A round table discussion was held at the end of the workshop, during which the discussion was about how and what we can learn from the research about stem cell immune privilege and use that knowledge to help design more effective cancer immunotherapy approaches. One challenge is that the research in this area requires diverse expertise including cancer cell biology, stem cell biology and tumor immunology, and it is recognized that multi-disciplinary approaches are necessary. Participants felt the workshop was helpful in bringing focused attention to the issue of cancer stem cell immune privilege and voiced their enthusiasm for support and continued discussion in order to design more effective strategies for cancer immunotherapy.

Participant information

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Agenda – May 1, 2023

8:00 – 8:10am **Dr. Daniel Gallahan (Division Director, DCB/NCI)**
Opening remarks and Logistics

Morning Session chairs: Drs. Justin Lathia and Tannishtha Reya

8:10 –9:30am **Session I: Immune Evasion Mechanisms of Stem Cells**

8:10 – 8:30am **Justin Lathia, PhD, (Cleveland Clinic)**
8:30 – 8:50am **Judith Agudo, PhD, (Dana Farber Cancer Institute)**
8:50 – 9:10am **Yuxuan Miao, PhD, (University of Chicago)**
9:10 – 9:30am **Omer Yilmaz, MD, PhD, (Massachusetts Institute of Technology)**

9:30 – 10:00am **Break**

10:00 – 11:40am **Session II: Signaling Networks, Transcriptional and Epigenetic Regulations Underlying Cancer Stem Cell Immune Evasion**

10:00 – 10:20am **Tannishtha Reya, PhD, (Columbia University)**
10:20 – 10:40am **Linheng Li, PhD, (Stowers Institute)**
10:40 – 11:00am **Bradley Bernstein, MD, PhD, (Harvard University)**
11:00 – 11:20am **Massague Joan, PhD, (Memorial Sloan Kettering Cancer Center)**

11:20am – 12:40pm **Lunch Break**

Afternoon Session Chairs: Drs. Elaine Fuchs and Ronald DePinho

12:40 – 2:00pm **Session III: Stem Cells, Niche Microenvironment and Immune Homeostasis**

12:40 – 1:00pm **Elaine Fuchs, PhD, (Rockefeller University)**
1:00 – 1:20pm **Alexander Rudensky, PhD, (Memorial Sloan Kettering Cancer Center)**
1:20 – 1:40am **Michael Karin, PhD, (University of California, San Diego)**
1:40 – 2:00pm **Rosandra Kaplan, MD, (National Cancer Institute)**

2:00 – 2:30pm **Break**

2:30 – 3:30pm **Session IV: Stemness, Plasticity in Immune Evasion and Immunotherapy**
2:30 – 2:50pm **Catriona Jamieson, MD, PhD, (University of California, San Diego)**
2:50 – 3:10pm **Carla Kim, PhD, (Boston Children's Hospital)**
3:10 – 3:30pm **Ronald DePinho, MD, (MD Anderson Cancer Center)**

3:30 – 3:50pm **break**

3:50 – 4:45pm **Session V: Round Table Discussion On Questions Below to be mediated by Drs. Ronald DePinho, Justin Lathia and Elaine Fuchs**

1. Mechanisms of stem cell immune evasion: whether and how it is connected to the initiation and maintenance of the immune suppressive environment in tumor?
2. What are the roles of transcriptional and epigenetic regulation, post translational modifications, metabolism and microbiome in immune evasion of cancer stem cells?
3. Immune cells and stem cell interaction: what are their roles in tissue homeostasis, and in health and diseases?
4. What is the relationship between cancer stemness/plasticity and immune evasion?
5. Can we target cancer stem cells in immunotherapy?