Eight big questions in cancer research

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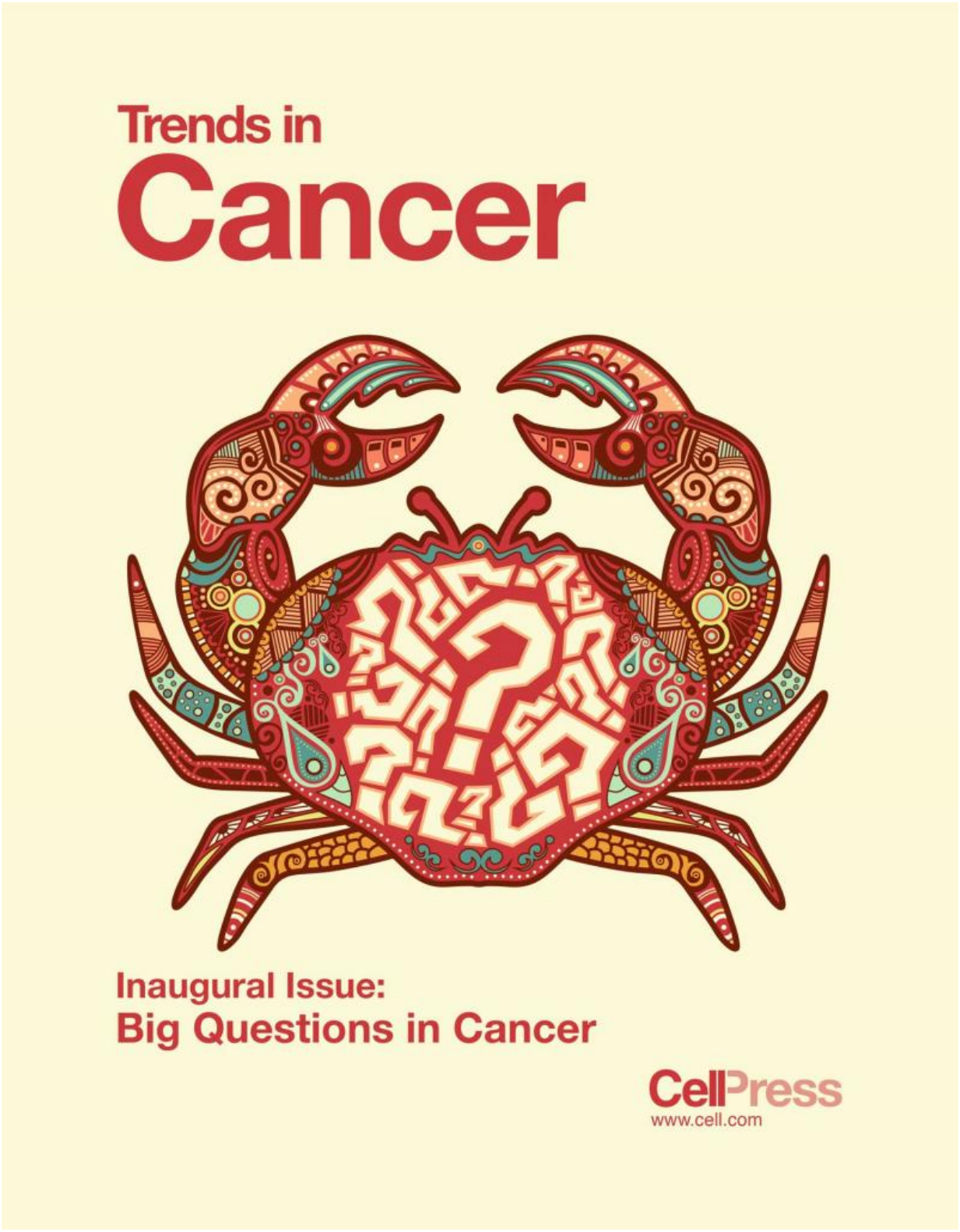

Cover of Trends in Cancer. Credit: Cell Press 2015

Leading cancer researchers address eight of the "big questions" facing the field as part of the inaugural issue of *Trends in Cancer*, published by Cell Press.

1. How can knowing the mutations that cause a patient's cancer shape treatment?

Scientists have spent decades learning the precise genetic mutations that can cause a cell to start dividing uncontrollably. Cancer patients can now have their tumors sequenced to identify the genetic root of their disease—and we have targeted treatments for many of these genetic alterations—but we are still very much in the early years of making the most of genomic data.

Enter the U.S. Precision Medicine Initiative (PMI), launched during President Obama's 2015 State of the Union Address. It includes a focus on cancer that aims to identify new clinical situations in cancer where targeted treatment will be effective, study potential resistances, and develop databases that aggregate patients' health data to help doctors make better clinical decisions.

"The precision medicine initiative in oncology is focused on treatment," says Douglas Lowy, Acting Director of the U.S. National Cancer Institute. "However, we also need to recognize that prevention and screening are key areas that do not fall within the PMI per se but are areas where we look forward to making substantial progress."

Source: "Douglas Lowy: Precision Medicine gets Presidential Treatment"
http://www.cell.com/trends/cancer/abstract/S2405-8033(15)00017-5

2. Can we reduce different cancers to a set of common traits?

In 2000, researchers Robert Weinberg and Douglas Hanahan proposed the "Hallmarks of Cancer" in a landmark *Cell* review (DOI: 10.1016/S0092-8674(00)81683-9). Their short list of underlying principles that define a cancer includes evasion of cell death, the ability to grow self-sufficiently, insensitivity to antigrowth signals, tissue invasion and metastasis, limitless cell division potential, and the development of blood vessels.

Since the paper (which is the most-downloaded and -cited paper ever published in *Cell*) was published, new studies have added two emerging hallmarks: abnormal cell metabolism and evasion of the immune system.

"The notion that cancer was a single disease (as might be concluded from the notion of a common set of hallmarks) was of course an illusion," says Weinberg, who studies the molecular mechanisms of cancer at the Whitehead Institute of Biomedical Research and MIT. "While the general principles of cancer formation may extend widely over many tumor types, the detailed behaviors of cancer cause each tumor to be a unique entity—a unique invention of nature."

Source: "Robert Weinberg: Beyond Hallmarks" http://www.cell.com/trends/cancer/abstract/S2405-8033(15)00013-8

3. Why should we care about the tumor microenvironment?

Cancer cells don't exist in isolation. They work together. They co-opt blood vessels and extracellular tissue. A well-developed cancer is like an unwelcome organ, stealing resources from the rest of the body. The idea

that the surrounding environment where a cancer grows is an essential part of the tumor and determines its survival has forced researchers to rethink how cancers form and grow.

"In the past three decades, I have shown with David Dolberg that even potent oncogenes are not sufficient to form a tumor, only under certain circumstances," says Lawrence Berkeley National Laboratory's Mina Bissell, a pioneer in this area. "They need to collaborate with the immune system and require many other steps and events to make a cell truly malignant. The architecture of the tissues is the key to understanding why cancer is an organ-specific disease."

If precision medicine is to be successful, Bissell argues that we need to further study the different environments that support a breast cancer tumor versus a liver tumor. She hopes that we can perfect and maximize 3D models of cancers by using organoids surrounded by their relevant microenvironments. Such studies could help us test therapies that keep tumors dormant or even prevent them from metastasizing.

Source: "Mina J. Bissell: Context Matters"
http://www.cell.com/trends/cancer/abstract/S2405-8033(15)00020-5

4. Does epigenetics play a role in cancer?

Cancers are often defined by the mutations that cause them, but mutations aren't the only way to change DNA. What we know about cancer is being changed by the rising field of epigenetics, which seeks to understand the physical changes made to DNA that do not alter the genetic code but change the message encoded (e.g., adding a chemical compound to a sequence of DNA so that those genes are no longer expressed).

"Cancer epigenetics was transformed by the unexpected finding that

many of the genes most commonly mutated in human cancers are epigenetic modifiers, thus clearly linking genetic and epigenetic processes in cancer," says Peter Jones, Research Director and Chief Scientific Officer of the Van Andel Research Institute.

"Indeed, some pediatric tumors seem to have DNA methylation alterations in the absence of detectable mutations," he says. "These findings strongly support the notion that epigenetic misregulation directly participates in carcinogenesis."

The future of cancer treatment may involve epigenetic therapies, which are currently being tested for particular lymphomas. Earlier success has been seen in blood cancers, rather than in solid tumors, but there is hope that they can be combined with immunotherapy to boost other patient responses.

Source: "Peter Jones: Leaving a Mark on the Cancer Genome" http://www.cell.com/trends/cancer/abstract/S2405-8033(15)00014-X

5. Will immunotherapy be a turning point in the fight against cancer?

Cancer immunotherapy—the harnessing of the immune system to fight cancer cells—was a quiet field until researchers began to prove that it could treat patients who cannot be helped by traditional therapies. Cancer cells are able to evade the immune system, and these immune strategies wake T-cells up. So far, the treatments work best with blood cancers and melanomas.

"Some patients whose whole life expectancies were measured in months when they began treatment are still alive and active today," says Suzanne Topalian, a major contributor to the field, of the Johns Hopkins

University School of Medicine and Sidney Kimmel Comprehensive Cancer Center. "These drugs are now showing activity in the first-line treatment setting, where they may replace or become an adjunct to conventional chemotherapies and kinase inhibitors."

Immunotherapy still faces some major challenges, such as how to select patients who are most likely to benefit from the therapy and how to determine the correct sequence to deliver therapies in combination with other treatments. Researchers are particularly optimistic about these combinatorial approaches, in which patients are treated with both immunotherapy and traditional chemotherapy and radiotherapy at the same time.

Source: "Suzanne Topalian: Unleashing the Immune System to Fight Cancer"
http://www.cell.com/trends/cancer/abstract/S2405-8033(15)00019-9

6. Will p53 ever realize its promise?

The gene that encodes for the p53 protein is among the most frequently mutated genes in cancer. The normal activity of p53 prevents cancer, and there are several different types of p53 mutations that cause tumor growth and aggressiveness. This has tantalized researchers because p53 represented a possible therapeutic target that could have a wide impact across many cancers. Unfortunately, the protein complexity proved to be more challenging than researchers anticipated.

"Ten years ago the function of p53 seemed clear, in that it activated cell cycle arrest and apoptosis in nascent tumor cells, thus preventing cancer development," says Karen Vousden, Director of the Cancer Research UK Beatson Institute. "However, over the past 10 years we have come to appreciate the many and diverse functions of p53—from roles in stem cell reprogramming to the control of the metabolism and the immune

response."

These complexities give researchers many more options to harness its functions for therapy, she adds. Current drugs work to turn p53 back on in cancer cells. The drugs can work very well, but they are associated with toxic side effects and drug resistance. Future approaches could focus more on targeting vulnerabilities that lead to p53 loss of function in the first place.

Source: "Karen Vousden: Guardian of the Genome"
http://www.cell.com/trends/cancer/abstract/S2405-8033(15)00018-7

7. Can differences in cancer cell metabolism be exploited?

Cancer cells use energy differently compared to normal cells because tumors require different kinds of fuel to continuously grow. This property of cancer has received a surge of interest in recent years as researchers consider how potential therapies could disrupt cancer cell energy consumption.

One major issue facing metabolic approaches to treating cancer is that normal cells also depend on the same metabolic pathways. This means that treatments that exploit cancer cell metabolism could have chemotherapy-like side effects.

"However, there is also some reason for optimism," says Craig Thompson, President and CEO of the Memorial Sloan Kettering Cancer Center. "Our expanding knowledge of anabolic metabolism [the fuel of cancer cells] should allow us to exploit metabolic dependencies of proliferating cells using agents that are not mutagens [such as chemotherapies]."

Source: "Craig Thompson: Fueling Cancer"
http://www.cell.com/trends/cancer/abstract/S2405-8033(15)00016-3

8. Are mouse models still relevant to study human cancers?

We are not too far away from a time when cancer 3D organoids, derived from patients' cells, can more faithfully replicate human cancers in a laboratory dish. After decades of curing cancer in mice, this new era redefines the preclinical step, by allowing us to test potential therapies in human tissue.

But mouse models of cancer have led to many groundbreaking insights into the disease, and with recent advances in genetic manipulation, no other experimental system can currently rival the customizability of the laboratory mouse. Scientists can now create humanized mice, with human versions of cancer-causing genes, to study multiple mutations at once.

"Mouse models are great to test cancer-relevant concepts in an in vivo setting, but one should realize that mice are not small humans," says Anton Berns, Sr., Group Leader at The Netherlands Cancer Institute. But for being able to study the complex genetics found in human tumors, "there are still quite fundamental lessons to learn here, and the mouse is the system of choice to answer these."

Source: "Anton Berns: Tackling Cancer with Mice"
http://www.cell.com/trends/cancer/abstract/S2405-8033(15)00015-1

Provided by Cell Press