The ‘intelligent’ human immune system can respond naturally to fight cancer

Dr Xuemei Zhong, PhD, is Assistant Professor of Medicine at the Boston University School of Medicine, in the Haematology and Oncology section of the department. Her research looks at how the ‘intelligent’ human immune system can be stimulated to fight diseases like cancer without reliance on high doses of drugs and short-lived therapies, with a particular focus on a process called immunosurveillance.

The ongoing battle against cancer may finally have an end in sight. According to Dr Xuemei Zhong’s ongoing research, our best hope for containing and clearing cancer lies in our first line of defence – our commander and army of foot soldiers, and our body’s very own doctor – the human immune system.

Dr Zhong and her team at Boston University are looking at ways of improving our understanding of this system as a tool to combat disease, to find new ways of reducing cancer rates without having to rely on the single-target-based treatments typically found in current therapies. Having identified a specific type of protective B cell (NIMPAB), her research has now established how vital these can be within the immunological process, due to their ability to mop up and kill cancer cells.

INTELLIGENT TACTICAL APPROACH

The part of the immune system that recognises and removes cancer cells naturally is called the ‘immunosurveillance’ system. This term describes the body’s ability to recognise and remove harmful cells. It differs from the conventional immune response in that it does not cause significant or systemic inflammation in order to remove threats to the body. Instead, it is an on-going, self-renewal maintenance process that operates in the background.

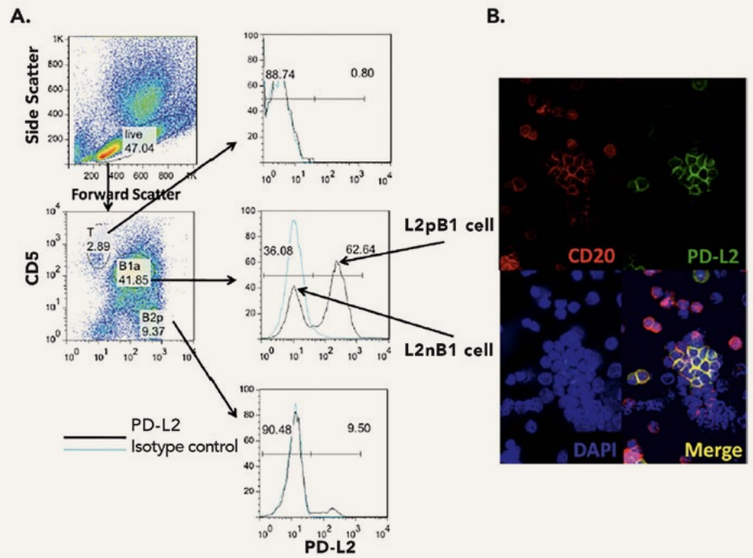
SURRENDERING THE VETERAN

Cancer treatments that stimulate the immune system typically induce the conventional inflammatory response. However, the effects of such methods are usually short-lived and difficult to control because cancer cells adapt rapidly and develop drug resistance.

Most cancer therapies focus on manipulating a single factor, such as a signal pathway or biomarker, without considering the 'ying and yang' sides of the same factor. For example, if you remove a causative factor, you may have removed the ‘attraction factors’ for healing. Dr Zhong says this slows down healing and explains the short-lived and ineffective nature of many current treatments.

LEARNING FROM FAILURE

When the body’s natural immunosurveillance system fails to remove cancer cells quickly enough, they accumulate and cause disease. By understanding what happens when this process goes wrong, Dr Zhong and her team aim to find methods of improving the system, and therefore of preventing cancer.



L2pB1 cells are a major B cell population in the peritoneal cavity. (A) Peritoneal washout cells from BALB/c mice were stained with anti-B220 (clone RA3-6B2, eBioscience), anti-CD5 (clone 53-7.3, eBioscience) and anti-PD-L2 (clone TY25, eBioscience) and analysed by flow cytometry. PD-L2 expression on each cell population is shown. L2pB1 cells and L2nB1 cells are highlighted by arrows. Isotype matched control antibody staining is shown as blue in the histograms. (B) A smear of peritoneal washout cells from BXSB mice was stained with anti-CD20 (clone L26 BioCare), anti-PD-L2 (clone TY25, eBioscience) and DAPI, as indicated, and examined by fluorescence microscopy.

In order to find ways of ‘restoring’ or ‘rebooting’ immunosurveillance, Dr Zhong has been focusing on specific and unique cells that are critical in the immunosurveillance system.

BUILDING AN ARTILLERY

Conventional B lymphocytes as we know from our biology text books are the B cells which produce antibodies against foreign bodies and inhibit their activity. Conventional B cells are also termed B-2 B cells to differentiate from the B cells that Dr Zhong's group has been studying in mice, which are termed B-1 B cells.

Both B-1 and B-2 B cells can fight against foreign invaders. However, B-1 B cells are also designed for immunosurveillance with their unique natural IgM antibodies and

Restoring the body’s natural ability to defend itself against disease is the key to unlocking more sustainable and effective cancer prevention and treatment”

other features to recognise, inhibit, kill and remove cancerous cells. Dr. Zhong named these cancer-fighting B-1 B cells "Natural IgM-Producing Phagocytic B Lymphocytes" (NIMPAB).

WAGING WAR

NIMPAB cells have been identified as a vital player in strengthening immunosurveillance. More specifically, Dr Zhong's team has found that a type of NIMPAB cells in mice, called L2pB1 cells, actively accumulate inside tumours. Depletion of L2pB1 cells in mice results in larger tumours. These cells displayed growth-inhibition and death-inducing functions in 3D tumour spheroid culture. Dr Zhong's group also found L2pB1 cells have potent antigen presentation capacity and thus are likely to present tumour antigens to T cells. These T cells are another type of white blood cell that form part of the immune system, which scan and kill tumour cells.

L2pB1 cells also secrete the highest amount of anti-inflammatory cytokine IL-10 among all B cells. This makes them the best B cell candidate to control inflammation in and around tumours. Regulating inflammation is critical for reducing angiogenesis and tissue damage to prevent tumour metastasis.

NIMPAB cells generate antibodies that are unlike those used in cancer drugs on the market. These antibodies occur naturally in both healthy individuals and cancer patients. The objective of Zhong's work is to stimulate the migration of these cells in and around tumours, which will allow them to kill and remove cancer cells without causing metastasis (the spread of cancer caused by cells breaking away and forming new tumours elsewhere in the body). Metastasis can often occur if an over-zealous inflammatory response is elicited.

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NO ATTACK, NO DEFENCE

It is difficult to manipulate the immune system without affecting its own healing mechanism. The ultimate goal for cancer immunotherapy is to restore immunity and then let it work on itself. To find a way of encouraging the production of NIMPAB cells around tumours, Zhong has been working with Dr Joyce Wong and Dr Tyrone Porter, who both specialise in nanomedicine, to develop novel nanotechnologies to mobilise NIMPAB cells in and around tumours.

Modern cancer treatments are limited by the rapid evolution and adaptation of cancer cells to new drugs and treatments. Zhong hopes that this more holistic approach to cancer treatment, which focuses on sustained, long-term improvements rather than single-focus, quick fix treatments, will improve patient outcomes and lead to better health. She believes that restoring the body's natural ability to defend itself against disease is the key to unlocking more sustainable and effective cancer prevention and treatment, and consequently better patient outcomes. It appears the foot soldiers on the frontline had the silver bullet all along.

Q&A

How crucial has your other work on diseases like lupus been in informing your research on cancer therapies?

Great question. We started to study the same type of B cells in autoimmune diseases like lupus. That was based on a traditional concept that autoimmune diseases are caused by auto-antibodies that recognise self antigens and consequently bring self-destruction to our body. Since the B cells we were interested in recognise mostly self-antigens, we thought they could be the cause of autoimmune diseases. Despite our finding that these B cells do generate antibodies that recognise self-antigens, our data showed something unique and contrary to what we hypothesised.

The auto-antibodies from these B cells do not just react to a single epitope of an antigen as with traditional B cells. Instead, the same antibody reacts to various self-antigens simultaneously. All these antibodies are IgM isotype with low affinity but high avidity and their DNA sequence is germline coded; they were the 'original design', not the result of external stimulation such as vaccination or infection. They exist in animals that have been born to totally pathogen-free, sterile environments. As reported by other groups, these IgM auto-antibodies are very different from those pathogenic auto-antibodies in autoimmune patients. Thus, this led us to hypothesise the function of these B cells in the opposite direction – their protective functions rather than pathogenic functions. This revelation led to our current research on the role of these B cells in the immunosurveillance of cancer because cancer cells are mostly 'self' and need to be recognised and removed. We believe the antibodies produced by NIMPAB cells recognise certain pattern of cancerous cells rather than a single marker. Moreoever, cancer cell elimination happens every day in healthy individuals without eliciting any autoimmunity. Our study led us to believe NIMPAB cells are the best candidate for such a job.

Are NIMPAB cells the only type of cells that stimulate the destruction of tumour cells?

No – in our immune system, no single type of cells or status of cells can work alone. It is always teamwork. However, NIMPAB cells play a very unique role. To put it in a metaphorical way, in healthy status, NIMPAB cells are like a custodian who patrols our body to remove senescent cells, cancerous cells, metabolic trash and toxins etc. In chronic disease status, NIMPAB cells are like rising liaisons or even commanders on the battlefield. They identify the problem as they are equipped with unique tools that others don't have, i.e., natural IgM antibodies and surface IgM and other receptors. They launch the first wave of solutions, secrete antibodies, regulatory cytokines to adjust inflammation level and phagocytose target cells and cell debris or vesicles. They relay the information to other cells by antigen presentation and cell–cell contact or by secreting chemokines to remotely recruit proper team members or soldiers to the battle ground. In summary, NIMPAB cells are not the only type of cells but play a central role in coordination.

Would an enhanced immunosurveillance response be more useful as a preventative or as a curative treatment for cancer?

The answer is 'both'. From a preventative point of view, the amount of NIMPAB cells and natural IgM in our body may indicate subclinical health status. Naturally boosting them may tip the scales and prevent the accumulation of small problems from mounting into chronic disease. In terms of treatment, supplementing NIMPAB cells and natural IgM will change the outcome of the on-going battle; like when your commander or troops are exhausted in a long battle and you suddenly airdrop fresh troops and a new commander to the front line.

How well do your findings translate from the mouse model to humans?

We have identified NIMPAB cells in both the mouse model and humans. We are confident that given the essential finances, personnel, and time, we will absolutely translate these into clinical treatment.

Can these treatments be applied to other diseases?

Absolutely. As we mentioned before, NIMPAB cells are the custodians of our body. Cancerous cells are one of the many things they take care of. All modern-day chronic diseases are a result of an imbalanced internal environment and the resultant accumulation of certain forms of cells, molecules and toxins in our body. NIMPAB cells and their natural IgM can benefit all kinds of chronic issues. One clinical example is IVIG. Through currently unknown mechanisms, IVIG can treat many diseases beyond its original use as a mere Ig supplement to help immunodeficiency patients battle infection. As large-scale industrial production techniques advance, you will see massive production of natural IgM for the treatment of many diseases.

Detail

RESEARCH OBJECTIVES

Dr Xuemei Zhong's work focuses on how the immune system works in dealing with chronic health issues like diabetes and cancer. The main objective for her work is to create an effective and self-sustainable immunotherapy against cancerous cells.

FUNDING

- Nanotechnology Innovation Center (BUnano)
- American Cancer Society (ACS)
- National Institutes of Health (NIH): National Cancer Institute (NCI)

COLLABORATORS

- Dr Tyrone Porter
http://www.bu.edu/medal/group-members/tyrone-porter/
- Dr Joyce Wong
http://people.bu.edu/wonglab/

BIO

Dr Xuemei Zhong received her PhD degree in Immunology and Pathology from Boston University School of Medicine. She is currently Assistant Professor in Medicine at the same school. Her research interest is to study the intelligent design of our immune system and the effects of our lifestyle on our immunity and most importantly how to restore our immunity to resolve top health issues like cancer. Her research project to develop a novel cancer immunotherapy, which is featured here, is laying the groundwork for a revolutionary future cancer therapy.

CONTACT

Xuemei Zhong, PhD
Assistant Professor of Medicine
Rm. 437A, EBRC, Section of Hematology and Oncology, Department of Medicine
Boston University School of Medicine
650 Albany St.
Boston, MA 02118
USA

E: xzhong@bu.edu
T: +1 617 638 7028
W: http://www.bumc.bu.edu/hematology/research/xuemei-zhong-phd-2/

/xuemei-zhong-09b55ba