It takes two to tango

Interplay between immunity and metabolism

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Interplay between immunity and metabolism

by **Nirmal Robinson**

Immunity can be defined as the ability of an organism to defend itself against invading microbes (bacteria, fungi and viruses) and the cells of its own origin which show abnormalities (e.g. cancerous cells). This protection is provided by various cells which originate from the bone marrow (Macrophages, neutorphils, B-cells and T-cells). These cells collectively form the immune system. The immune system is further classified into innate and adaptive immunity.

Innate Immunity

Innate immunity is the in-built protective mechanism in all kinds of cells and is conserved in all living beings. These non-specific mechanisms are always ready to respond to any invading organism. This type of defense in mammals is provided by:

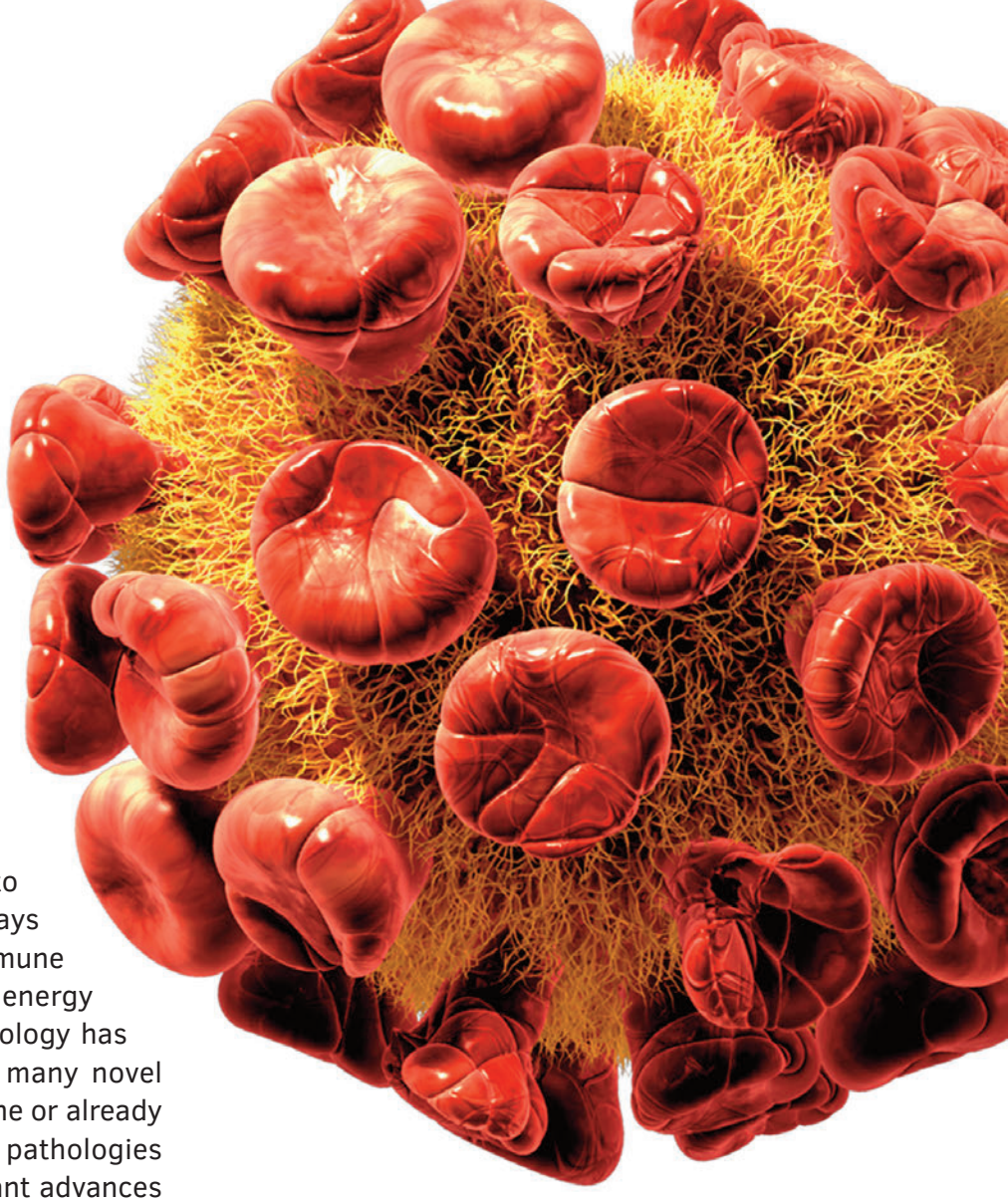
- The skin around the body
- The cells lining the gut and lungs, which produce mucous and trap invading bacteria
- Acid in the stomach that prohibits proliferation of microbes.
- Beneficial bacteria those are present in the gastrointestinal tract (GI), which prevent the growth of other bacteria and also help in digestion.
- Immune cells such as macrophages and neutrophils constantly scan the body for invading pathogens and they engulf and kill bacteria and other microbes.

Adaptive Immunity

The adaptive immune system, unlike the innate immune system is highly specific to a particular pathogen. It is mainly made up of T-cells and B-cells but they are primed to respond by the innate immune cells such as dendritic cells and macrophages. Once an adaptive immune response against a particular pathogen is triggered by T-cells or B-cells, they also keep the pathogen in their memory. A pool of cells specific against the pathogen is maintained over the life time to provide long-lasting protection. For example, a person who recovers from chicken pox is protected for life against the virus that causes chicken pox. This forms the basis for vaccination, which has been the corner stone for the increased longevity we cherish today. The ability to distinguish the molecules that originate from the pathogens and from the host is a fundamental feature of the adaptive immune system. Occasionally, the adaptive immune cells fail to make this distinction and turn out to be destructive to the host. Such an immune disorder is termed as autoimmune disease (e.g. multiple sclerosis, rheumatoid arthritis).

Immunometabolism

Thus, the immune cells perform various activities such as engulfing the pathogen (phagocytosis), producing anti-microbials and other proteins to attract other immune cells (cytokines and chemokines), disintegrating the pathogen, migrating to sites of infection, differentiation and trigger immune responses in other cells etc. Most of these actions



consume a lot of energy therefore the immune cells require considerable and rapid changes in metabolism in a very short period of time to meet the energy demand. Because of the numerous functions of immune cells under varied stressful conditions, metabolism is wired differently than the other cells in the body. Therefore, to bolster the immune function it is important to understand the metabolic pathways and the energy resources the immune cells use to meet the energy requirements. The field of immunology has been growing exponentially and many novel immunotherapies are in the pipeline or already in market to treat complicated pathologies such as cancer. Similarly, significant advances have been made in the field of metabolism. Interestingly, there is a growing interest in understanding how immune cells regulate their intracellular metabolism and how metabolic pathways converge in facilitating immune responses. Put together an area of research known as immunometabolism has emerged.

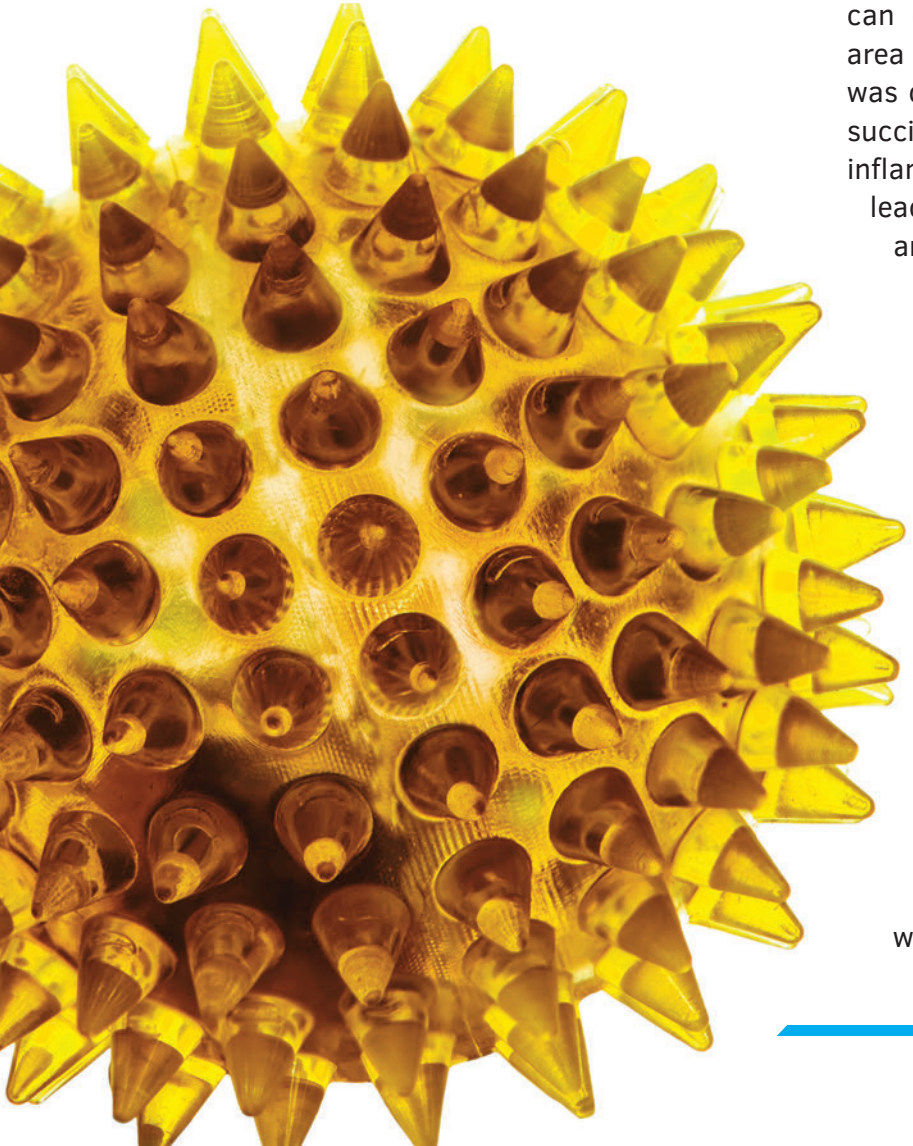
Cellular Metabolism

Cellular metabolism is vital for generating energy. The process begins with the break down of energy sources such as glucose, lipids and proteins. These molecules are metabolized (converted) in cells through a series of steps in glycolysis (glucose), fatty acid oxidation (lipids), and amino acid (proteins) oxidation into energy. This energy is better known as adenosine triphosphate or ATP. All the metabolic pathways mentioned above end up producing acetyl-CoA, which is the key source of carbon for the tricarboxylic acid (TCA) cycle.

During TCA cycle, acetyl coA is modified in the mitochondria to produce energy precursors such as NADH and FADH2. These energy precursors transfer electrons to Oxygen (O2) along the electron transport chain within the inner mitochondrial membrane resulting in the phosphorylation of ADP to ATP. This process is known as oxidative phosphorylation (OxPhos). It has been discovered that some cells (cancer cells) predominantly have a higher rate of glycolysis and the pyruvate generated via glycolysis is not converted to acetyl coA but is fermented to lactic acid in the cytoplasm. This occurs independent of the mitochondrial OxPhos to produce ATP, even when the components are available for OxPhos. This phenomenon was discovered by Otto Heinrich Warburg and is termed as the Warburg effect. On the other hand, some cells use the glycolytic pathway along with the OxPhos, to generate ATP.

Metabolism in Immune cells

All immune cells are not metabolically wired alike. For instance, Warburg effect is preferentially used by neutrophils, as this metabolic pathway produces the most hydrogen peroxide (H_2O_2), which is used by neutrophils to kill pathogens. Likewise, dendritic cells that are stimulated with lipopolysaccharide (LPS) or other toll-like receptor agonists also use the Warburg effect for its immune functions. Pro-inflammatory macrophages known as M1-macrophages also depend on Warburg effect to make ATP. Glycolysis and OxPhos are coupled when the pyruvate from the glycolytic pathway is converted to acetyl-CoA, which is further utilized by TCA cycle. Immune cells such as the activated T-cells, M2 macrophages (anti-inflammatory), and the Th17 T-cells are known to metabolically skew towards OxPhos. Finally, memory T-cells, regulatory T-cells and M2 macrophages undergo fatty acid oxidation, the process of using lipids to make ATP.



Bidirectional Crosstalk between Immunity and Metabolism

Metabolism not only determines the activation status of the cells but it is also involved in maintaining homeostasis among the immune cells and at various sites of infection and injury. Metabolite abnormalities in immune cells can cause deleterious effects, which is an area of intense investigation. In this regard, it was discovered recently that accumulation of succinate a product of the TCA cycle enhances inflammation. Dysregulation of metabolism leads to many pathologies such as diabetes and obesity, which closely involves immune responses. It also results in immune dysfunctions such as enhanced inflammation and susceptibility to infection. Susceptibility to infection is thought to be due to decline in innate immune responses by immune cells such as macrophages. Furthermore, the metabolic hormones such as insulin (produced in pancreatic beta cells) and leptin (secreted by adipose tissue) which malfunction in patients with metabolic disorders also critically regulate immune functions. Insulin signaling which facilitates glucose uptake, amino acid transport and lipid metabolism is known to be anti-inflammatory. However, leptin, which regulates food intake by inhibiting

appetite, is pro-inflammatory under a well-nourished condition. Moreover, in obese patients, accumulation of fat serve as a reservoir of immune cells resulting in the formation of increased lymphoid structures; meaning enhanced inflammation but reduced immune function.

Metabolism and Immunity declines with Age

Functional decline of immune cells termed as immunesenescene occurs in the elderly. Decline in various metabolic pathways and mitochondrial dysfunction are considered to cause immunesenescence. Immune cells are the major producers of reactive oxygen species (ROS) due to their metabolic nature. OxPhos in mitochondria is responsible for the generation of mitochondrial reactive oxygen species (ROS), which is linked to age-related pathologies such as autoimmune diseases, neurodegeneration and cancer. ROS is normally counter balanced by antioxidants, which is elevated in immune cells. However, with age the antioxidative responses decline resulting in overwhelming production of ROS and damage to various organs.

Therapeutic potential of immunometabolism

Improper immune function is associated with various complex pathologies including metabolic disorders. Therefore developing immunotherapies have taken a center stage. Many therapeutic strategies have been proposed at changing the metabolic system of immune cells. For example, metformin a drug that is used for the treatment of diabetes is now actively investigated as an anti-aging drug. US FDA has given the allowance to start the TAME (Targeting Aging with Metformin) trial to test the drug metformin in older adults who either have an age-associated disease or who are at risk of developing one. As we progress to understand the intracellular metabolic pathways that contribute to various immune functions and the role of the immune system in regulating metabolism, we will be able to develop better therapies for treating metabolic and immune disorders.

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Funding research excellence in Germany

Adjacent Government highlights the work of the German Research Foundation and in particular their Excellence Initiative…

Research and development (R&D) are 2 key areas for public funding in Germany, as they are the basis for new ideas and technologies of the future. In 2013 the gross domestic expenditure on R&D in Germany was estimated at €80bn. Higher education institutions are said to account for 18% of this spending, while non-university research institutions such as the Helmholz Centres and the Institutes of Fraunhofer-Gesellschaft invest 15% of the R&D total.

In recent years, Germany's power to innovate is said to have grown considerably. In order to further the growth in R&D, research organisations such as The German Research Foundation (DFG) aim to support and promote research excellence and facilitate national and international collaboration among researchers.

In its mission statement, the Foundation states: "In meeting its responsibilities as a research funding organisation, the DFG must remain abreast of current developments in higher education. In doing so, the DFG is able to address challenges such as the need to provide sustainable support for young researchers, the interdisciplinarisation of the sciences and humanities, and support for networking in the field of research."

The DFG can achieve their mission through funding programmes such as The Excellence Initiative. This began in 2006/2007 and aims to promote top-level research and to improve the quality of German universities and research institutions in general. Through this programme the DFG hopes to make the country a more attractive research location, and internationally competitive.

At the beginning of the year the DFG outlined expectations of the research community with regards to the planned new federal-state initiative for further development of the Excellence Initiative.

Speaking in January 2016, Professor Dr. Peter Strohschneider, President of the DFG, detailed the aims of the Initiative.

"The Excellence Initiative had a clear objective, towards which the funding lines, clearly categorised by function and format, were oriented," he said. "The different criteria of the funding lines determined the competition, and the distribution if funds was in accordance with the results of this competition, as established through scientific review and evaluation and therefore with the aims of the Excellence Initiative.

"The key features of the new federal-state initiative will include a science-based selection process that will promote the transparency and acceptance of funding decisions. Indeed, it was

the very nature of the trusting collaboration between politicians and the research community in the realisation of the aims in the Excellence Initiative, as well as the science-based nature of its processes, that earned this competition and the resulting funding decisions such exceptional recognition both nationally and internationally."

The DFG is jointly responsible for running the initiative together with the German Council of Science and Humanities. Between 2006 and 2011, €1.9bn in additional funding was received by the DFG for 3 funding lines of the Initiative:

- Graduate schools to promote early career researchers;
- Clusters of excellence to promote top-level research;
- Institutional strategies to promote top-level university research.

In June 2009 the Initiative was given approval for a further 5 years from the federal and state government, allocating €2.7bn of funding for the period 2012 to 2017.

"The DFG, which has acquired a wealth of experience in the Excellence Initiative, has described many times over the last 2 years the directions that it believes the funding formats and processes of the new round of competition should follow," said Strohschneider.

"We have proposed concrete development measures for the clusters of excellence funding line, which have been broadly welcomed both in the research community and by politicians.

"The broad consensus in the DFG is that the following points are crucial in the new initiative as a whole: Funding lines and procedures must satisfy the standard of excellence; universities and top level research must be the focus of all measures; and there must be a competitive process at the level of both research fields and institutions.

"Equally importantly, there must be openness in competition for all research fields and topics, there must be funding periods that can extend beyond normal project durations, and there must be access to the competition for both previously funded projects and new proposals," he said.

The DFG is the largest independent research organisation in Germany and its work to support and promote research across the country is integral to its success. As well as supporting researchers already in work, the DFG is leading the charge to support new young researchers make their first proposals for creative and innovative ideas.

The DFG provides useful information to young scientists in the process of submitting their first funding proposal. Through programmes such as this and the Excellence Initiative, research in Germany has some great backing and the ability to grow and tackle some of society's main challenges. ■

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