November 6-8, 2014

Immune Homeostasis and Inflammatory Disease

A Herrenhausen Symposium by *Nature Medicine* and the Volkswagen Foundation

Summary Report

Hygiene and medicine have overcome many infectious diseases but this has come at a price. As their impact declined, allergies and inflammatory diseases have become more prevalent in Western societies and developing nations. The reason for this shift in disease burden is a complex interplay between the environment, infection and chronic inflammation as the immune system has to keep a balance between pathogens, beneficial microbes and environmental factors; a major role of the immune system is therefore not only fending off pathogens but tolerating harmless or even beneficial bacteria. Removing an element, even pathogens or parasites, could disturb this carefully balanced system, which can cause allergies and inflammatory diseases, such as Crohn's disease, ulcerative colitis, chronic lung diseases and autoimmune diseases.

At the 9th Herrenhausen Symposium on Immune Homeostasis and Inflammatory Disease, 24 speakers and 180 participants discussed emerging data (derived largely from studies in mice but also clinical studies) on understanding host-microbe interactions and immune homeostasis, the ability of the immune system to keep a healthy balance between tolerance and defense, and how this could lead to new therapeutic approaches.

A pivotal interaction point of host-microbe interactions is at the level of innate immune receptors. There are now expanding families of innate immune receptors and sensors, and Jenny Ting started the meeting by describing innate immune sensors that can serve as activators of innate immunity, balanced by those which serve as checkpoints of inflammation to achieve homeostasis. Another crucial element is played by the human microbiota, particularly in the intestinal tract as gut bacteria outnumber human cells in the body by at least 100 times. Gerard Eberl[1] explained, that, as much as the host immune system can adopt any response between tolerance and inflammation to viruses, parasites, and bacteria, bacteria too can shift between mutualism and pathogenicity.

Add to this, environmental factors, in particular diet, and the gut is a good organ to study the intricate relationship between bacteria, diet and immune responses.

[1] All academic titles have been omitted.

These relationships are regulated by both immune and bacterial molecules – Eberl explained the role of vitamin A in shifting the balance between pro- and anti-inflammatory T-cells. Yang-Xin Fu similarly highlighted the role of lymphotoxin in regulating the function of tolerance-promoting T-cells. He also presented evidence that lymphotoxin regulates metabolism: a high-fat diet changes the microbiota, which induces lymphotoxin-dependent host responses, which in turn create a feedback loop to maintain an “obese”-specific host and gut microbiota.

The question is how to use this knowledge to manipulate this ecosystem and enhance health. Wendy Garrett presented her work on the role of short-chain fatty acids – the end products of bacterial fermentation of dietary fibers – which can increase the number and activity of anti-inflammatory immune cells in the gut and can even ameliorate chronic inflammation of the colon.

But, as Garrett pointed out, “there’s so much biology that we don’t understand”. Indeed, there is. Andrew Macpherson showed that the colon does not just contain one bacterial community but found at least two different ones in the lumen and the mucosal layer that covers the epithelial cells. As these are different ecological niches, it does not come as a surprise that these also harbor distinct microbiota.

Gut microbiota directly affect the health of the intestinal tract; Eugene Chang presented his work on the role of bacteria in Crohn’s disease and ulcerative colitis that have increased in prevalence during the past decades together with a high-fat diet. He demonstrated how milk fats can change the composition of the gut microbiome, which in turn can cause these inflammatory bowel diseases in genetically susceptible individuals. He also showed how the colonization of the gut by bacteria early in life sets the stage for allergies and inflammatory disease risk later in life as the newborn’s immune system “learns” the right balance between tolerance and defense.

The effects of diet and immune homeostasis in the gut affect other tissues and organs too. Ajay Chawla demonstrated how macrophages, a specific type of immune cells, act as messengers between the nervous system and fat tissue to help the body adapt to cold: fat cells short-circuit their metabolism to generate heat. Disturbing this communication not only dampens this adaptation but it could also contribute to obesity and metabolic disease; vice versa, manipulating this process could become a possible treatment for obesity.

Moving on to the lung, Benjamin Marsland showed that bacteria play an important role in inflammatory lung disease and how they can set up a tolerant state to protect from allergies when they colonize the respiratory tract. He also explained how diet and its effect on immune cells can influence the risk of inflammation in the lung via regulatory T-cells. It does not stop there: Stefanie Jörg presented data on how the composition of fatty acids in the diet may influence the development of autoimmune diseases elsewhere in the body.

Neutrophils are often the first immune cells to arrive at the site of infection and therefore play a crucial role in defining the immune reaction later on. Venizelos Papayannopoulos discussed how these cells make decisions about the proper strategy to attack invading fungal cells that, if they go wrong, can lead to either a cytokine storm, a massive overreaction by the immune system that can kill the patient, or chronic inflammation and ultimately disease.

Another first line of defense against pathogens is the innate immune system, a set of cellular and chemical general defense mechanisms to fend off pathogens until the adaptive arm of the immune system mounts a more targeted attack. Similar to how the communication between bacteria and the host can determine health and disease, the intricate chemical crosstalk between these cells is crucial for maintaining homeostasis. Andrew McKenzie, Jenny Mjösberg and Gregory Sonnenberg gave examples of how the innate immune system keeps a proper balance between tolerance and inflammatory responses. So-called innate lymphoid cells (ILC) play a crucial role in this process by triggering an early response to environmental cues and pathogens via a range of cytokine messenger molecules.

Some of these early responses are an important form of communication with the adaptive part of the immune system early during infection to prime the later defense. Again, communication failures can tip the system towards an overzealous immune reaction and inflammatory diseases. Thomas Korn further showed how the adaptive immune system can lose its balance and cause inflammatory disease in the brain: wrongly programmed immune cells migrate to the brain where they establish chronic inflammation.

The brain is a somewhat privileged organ as it lacks most of the cells that make up the immune system. Marco Prinz showed how microglia cells specific for brain tissue maintain homeostasis. Targeting these microglia with drugs could potentially help to treat inflammatory brain diseases.

Yet, microbes and cancer cells can also manipulate the chemical communication of the immune system to tip immune homeostasis to their advantage. Tim Sparwasser's group described a molecule that transforms pro-inflammatory T-cells into tolerance-inducing Treg cells, which could be a potential therapeutic for multiple sclerosis. Caetano Reis e Sousa explained how tumor cells exploit immune cell cross-talk by creating a "bad" inflammatory environment that suppresses immune responses and promotes cancer growth. Again, this could help to identify potential targets for drug development.

Innate immunity already begins before birth: Immo Prinz and Alberto Bravo-Blas showed how gamma delta T-cells and macrophages develop in the fetus to provide the newborn with a broad and generic immunity as soon as it is exposed to the environment.

To alarm the immune system of infection, body cells need to be able to identify pathogens. Jenny Ting, in her keynote talk, explained the role of receptor proteins that sense the presence of viral and bacterial DNA and other molecules, and toxic compounds such as asbestos and how these activate the so-called inflammasome. This process involves an array of sensors and modulators, many of which have more than one function which can also be negative or positive depending on the context.

Veit Hormung explored the role of molecules that recognize viral and bacterial DNA in the cell to warn the immune system. They also spread the message to neighboring cells in order to boost the immune response.

Fayyaz Sutterwala discussed how failure of this process can prevent cells from attracting immune cells to the site of infection. Andrea Puhar explained how infected cells release ATP as a general warning signal about infection. These sensory and warning systems also sense damage of the cell and can therefore trigger chronic inflammatory processes in the absence of pathogens.

Vishwa Deep Dixit discussed how manipulating this damage-sensing mechanism could help to treat age-related diseases and decay, which are often characterized by chronic inflammation. Specific drugs against these molecules could prevent age-related inflammation and allow the elderly to live healthier lives. Thirumala-Devi Kanneganti showed that blocking specific cytokines in mouse models prevents the symptoms of congenital inflammatory diseases characterized by rashes and severe joint arthritis in children; intriguingly, a high-fat diet also ameliorates arthritis in this model, highlighting again the role of the microbiota.

Immune homeostasis is a complex topic and much remains to be explored: from analyzing the composition of microbial communities, their metabolism of dietary components, the effect of environmental factors on the risk for inflammatory disease, and unraveling the crosstalk with and within the immune system. It requires bioinformatics and databases to better characterize the role of microbiomes in health and disease. It requires more clinical studies of inflammatory diseases in humans to overcome the limits of animal models. Scientists also need to better understand the function of immune cells and cytokines in the context of specific organs and tissues.

Understanding immune homeostasis and the relationship with microbial communities and the environment may generate new therapeutic approaches for inflammatory diseases. It will also help to inform lifestyle choices to decrease personal disease risk by manipulating our microbiota and reducing inflammatory responses. The research further supports the ‘hygiene hypothesis’ that exposure to many diverse microbes early in life guides the development of the immune system and helps maintain immune homeostasis. Given the increasing prevalence and burden of inflammatory diseases in the aging population, further research into immune homeostasis has great potential to improve human health.

Speakers (including short talks)

- Albert Bravo-Blas (University of Glasgow, UK)
- Eugene Chang (University of Chicago, USA)
- Ajay Chawla (University of California, San Francisco, USA)
- Thirumala Devi-Kanneganti (St. Jude's Children's Research Hospital USA)
- Vishwa Deep Dixit (Yale University, USA)
- Gerard Eberl (CNRS - Centre National de la Recherche Scientifique, France)
- Yang-Xin Fu (University of Chicago, USA)
- Wendy Garrett (Harvard School of Public Health, USA)
- Veit Hornung (University of Bonn, Germany)
- Stefanie Jörg (Universitätsklinikum Erlangen, Germany)
- Thomas Korn (Technische Universität München, Germany)
- Andrew MacPherson (University of Bern, Switzerland)
- Benjamin Marsland (University of Lausanne, Switzerland)
- Jenny Mjösberg (Karolinska Institute, Sweden)
- Andrew McKenzie (Medical Research Council, UK)
- Venizelos Papayannopoulos (Medical Research Council, UK)
- Immo Prinz (Hannover Medical School, Germany)
- Marco Prinz (University of Freiburg, Germany) Caetano
- Andrea Puhar (Institut Pasteur, France)
- Caetano Reis e Sousa (London Research Institute, UK)
- Gregory Sonnenberg (University of Pennsylvania, USA)
- Tim Sparwasser (Hannover Medical School, Germany)
- Fayyaz Sutterwala (University of Iowa, USA)
- Jenny Ting (University of North Carolina Chapel Hill, USA)

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