



# Immunotherapy

NEWS



CONFERENCE SCENES



## Researchers identify new type of B cell involved in protection against sepsis

Named innate response activator (IRA)-B cells by the authors, a previously unknown type of B cell that can produce GM-CSF – a growth factor involved in the stimulation of various immune cells – has been described by a group of researchers from the Massachusetts General Hospital Center for Systems Biology (Boston, MA, USA). The team describes the cells as “gatekeepers of bacterial infection,” highlighting their role in the prevention of sepsis.

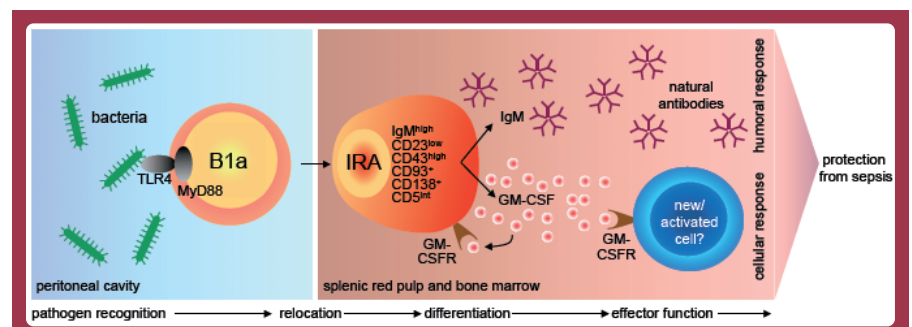
Sepsis is a life-threatening condition that currently has few treatment options. While it results from failure of the immune system to control the infection, the cells that do respond to the infection cause damage and septic shock. A therapy that provides a balance between controlling both infection and inflammation is therefore a necessity.

Based on their observation that GM-CSF was produced by a distinct group of B cells in the spleen upon challenge by a bacterial molecule, the group produced a mouse model that was incapable of generating IRA-B cells. The team discovered that the mice were subsequently unable to clear bacteria, exhibited exaggerated

inflammatory responses and were more likely to succumb to infection.

Speaking to *Immunotherapy*, Clinton Robbins, co-lead author of the study, noted that the team found their discovery surprising, considering that B cells were not previously known to produce GM-CSF *in vivo*. The team has also identified GM-CSF-producing B cells in humans, and Robbins explained that “It will be of interest to assess the relationship between the number and function of human IRA-B cells and the risk of developing sepsis and/or the capacity to respond to infection. We can then determine the diagnostic utility of IRA-B cells as well as their therapeutic potential.”

The group’s *in vivo* work has suggested that IRA-B cells, which develop from B1a B cells, respond to multiple pathogens, including bacteria and viruses. They may also be involved in regulating sterile inflammation. On recognizing bacterial infection within the peritoneal cavity, the B1a B cells migrate to and accumulate within the spleen or bone marrow, where they become IRA-B cells and secrete GM-CSF. This subsequently activates cells carrying the receptor for the growth factor,



### Development and function of innate response activator B cells.

Figure courtesy of Filip Swirski (Center for Systems Biology, Massachusetts General Hospital, MA, USA).



initiating the cellular immune response. IRA-B cells also produce IgM, activating the humoral response. These responses then result in protection from sepsis.

“We are currently determining the role of IRA-B cells in the development of many types of inflammatory responses,” explained Robbins. “Ultimately, our work may show that IRA-B cells are ubiquitously involved in the development and/or resolution of inflammation. In addition, we continue to decipher optimal conditions for

expanding IRA-B cells *in vitro*. This work will provide us with an important tool for mechanistic studies and allow us to assess the effects of autologous transplantation.”

Source: Rauch PJ, Chudnovskiy A, Robbins CS et al. *Innate response activator B cells protect against microbial sepsis*. *Science* 335(6068), 597–601 (2012).

## Researchers report boosted vaccine response using mast cell-inspired nanoparticles

A team from the Duke University Medical Center (Durham, NC, USA) has demonstrated a new strategy using synthetic nanoparticles as an adjuvant, enhancing immunity by targeting the lymph nodes. This is a more effective approach than exhibiting their activity at the skin, where other adjuvants exert their effect.

The adjuvant, shown to be effective in mice, consists of biocompatible and biodegradable materials, the core structure of which can be loaded with a variety of cytokines. The materials used in the particles are currently used in human medical applications and, as the delivery strategy is based on charge and the components have not undergone any chemical modifications, the group believes the particles will prove to be safe in humans.

The nanoparticles were developed based on the team’s observation of mast cells, which release granules upon an immune challenge in order to communicate directly with the lymph nodes. Ashley Lauren St John, lead author of the study, believes that their work can serve as a platform for the delivery of a variety of immunomodulatory cytokines to the lymph node. She explained to *Immunotherapy* that “Cytokines, which are carried in the backbone structure of these particles, have been effectively used in similar applications, but by targeting them to the lymph node we are able to extend their activity and allow smaller amounts of cytokine to be injected. As a result, we were able to achieve an antibody response in mice against influenza virus that was broader than that of the standard vaccine adjuvant, alum, in terms

of the antibody subclasses generated, and with higher avidity antibodies.”

“We see an opportunity to engineer vaccine formulations that would include a combination of cytokines, directing immunity towards the most efficient profile to promote clearance of a unique challenge,” noted St John. “We are exploring the possibilities of using this strategy to modulate lymph nodes to purposefully direct immune responses in additional inflammatory contexts.” The team now hopes to explore whether the strategy is effective in a therapeutic context, and to test the strategy in humans.

Source: St John AL, Chan CY, Staats HF, Leong KW, Abraham SN. *Synthetic mast-cell granules as adjuvants to promote and polarize immunity in lymph nodes*. *Nat. Mater.* doi:10.1038/nmat3222 (2012) (Epub ahead of print).

## Study demonstrates role of CD4<sup>+</sup> T cells in the immune suppressive role of myeloid-derived suppressor cells

Myeloid-derived suppressor cells (MDSCs), which normally have a role in keeping the immune system under control, can suppress the antitumor response and result in tumor escape. Recently, a team including researchers from the H Lee Moffitt Cancer Center (Tampa, FL, USA) and the University of South Florida (Tampa, FL, USA) has elucidated the cause of CD4<sup>+</sup> T-cell tolerance

in cancer, demonstrating that CD4<sup>+</sup> T cells themselves have a role in the enhanced immune suppressive activity of MDSCs.

Concentrating on two specific murine tumor models, the team discovered that MDSC-mediated T-cell tolerance is dependent upon cross-linking between MDSCs and MHC class II, an effect mediated by an increase in COX2 and

prostaglandin E2 expression. The relationship between activated antigen-specific CD4<sup>+</sup> T cells and MDSCs is thought to be involved in the control of the immune response via a negative feedback loop, which the researchers believe may become dysregulated in cancer.

Speaking to *Immunotherapy*, Dmitry Gabilovich (H Lee Moffitt Cancer Center)



explained that “This may present a novel powerful mechanism limiting the extent of immune activation in general and antitumor activity in particular.” He noted that “As we have shown that prostaglandin E2, via upregulation of COX2, was primarily responsible for the increased suppressive activity of MDSCs, this work gives additional impetus to the testing of therapeutic strategies targeting COX2 in combination with cancer immune therapy.”

The team is now interested in discovering whether CD4<sup>+</sup> T cells have the ability to cause a similar effect on myeloid cells in tumor-free hosts. Gabrilovich noted that “We are studying a possible implication of this work on induction and maintenance of immune responses in cancer and infectious diseases. We also plan to further explore the possible role of therapeutic regulation of prostaglandin E2 to enhance the effect of immunotherapy.”

Source: Nagaraj S, Nelson A, Youn JI, Cheng P, Quiceno D, Gabrilovich DI. Antigen-specific CD4<sup>+</sup> T cells regulate function of myeloid-derived suppressor cells in cancer via retrograde MHC class II signaling. *Cancer Res.* 72(4), 928–938 (2012).

## NIH provides grant to determine whether controlling inflammatory mediators can prevent obesity-related diseases

Researchers from the Eastern Virginia Medical School (Norfolk, VA, USA) have been provided with a 5-year grant by the NIH to study methods to reduce chronic inflammation, which is believed to cause many obesity-related diseases such as diabetes and heart disease.

The group, led by Jerry Nadler (Strelitz Diabetes Center for Endocrine and Metabolic Disorders, Norfolk, VA, USA), intends to study the regulation of the gene switch STAT-4, which is triggered by an increase in IL-12, an interleukin activated in obesity. The team has already demonstrated that control of STAT-4 can prevent long-term inflammation and its related diseases, discovering in preliminary studies that mice fed a high-fat diet develop insulin resistance and atherosclerosis, whereas mice fed the same diet yet

lacking the *STAT-4* gene do not develop these issues, appearing normal.

“If this works, it will open up a whole new idea of how to treat people with obesity and heart disease, and maybe even how to prevent diabetes.”

The group expects to investigate whether the fat surrounding the blood vessels feeds the vessel walls with inflammatory cells, a process that results in vascular disease. They will use mice and donated human tissue to determine the safety of controlling the STAT-4 switch and its efficacy regarding development of disease. “The cross-talk between visceral fat, vascular fat and blood vessels is an exciting, novel concept that may explain

better the complex relationship between obesity, diabetes and heart disease,” explained Anca Dobrian, a researcher on the team.

Nadler noted that “Right now we don’t have any treatments like this. Nothing is on the market to target that kind of inflammation. If this works, it will open up a whole new idea of how to treat people with obesity and heart disease, and maybe even how to prevent diabetes.” However, he highlighted that the treatment will not help to prevent obesity, simply to reduce its damaging effects.

Source: Eastern Virginia Medical School News Release: [www.evms.edu/eastern-virginia-medical-school/nih-grant-targets-obesity-and-disease.html](http://www.evms.edu/eastern-virginia-medical-school/nih-grant-targets-obesity-and-disease.html) (Accessed 3 February 2012).

– All stories written by Francesca Lake

### About the News & Views

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