Molecular Medicine



Podcast Transcript
Episode 24

Hello fellow scientists and welcome back to *Mollie Medcast*, the podcast for the biomedical journal *Molecular Medicine*. My name is Margot Puerta, I'm the Associate Editor for *Molecular Medicine* and I'm coming to you from Long Island, New York. In this week's *Mollie Medcast*: "New Risk Loci For RA," "Restoring Septic Immune Dysfunction," and a review paper discussing "TLR4 Polymorphisms."

Our mission here at *Molecular Medicine* is to publish biomedical research that helps us understand disease pathogenesis on a molecular level, which may lead to the design of specific molecular tools for disease diagnosis, treatment and prevention. Our podcast, *Mollie Medcast* includes short summaries of our recently published papers. If you're interested in submitting a manuscript to *Molecular Medicine* or just finding out more about any of the papers I discuss today, please visit our website for information, www.molmed.org. Okay so let's start with our first research paper:

**New Risk Loci For RA**

Rheumatoid arthritis or RA is a chronic autoimmune inflammatory disease and it's characterized by joint inflammation and progressive joint destruction. If you know someone who suffers from RA, you know their swollen joints can restrict movement and interfere with daily activities. Recently, several new genes with modest levels of risk for RA have been identified in various populations. Nevertheless, the major histocompatibility complex, or MHC, remains the strongest region of genetic association with this disease. Until recently this was assumed to be entirely due to the well-defined allelic associations with the class II HLA-DRB1 locus. However, it's also likely that additional risk loci for RA are present within the MHC, independent of the HLA-DRB1 locus. In this manuscript, Dr. Hye-Soon Lee and her colleagues now provide evidence for several new risk loci for RA which are located in the Class I region of the MHC, as well as in the region centromeric to the DRB1 locus. These data emphasize the need for more detailed analysis of the major histocompatibility complex in rheumatoid arthritis, a theme that is also emerging for other autoimmune diseases such as type 1 diabetes.

For those who are interested, the North Shore-LIJ Health System on Long Island (http://www.northshorelij.com) has over 1000 clinical research studies going on right now in a variety of diseases. Several of these studies deal with rheumatoid arthritis. So if you are interested in finding out more about this or any of our other studies, you can call the following number 516-562-4874. That number again is 516-562-4874 and ask for Ruth. You can also find this information on our Molecular Medicine website www.molmed.org. Go to the podcast link and select the transcript for this episode which is number 24. You'll be able to see the website for North-Shore-LIJ and see this phone number.

**Restoring Septic Immune Dysfunction**

Sepsis is the third leading killer in the US costing billions of dollars every year. Sepsis is associated with immunosuppression and this prevents the patient from developing an effective immune response against invading microorganisms. This may lead to the unrestricted spread of bacteria as well as multiple organ failure and death. Dendritic cells usually mount a protective T helper cell type response, also called a TH1 response. The impaired capacity of dendritic cells to mount such a response contributes to the immunosuppression seen in sepsis. Dr. Stefanie Flohé and her colleagues at the University of Essen, Germany and Oklahoma Medical

Research Foundation in Oklahoma looked at dendritic cells, which exhibit a suppressed cytokine secretion pattern during sepsis. Dr. Flohé and her colleagues analyzed immunomodulatory approaches to restore secretion of the cytokine IL-12, which is the key cytokine in TH1 cell development. Results show that the development of immunosuppression during sepsis is associated with an impaired capacity of splenic dendritic cells and macrophages to release TH1-promoting cytokines upon stimulation with bacterial products. Immunomodulatory cytokines not only increased IL-12 synthesis by dendritic cells early during sepsis, but also increased monocyte activity. Therapies that modulate the dysfunction of dendritic cells might have beneficial effects on the outcome of sepsis.

And now let's take a look at our review and assess paper:

**TLR4 Polymorphisms**
The innate immune system recognizes a broad range of pathogens and initiates protective responses. In order to initiate the proper response to a specific pathogen the innate immune system relies on pattern recognition receptors that detect preserved structures from bacteria, viruses, protozoa and fungi. Toll-like receptor 4 (TLR4) is an important pathogen recognition receptor that binds lipopolysaccharide of Gram-negative bacteria, structures from fungal and mycobacterial pathogens, and endogenous ligands. Two nonsynonymous polymorphisms of TLR4 may alter the function of the receptor. Dr. Bart Ferwerda and his colleagues in the Netherlands compare studies that assessed the effect of these polymorphisms on susceptibility to Gram-negative infections, and examine the phenotypic consequences of these polymorphisms. In addition, the geographical distribution of the TLR4 polymorphisms is reviewed, and a model for the evolutionary pressures on the TLR4 genetic make-up is presented. The title of their manuscript is, "Functional consequences of Toll-like receptor 4 polymorphisms."

That's it for this week's episode of "Mollie Medcast." Check us out again next time when we'll be 'Smoking Out Oxidants' and getting 'Stuck In A Filter.' You can find all these research papers and review articles on our website, www.molmed.org that's www.m-o-l-m-e-d.org. For questions or comments regarding this podcast, please send me an email at: margot@molmed.org. If you are thinking about submitting a manuscript but you're not sure if it fits within the scope of what we normally publish send me an email with an abstract and a few comments about your work and I'll get back to you. This podcast is available on molmed.org and is up in iTunes. Just go to iTunes and type *Mollie Medcast* in the search bar. If you've enjoyed listening to the podcast it would be great if you could post a comment. *Molecular Medicine* is published bimonthly by the Feinstein Institute for Medical Research.

From Long Island, New York, this is margot@molmed.org, thanks for listening!

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