Molecular Medicine

Mollie Medcast
Episode 6 Transcript: Metachromatic Leukodystrophy, Septic Shock

Good morning, afternoon, or evening, and welcome to "Mollie Medcast," the podcast for the biomedical journal, *Molecular Medicine*. This is Margot Gallowitsch-Puerta, Associate Editor for the journal and in this week's podcast: "STAT4 in the Korean RA Population," "These Transgenics Are Knockouts," and our feature cover article for the September-October Issue, "Pathways To Pediatric Septic Shock."

Before we get started with that, let's review our mission. *Molecular Medicine*'s mission is to publish novel work that's concerned with understanding the pathogenesis of disease at the molecular level, which may lead to the design of specific molecular tools for diagnosis, treatment and prevention. *Molecular Medicine* is published bimonthly by the Feinstein Institute for Medical Research located in Manhasset, New York.

Alright, so let's get started with the papers for this podcast.
The first paper in this podcast episode is:

STAT4 in Korean RA Population
Episode 5 from this podcast has a special scientific briefing interview with two of the authors from this manuscript Drs. Peter Gregersen and Dan Kastner. So if you find this summary interesting you may want to go there for some more information. Rheumatoid arthritis affects about 2.1 million Americans. The cause is unknown and there is no cure but managing the disease has become easier due to the use of new drugs, exercise, joint protection techniques and self-management techniques.1 Now, risk genes for rheumatoid arthritis have been identified in both White and Asian populations. However, divergent study results suggest genetic heterogeneity of rheumatoid arthritis across the major racial groups. A recent study in the North American White population has documented the association of a common STAT4 haplotype with risk for rheumatoid arthritis and systemic lupus erythematosus. So to examine this finding in the Korean population, Hye Soon Lee and her colleagues performed a case-control association study. Sixty-seven single nucleotide polymorphisms SNPs, or "SNPs" as we like to say, were genotyped within the STAT1 and STAT4 regions in over one thousand Korean patients with rheumatoid arthritis and also in over one thousand ethnicity-matched controls. The most significant four risk SNPs are identical with those in the North American study. All four of these SNPs have modest risk for rheumatoid arthritis susceptibility and a common haplotype defined by these markers carries significant risk for rheumatoid arthritis in Koreans. Unlike several other risk genes for rheumatoid arthritis, a haplotype of the STAT4 gene shows consistent association with rheumatoid arthritis susceptibility across Whites and Asians, and this suggests that this risk haplotype predated the divergence of the major racial groups.

So if anyone is 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. Over 15 of these studies deal with Rheumatology. So if you are interested in finding out more about this or any of our other studies really, you can call 516-562-4874 for information and ask for Ruth. That number again in case you need it is 516-562-4874. And if you want to look at the website, you can find the transcript for this episode at www.molmed.org and this phone number and the website to contact are in there.

The next paper for this podcast episode has the summary title:

These Transgenics Are Knockouts
I love that one. This paper deals with Metachromatic Leukodystrophy, which is abbreviated MLD, and Metachromatic Leukodystrophy is a member of a family of genetic diseases known as leukodystrophies. These diseases affect the growth, development and maintenance of myelin. And as we know, myelin is a covering that acts as an insulator around nerve fibers. MLD is a lysosomal storage disease, which is caused by a deficiency of arylsulfatase A (ASA). And this leads to the accumulation and deposition of sulfatide in oligodendrocytes and Schwann cells. The result is demyelination of the peripheral and central nervous system, and this can lead to neurological symptoms and unfortunately premature death. Enzyme replacement therapy is a putative treatment for Metachromatic Leukodystrophy, however, repeated injection of human arylsulfatase A (hASA) in ASA knock out mice elicits an immune response leading to treatment resistance, anaphylactic reactions and high mortality. In contrast to arylsulfatase A knockout mice, the majority of patients are not completely arylsulfatase A deficient. Rather they expresses a low or normal arylsulfatase A level with reduced specific activity or stability. Therefore, knockout arylsulfatase A animal models, which are currently the only available model for this disease, may not be truly representative of the patient population. So in this work entitled, "Induction of tolerance to human arylsulfatase A in a mouse model of metachromatic leukodystrophy," Dr. Matzner and his colleagues transgenically expressed an active site mutant of human arylsulfatase A in the knockout animals. This allowed tolerance to hASA and maintained the MLD-like phenotype. This novel transgenic strain may be advantageous to assess the benefit and risk of long-term enzyme replacement therapy in MLD.

The final summary that I'm going to go over in this podcast episode is from the cover of our September-October issue. It's the main image and there is a cute little girl holding a sunflower on there and the summary title is:

Pathways To Pediatric Septic Shock
Septic shock affects a large number of children worldwide. Morbidity and mortality associated with pediatric septic shock remain high and current therapy is limited to prevention and supportive care. Translational research at the genomic level may represent a powerful approach to more comprehensively understand the biological complexity of pediatric septic shock. In this paper, Dr. Thomas Shanley and his colleagues generated genome-level expression profiles from children with septic shock. They found that gene expression and functional analyses demonstrated time-dependent, differential regulation of genes involved in multiple signaling pathways and gene networks, primarily related to immunity and inflammation. The data in this paper represent the largest reported cohort of patients with septic shock subjected to longitudinal genome-level expression profiling. These data further advance our genome-level understanding of pediatric septic shock and support novel hypotheses. There is huge amount of data that goes along with this paper and there are several supplemental files on your website and if this topic interests you might want to check it out. Go to ***molmed.org*** and look for the September-October issue, which is currently up.

That's it for this week's edition of "Mollie Medcast." For more information on any of the manuscripts discussed in this episode or to submit a manuscript of your own (which I'd love), please visit our website, ***www.molmed.org*** that's www.m-o-l-m-e-d.org. This podcast is available on molmed.org and is up on also up in iTunes. For questions or comments regarding this podcast, please send me an email at: margot@molmed.org.

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