Importance of Metabolism in Drug Discovery

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Q&A

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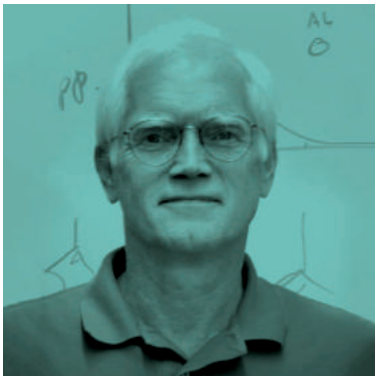

Understanding Complex Interactions in Metabolic and Cardiovascular Disease: Genetics, the Microbiome, Sex and Diet

Jake Lusis uses a systems biology approach to understand complex traits and diseases like diabetes and heart disease in humans and in animal models. By integrating clinical trait phenotypes with genetic, epigenetic, transcriptomic and other high-throughput data, his lab elucidates how genes interact with each other and with the environment, and how these interactions shape our health and diseases.

Could you give a brief introduction to your lab's work and its significance?

We do studies in humans, but most of our studies are focused on animal models. There are a number of advantages of course in using animal models; an important one is that we can control the environment. And another big advantage for us is that we have access to tissues and so on. And so we can apply high-throughput techniques, expression profiling or proteomics and so on, to the various tissues. This sort of multi-omics approach allows us to have a better idea of the pathways as well as the genes that are involved in various complex traits. It also helps us understand how these genes interact with each other and with the environment.

How does this approach help us develop better animal models for these complex diseases?

One of the issues in translating studies in mice or other animal models to humans is that, I think, a lot of people have the idea that all mice are pretty much the same. And that's really not the case at all. There's huge variation in any species and the way individuals respond to the environment, let's say for example, response to a high-fat diet, varies enormously. In the case of high-fat diet, what we find is that some inbred strains of mice don't experience any increase in body fat whatsoever. While other strains increase their body fat up to sevenfold.

So there's a huge, huge variation and let's say that you're interested in a particular pathway or particular gene and let's say you perturb that gene in a black six (C57BL/6) mouse. You make a transgenic or a knockout and you study the effects, and you draw certain conclusions. And on this basis you come up with some ideas in humans or a therapy in humans and so on. Well, you know, that doesn't mean that you would have seen those same findings in another strain. They may have been very different. And similarly, it also of course, depends on which humans you look at.

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So there’s just a lot of genetic diversity among inbred strains of mice and among humans. And I think very often that isn’t taken into account. A lot of people don’t even appreciate how much diversity there is.

I think one thing that I would recommend is that diversity be taken into account at least to some extent. Not everybody can study their favored gene on a hundred different genetic backgrounds. But I think being aware of those kinds of things is important.

And this sort of addresses the issue of epistasis as well. I think a lot of problems in human genetics arise just because genome-wide association studies ignore epistasis. In animal studies that we do, we see a tremendous amount of variation, a large fraction of the overall heritability, appears to be due to gene-by-gene interactions. If we’re ever going to have the ability to predict based on genotype and if we’re ignoring this complex part of it, the gene-by-gene interactions, I think we won’t really be very successful.

So how do you even begin to solve these problems and account for all of these interactions?

I think that you have to try to deal with the complexity. I’m not a bioinformatics person, but I work with bioinformatics people a lot. I have a colleague here at UCLA, Xia Yang, who’s developed a modeling approach that integrates a variety of omics-level data and also integrates GWAS-type data.[1]

As you know, for GWAS we set this very high threshold for significance to really say, ‘this locus has done something.’ It makes a lot of sense. But what she does is she takes the overall associations, even for associations that don’t meet this threshold for genome-wide significance. She carries out statistical modeling called driver analysis. On that basis, we have been making predictions about pathways and about genes that are involved in certain diseases and so on. We’ve been studying liver disease, where we feed mice a high-fat diet and some of the strains show a lot of accumulation of triglyceride and fibrosis. And others are totally resistant. And so we’ve done expression arrays and we’ve done some metabolomics in various tissues we’ve looked at. Xia has used her online platform, called Mergeomics, to predict four genes that we’ve tested in some detail. And the results have been really remarkable.

So, one way of dealing with this is to use math and statistics to integrate the data. And I think there’s been a lot of hype in that area. A lot of people who have done those kinds of studies are computer people who haven’t really tried to follow up on the biology and so on. But I think we’re getting there.

What single change do you think would have the greatest impact on our approach to modeling diseases for drug discovery?

It really boils down to how you view common diseases, and appreciating that really interactions are crucial. I think very often, people come up with simplistic models or animal models for these common diseases. You know, they come up with leptin. Leptin is obviously very powerful, right? But leptin never really, as far as I know, led us to a therapy.

Rather than being simple-minded and having your favorite gene and that is the answer, we have to understand interactions. We have to look at complex things.

Improving Translatability of Animal Models in Drug Discovery

By Arun Sanyal, Lauren Koch, and Anthony G. Comuzzie

Obesity and its consequences pose one of today's biggest public health challenges. This crisis has inspired numerous efforts to develop animal models that can recapitulate aspects of obesity-related diseases and conditions in humans, and provide insights into major contributing factors such as diet and exercise.

For instance, there is an urgent need for effective intervention in nonalcoholic fatty liver disease (NAFLD), a condition that can ultimately lead to liver transplantation for end-stage liver disease as well as liver cancer.

A mouse model, the Diet Induced Animal Model Of Non-alcoholic fatty liver Disease (DIAMOND™), recapitulates the stages of NAFLD. Created through[1] inbreeding[2] to produce an isogenic strain, DIAMOND mice initially become insulin resistant, obese and dyslipidemic, developing a condition similar to metabolic syndrome in humans.[3] The mice develop fatty liver disease in a manner that is similar clinically, metabolically and histologically to human disease progression.

Gene enrichment analysis indicates that the pathways activated have a strong concordance with human NAFLD. The mice also develop malignancies with tumor gene signatures similar to those in humans with NAFLD-associated hepatocellular carcinoma.

The DIAMOND mouse provides a tool to better understand interrelationships between pathways of disease progression and allows testing of the therapeutic potential of individual or combination therapies for NAFLD, related diseases and even heart failure associated with obesity. A number of compounds have been tested; some, showing therapeutic benefit, are in human trials.

Selective Breeding for Fitness

Lack of exercise is a major factor associated with obesity and metabolic syndrome. Researchers have conducted a large-scale, multi-generational study of rats to examine whether exercise capacity predicts metabolic health and disease. The study began by screening

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a large population of genetically heterogeneous rats for their ability to complete a treadmill exercise test. Some rats quit running after 10 minutes, while others ran up to four times as long.[4] The rats were then selectively bred over several generations to develop High-Capacity and Low-Capacity rats—that difference in exercise capacity has now doubled to over eightfold. Low-Capacity rats' average lifespan is around 2 years old, about six to eight months shorter than High-Capacity rats, indicating that exercise capacity predicts longevity.[5] Low-Capacity rats are at higher risk not just for metabolic syndrome, but also for its co-morbidities such as Alzheimer's-like neurodegeneration, cognitive decline, susceptibility to inducible breast cancer and premature aging.

Researchers also selectively bred rats for response to treadmill exercise training. Low-Response rats showed pronounced metabolic dysfunction characterized by insulin resistance and obesity compared to High-Response rats. Low-Response rats have less benefits from training, especially for blood vessel growth and remodeling, mitochondrial expansion and brain neurogenesis.

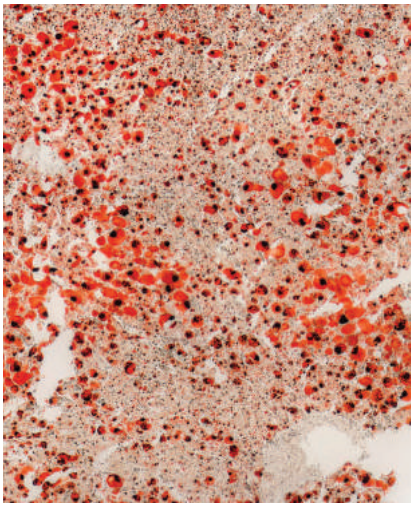
Studies using animal models developed by selective breeding bring together genetic history, current health status and health choices, such as lack of physical activity, in drug discovery. One recent study looked at why humans lose exercise capacity and gain weight with age. Researchers showed that aging increases DNA breaks and activates DNA-dependent protein kinase (DNA-PK) in skeletal muscle, which suppresses mitochondrial function, energy metabolism and physical fitness and leads to weight gain and chronic diseases.[6] There is 60 percent less DNA-PK activity in High-Capacity rats than in Low-Capacity rats. Researchers suggest that DNA-PK inhibitors may have therapeutic potential in reversing obesity and increasing exercise capacity.

The Power of Palatability

Non-human primates have proven especially useful to explore relationships between diet, obesity and related conditions.[7] Due to their similarity to humans, baboons can be used to study diet-induced metabolic dysregulation and to test compounds to treat this condition. They also can allow us to test more complex diets, manipulate elements of those diets and help develop diets that are palatable without encouraging overeating.

Palatability has been shown to be a surprisingly significant factor in how much the baboons eat. By adding fruit flavoring to food and baking it to increase palatability, for example, researchers have found that young baboons fed a high-sugar, high-fat diet consume larger amounts and develop increased body fat and triglyceride concentrations, altered adipokine concentrations and evidence of altered glucose metabolism.[8]

Although animals have long been used to help us discover new drugs, they have often proved to be imperfect models for humans and their diseases. Better animal models like these can help us understand diseases and find possible drug candidates that can successfully treat them.



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