Role of Human Immunogenetic Variation in Determining Susceptibility and Outcome of Infectious Diseases

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My responsibility here is to give you an overview of the importance of genetic variations in determining the host susceptibility and outcomes of infectious diseases. As most of you know, microbes can suddenly emerge or remerge, gaining new virulence, or they can mutate in ways that makes them better able to invade us, evade or exacerbate our immune system to cause disease. Meanwhile, the host is constantly trying to adapt to these changing pathogens, except that they (the microbes) are much better than we are in terms of being able to mutate, adapt and gain virulence. So, there is constantly a dynamic interaction between the host and the pathogen, and this interaction determines the outcome of the infection. Maintaining a balance is healthy, but sometimes it takes very little to tip this balance to where disease sets in.

So, what determines the outcome of the infection with respect to host susceptibility? There are non-specific factors, like age, gender, general health, pre-existing conditions of the host, or sometimes, a superimposed infection. There are also inherent host factors, of which the most important are the genetic factors, particularly those that regulate our immune response to pathogens. Variations in certain factors can determine whether we mount a protective immune response, an ineffective response or an aberrant immune response that actually elicits pathology (e.g. chronic autoimmunity or acute severe host-mediated pathogenesis and severe systemic disease).

When talking about genetics, we need to realize that virtually all human diseases have an underlying genetic component. Sometimes it is overwhelming, as in cystic fibrosis, sometimes disease is affected by a mix of environmental and genetic factors, but even in diseases where the environmental factors play a major role, such as in AIDS, we find that the genetic factors still contribute importantly to the progression of the disease, response to therapy and overall outcome.

So, from your practice, we know that in certain infections we find certain individuals to be highly predisposed and susceptible, others are totally resistant and protected and then, of course, there are some in-betweens. We believe it is important to study differences in immune responses of susceptible and resistant individuals to the specific pathogen, as well as determine genetic differences that may contribute to starkly different outcomes of the infection. This information gives us some clues as to the disease mechanism and can reveal the network of

interactive pathways that modulate infection outcome. The ability to identify those that are at high-risk versus low-risk of infection is important, especially when we are facing emerging pathogens and possibility of bioterrorism. We can devise means to allocate limited resources more effectively to those who need it the most. Also, information about disease mechanism provides potential targets for better diagnostics and therapeutics.

When we talk about genetic factors that affect infectious disease outcome we need to realize that all infectious diseases have important immunological component. So whereas many different genes could be interacting together to influence the outcome, immunogenetic variation among individuals plays a very important role in infectious diseases.

Immunogenetic factors that have been shown to be variable and that can influence infectious diseases include those encoding HLA, cytokines, chemokines, adhesion molecules, innate immune-response receptors etc. For example, variations in toll-like receptors can alter the magnitude of the signaling into the cell and therefore susceptibility to infection. Sometimes it is not the variation in the receptors, but in adaptor molecules that mediate their signals or that allow them to interact with other molecules. As well, polymorphism in members of the signaling pathways can have a major effect on the quality of the immune response to pathogens. In some cases, the same polymorphism that protects us from pathogen A can predispose us to pathogen B, and vise versa etc.

Because variations in HLA genes play a very important role in regulating the immune response, I will spend a few minutes discussing them. Major HLA genes are the class I, II and III. HLA class I mainly present antigens to CD8 T cells; the class II present processed peptide antigens to CD4 T cells. Both are important in selecting and shaping the T cell repertoire, and so they play a key role in regulating the development of our immune system and how we respond to pathogens. HLA class I antigens are denoted A, B and C; the class II are DP, DQ, DR. Each molecule is a heterodimers of an alpha and a beta chain. All class I and class II alpha chains, except for DR alpha, are highly polymorphic. Whereas the beta 2 microglobulin subunit of the HLA class I molecule is monomorphic, all of the HLA class II beta chains are highly polymorphic. In fact, HLA polymorphic genes exhibit the highest polymorphism in humans with over 1400 different class I alleles and about 800 different class II alleles identified to date. The polymorphism is not all over the molecule; rather, most of it lies in the antigen-binding groove.

When the structure of the antigen-binding groove is changed because of amino acid polymorphism, different peptides are bound. So, our MHC molecule may present to the T-cells certain peptides but not others. And, our neighbor who has different HLA allelic molecules, can present yet another set of peptides but not others and so on. If we had only one variety of HLA molecules (X), and we are infected with a pathogen whose protective antigen cannot bind into our MHC binding groove, we cannot mount a protective immune response to that pathogen, we can all die and the human population is extinct. Now, if we have two HLA varieties, e.g. an X and Y variety, and same pathogen still cannot be presented

by HLA type X, but can be presented efficiently by HLA type Y, then what will happen is all the homozygous X will die, all the homozygous Y will survive and are well protected, and the heterozygous are in-between. The problem is that this pathogen is very likely to mutate under the pressure of the immune response against it. It can mutate to where it is cannot presented by either X nor Y, and everyone dies again!

So the idea, as you can see, is the more HLA variation, the more likely the species is preserved. There is a lot of positive pressure on this particular locus to mutate the genes. That is why we have over 1400 different allelic values of class I, and 800 of class II, and then we have, of course a lot of permutations, in this individual.

And the idea is that the more we have, the more chances that at least some of us will survive in major pandemic and preserve the human population.

So, the idea here is that we are protected by the variation in the MHC molecule in 2 different ways. First polygenism, where we have different HLA alleles: class I, A. B, C and class II, DP, DQ, DR. Second, each one of the polymorphic HLA genes has so many allelic variants. The whole idea is that this variation allows the antigen binding grooves to present different peptides, and therefore, some individuals will be protected against certain infections; others will not – yet those could be better protected against yet a different pathogen. As these pathogens mutate, other individuals will still be protected as we constantly try to cope with these evolving pathogens.

I am going to cover some important concepts and variations on this genetic association issue. In some cases, the same allelic variants that protect us against a particular pathogen predisposes us to another. And this is very important, again, because we can be protected against pathogen A, but the same genes, mechanistically, can predispose us to pathogen B, and we have seen this in many infectious diseases. And you often will find in certain areas of the world, where certain infectious diseases seem to be pandemic, or prevalent, that most of the survivors have developed resistant genes (they were selected). A good example of that is malaria, in some areas of Africa. In other cases you will find that the protective HLA allelic variants for a particular pathogen, does not protect us against a mutant variant of the same pathogen, so that now people who used to be protected are no longer protected. An example of this came from this study by the CDC, where they looked at AIDS susceptibility and the effect of genetic mutation in the chemokine receptor, CCR5. There is a mutation when there is a deletion in the CCR5, a receptor for nonsyncytium-inducing form of HIV. The deletion prevents CCR5 from binding to the virus and thus people who are homozygous to this mutation are protected, while heterozygous people or those who do not have this mutation are susceptible o infection by this form of the virus. However, unfortunately in the same individual the virus can mutate from the nonsynctium-inducing form to the syncitium inducing form, which uses a totally different receptor, CXCR4 to get into the cell and targets a different cell population. The immune response to the first form of the virus puts pressure on the virus to mutate. You see this a lot in HCV and other viral infections, where as we mount immune

responses to the virus, they keep mutating, generating quasi species. This is an important thing to pay attention to when one is trying to develop a therapy for these individuals.
In some cases you have a risk allelic variant for a particular pathogen, and it converts into a protective phenotype against the same pathogen when present together with another gene variant. In other words you can have 2 different genetic variants where each alone could have a very different effect on the outcome of infection with say pathogen A, but when you put the two variants together, there is a totally different effect than with each one of them alone. This is called an epistatic interaction. A very nice example of that is in the KIR receptors, which are very important receptors on NK cells but also on some T cells. Those KIR receptors bind to very specific HLA class I molecules and they can either cause activation of NK cells, which then can fight the infection, or they can inhibit the activation of NK cells and, in this case, they cannot fight the infection.
So, Mary Carrington and her colleagues at Frederics did a very nice study in which she found that a certain variant of the KIR receptor, when it is present together with a certain variant of the HLA class I molecule B4 protects and delays the progression of AIDS in HIV infected individuals. However, when they looked at the effect of B4 alone, there was no association with disease outcome and when they looked at this KIR variant alone, it actually was associated with more rapid disease progression. So it turns out when you put the two variants together there was a strong protective effect. They hypothesized that when this HLA class I variant is binding HIV peptide (s), it actually allows interaction with this KIR variant in a way that activates NK cells to fight the infection. These are very interesting dynamic models.
Another last concept is that sometimes the association with HLA is not direct, but because of other genes that are in linkage with disequilibrium with particular HLA alleles. The MHC locus is so rich with important polymorphic genes, including those within the TNF locus, so one has to pay attention whether the association with disease outcome is direct or indirect.
There have been several direct associations between specific HLA alleles and a number of infectious diseases. We have been able to define HLA class II associations with different outcomes of group A streptococcal infections. The bacteria can cause minor sore throat, autoimmune diseases, or invasive infections (e.g. bacteremia) that can manifest in severe toxic shock and necrotizing fasciitis – the flesh eating disease – or non-severe mild cellulitis. Our studies showed is that individuals with certain HLA class II alleles seem to mount a much lower response to certain toxins called superantigens produced by the bacteria, and individuals who have this particular variant are strongly protected from the toxic shock. Whereas other variants cause the individual to be a high responder, producing very high levels of inflammatory cytokines that cause this person to be highly susceptible to the severe form of flesh eating disease. Group A strep is really a fascinating organism because of the large number of diseases it can cause, including diseases caused by the exact same strain. So, we have been able to map different genetic susceptibility in toxic shock, in necrotizing fasciitis and

in rheumatic carditis leading to rheumatic heart disease showing different HLA associations with each. This is important because it shows that there are different mechanisms for this disease.

This is my last comment, this is just to summarize that host-pathogen interaction is very important in determining the outcome. And that we are constantly trying to achieve a balance but it takes very little to cause disease. The genetic component plays a very important role in determining disease susceptibility and outcome. But why is it important? We're way past the time of just doing observation: ok, this gene is interesting; there is an association. That is not what we are after. We need to use this information to understand disease mechanism and thereby expedite the process of discovery and move forward to develop better diagnostics and therapeutics. This is our bottleneck here, and this what identifying the genetics of susceptibility to infectious diseases can do – it helps fish out the interactive network of pathways that modulate disease outcome, it helps us get the disease roadmap so we can prevent it or cure it.

Recommended readings

1. Kotb M, et al. An immunogenetic and molecular basis for differences in outcomes of invasive group A streptococcal infections. Nat. Med. 2002;8:1398-404.
2. Kotb, M., 2004. Genetics of susceptibility to infectious Diseases: How microbes select us. ASM News. 2004;70(10):457-463
3. Dean M, Carrington M, O'Brien SJ. 2002 Balanced polymorphism selected by genetic versus infectious human disease. Annu Rev Genomics Hum Genet. 2002;3:263-92. Epub Apr 15. Review.
4. Frodsham AJ, Hill AV. 2004 Genetics of infectious diseases. Hum Mol Genet. Oct 1;13 Spec No 2:R187-94. Review.
5. Blackwell JM. 2001. Genetics and genomics in infectious disease susceptibility. Trends Mol Med; 7:521526.