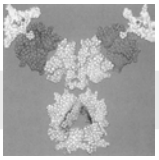

Immunodeficiency: Nobody is Immune

Amos Etzioni MD

Meyer Children's Hospital, Rambam Medical Center, Haifa, Israel
Affiliated to Rappaport Faculty of Medicine, Technion, Haifa, Israel

Key words: primary immunodeficiency, immunocompetent, genetic mutation

IMAJ 2005;7:756–757

At the WHO meeting on primary immunodeficiency held in Orvetto, Italy in 1994, mutations in the genes involved in the classical PID[1] disorders, such as X-linked agammaglobulinemia (Bruton), X-linked severe combined immunodeficiency and hyper-immunoglobulin M syndrome, were discussed for the first time. It was clear that very soon the primary molecular defect in many other PID disorders will be elucidated and that research in the field would thus come to a natural end. In the concluding remarks of the meeting however, the late Dr. Robert Good, founder of clinical immunology, challenged the point. In his opinion, "this was not the beginning of the end but just the end of the beginning of the PID field." He was utterly right, of course. Today, new insights regarding the definitions, classifications and ways to investigate immune deficiency have emerged. The current concept has been proposed in several recent papers, led mainly by Jean-Laurent Casanova from Paris [1–3].

The role of the immune system is to fight any infection. If an individual does not survive an infectious episode he/she is by definition "immunodeficient"! Infectious diseases have been the leading cause of death throughout history in most parts of the world [2]. Life expectancy in the industrial countries has risen, due to medical progress in three main areas: the development of the hygiene concept in the mid-19th century (preventing transmission), the invention of vaccine at the beginning of the 20th century, and the production of anti-infectious drugs. Thus, the ability of the human individual to defeat the infectious agent is not due to an improved immune system in the last 200 years but to improved medical care [2]. Higher life expectancy is not attributed to the natural selection of high quality immune system genes. Rather, the persistent defects in our immune functions have been masked by medical progress.

Today it is widely recognized that the immune response to various infectious agents involves a complex interplay between environmental and human (genetic and non-genetic) factors. Every winter infants are hospitalized in need of oxygen or assisted ventilation for bronchiolitis due to respiratory syncytial virus, yet the majority of those infected with the same virus have little more than a runny nose. A large epidemiologic study on the genetics of infections showed that individuals who were adopted in childhood display a markedly increased risk of death from infection if a biological parent had died prematurely of infection [4]. Previously, faced with a patient, so-called immunocompetent, with a life-threatening infection, we used to talk of "bad luck." But not anymore, with the comprehension that genetic and environmental factors contributed to the severe clinical symptoms in this specific individual. Natural immunity ensures the survival of the species, rather than that of every individual.

Recently it was shown that a single nucleotide polymorphism in caspase 12 is associated with reduced cytokine production and increases susceptibility for developing sepsis [5]. Although, in most cases, mutations are linked to a defective immune response to infections, in some cases they may be advantageous in the encounter with specific pathogens [6]. One excellent example is the fact that mutations in the CC-chemokine receptor 5 provide resistance to human immunodeficiency virus-1 infection. CCR5 was found to be a crucial molecule for HIV binding to CD4 T cells, and thus mutations in CCR5 prevent HIV entry into the T cells [7]. Resistance to malaria, in individuals with a mutation in the Duffy antigen promoter, provides another example. *Plasmodium vivax* invades human erythrocytes by binding to the Duffy antigen. Individuals with the mutation do not express Duffy on their erythrocyte surface, thus refuting the notion of parasite binding [8].

Until now our attention focused mainly on those rare cases with typical clinical symptoms and a marked abnormal immune function. The so-called conventional primary immunodeficiencies are classified mainly by their immunologic phenotype: defect in

PID = primary immunodeficiency
CCR5 = CC-chemokine receptor 5

HIV = human immunodeficiency virus
Ig = immunoglobulin

T cell, B cell, combined, neutrophils or complement. More than 100 different genes causing immunodeficiency have been identified and more are expected to be uncovered in the near future. It should be mentioned that different clinical syndromes might be caused by different mutations in the same gene. Mutations in the *WASP* gene can cause Wiskott-Aldrich syndrome, X-linked thrombocytopenia and, very rarely, X-linked congenital neutropenia [9]. The classical classification of PID, which took into account only the immunologic findings and the mode of genetic inheritance, poses several problems. For example, asymptomatic IgA-deficient individuals are "immunodeficient," while patients dying of infectious diseases without immunologic abnormality measured by current technology are defined as "immunocompetent."

The well-known fact that even with the same mutation, the severity of disease varies from patient to patient, further complicates the picture. To address this question Foster et al. [10] studied 129 patients with chronic granulomatous disease and different clinical symptoms. They looked at several host genetic factors, other than NADPH oxidase, that might influence the clinical outcome. They found that subtle changes (polymorphisms) in genes involved in the immune function, which may have little or no effect in the general population, could assume greater significance in individuals with defects in the host defense system, such as chronic granulomatous disease. It should be stressed that these polymorphisms act upon one or more pathways not disrupted by the primary defect [10].

Non-conventional primary immunodeficiencies include several cases with a genetic predisposition to a specific type of infection. The best example for such a PID is the "Mendelian susceptibility to mycobacterial diseases," where patients have mutations in the genes involved in the interleukin-12/interferon-gamma pathway [11]. Many life-threatening infectious diseases might indeed result from the Mendelian inheritance of a specific mutation. A number of common infectious diseases are likely to reflect non-conventional PID. Even more intricate is the common condition where infants suffer from recurrent infections during the first 2 years of life, mainly after entering kindergarten. The increased frequency of these benign fever attacks, in a subset of children with a completely normal immune function, reflects a combination of polymorphisms in many genes, which together invoke a more pronounced clinical picture, in face of common viral agents.

The criteria for normalcy, in a system, are based on the immunologic phenotype related to population distribution of laboratory data collected for various immune function tests. It is clear that we still have incomplete knowledge about how the organism as a whole, including the immune system, protects itself from infection. The importance of the innate immune system was only recently recognized and new classifications, which will take into account additional factors other than the classical known adaptive immune components, are now being considered [12].

In summary, although the human species survived for more than 250,000 years, is even expanding and is thus immunocompetent overall, it is most unlikely that there has ever been a truly immunocompetent individual who was resistant to all pathogens [2]. The concept that immunodeficiency is a rare condition should be changed, and as Casanova and Abel wrote: "Inborn errors of immunity are – unfortunately but inevitably – the rule rather than the exception" [2]. Much more basic and clinical research should be carried out to explore the exact relationships between the various infectious agents and the human body in order to devise novel therapeutic tools for our continuous fight against microorganisms that have improved their strategies to resist our host defense mechanisms.

References

1. Casanova JL, Abel L. The human model: a genetic dissection of immunity to infection in natural conditions. *Nat Rev Immunol* 2004;4:55–66.
2. Casanova JL, Abel L. Inborn errors of immunity to infections: the rule rather than the exception. *J Exp Med* 2005;202:197–201.
3. Casanova JL, Fieschi C, Bustamante J, et al. From idiopathic infectious diseases to novel primary immunodeficiencies. *Allergy Clin Immunol* 2005;116:426–30.
4. Sorensen RI, Nielson GG, Andersen PK, Teasdale TW. Genetic and environmental influences on premature death in adult adoptees. *N Engl J Med* 1988;318:727–32.
5. Saleh M, Vaillancourt JP, Graham RK, et al. Differential modulation of endotoxin responsiveness by human caspase 12 polymorphism. *Nature* 2004;429:75–9
6. Kwiatkowski D. Science, medicine and the future: susceptibility to infection. *Br Med J* 2000;321:1061–5.
7. OBrian SJ, Dean M. In search of AIDS resistance genes. *Sci Am* 1977;277:44–51.
8. Tournaimille C, Cloin Y, Cartron JP, LeVan Kim C. Disruption of a GATA motif in the Duffy gene promoter abolishes erythroid gene expression in Duffy negative individuals. *Nat Genet* 1995;10:224–8.
9. Ochs HD, Notarangelo LD. Structure and function of the Wiskott-Aldrich syndrome protein. *Curr Opin Hematol* 2005;12:284–91.
10. Foster CB, Lernbecher T, Mol F, et al. Host defense molecule polymorphisms influence the risk for immune-mediated complications in chronic granulomatous disease. *J Clin Invest* 1998;102:2146–55.
11. Casanova JL, Abel L. Genetic dissection of immunity to mycobacteria: the human model. *Ann Rev Immunol* 2002;20:581–620.
12. Bonilla FA, Geha RS. Are you immunodeficient? *J Allergy Clin Immunol* 2005;116:423–5.

Correspondence: Dr. A. Etzioni, Meyer Children's Hospital, Rambam Medical Center, Haifa 31096, Israel.
Phone: (972-4) 854-2646
Fax: (972-4) 854-2441
email: etzioni@rambam.health.gov.il

Those who wish to sing always find a song

Swedish proverb