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RECENT TRENDS IN IMMUNOPARASITOLOGY

A brief survey of papers presented at the 8th International Congress of Immunology (Budapest, August 23-28, 1992)

Immunoparasitology has become one of the most rapidly developing disciplines of modern immunology in last few years. This fact was again confirmed by the attention paid to this discipline at the 8th International Congress of Immunology. Two plenary symposia ("Parasites' strategies to avoid immune response" and "Immunology of tropical diseases") and three workshops ("Im- munobiology of helminth infections", "Immunopathology and immune prophylaxis of tropical infectious diseases", "Escape mechanisms in host-parasite interactions") were fully devoted to interactions between parasites and immune system. In addition, numerous contributions were presented by other related sections - in total, these represented over 150 papers. These papers covered a wide spectrum of research interests from fundamental investigations performed on the cellular and even molecular level up to clinical and epidemiological studies. The objective of this article is therefore restricted only to a brief survey of dominant trends in 4 following important fields:

1. Evasion of host immunity by parasites
2. Regulation of host immune response induced by parasites
3. Immunodiagnosis
4. Immunotherapy of parasitic diseases

1. Evasion of host immunity by parasites

It has been proved that parasites can survive within the host for a relatively long time due to the evasion of the host protective immunity. At the present time, overcoming this evasion seems to be essential to the development of new effective vaccines.

Five plenary lectures were presented within the symposium "Parasites' strategies to avoid immune response". Dr. Zinkernagel (University of Zürich, Switzerland) briefly summarised the history of the co-evolution of parasites and the immune system. Dr. Sadoff (Walter Reed Institute of Research, Washington, USA) mentioned 5 strategies of malarial parasites to avoid the induction of an efficient immune response (low amounts of antigens released, hiding inside host cells, antigenic variation during life cycle, antigenic mimicry, production of immunosuppressive substances). Dr. M. Capron (Institute Pasteur, Lille, France) described the very interesting escape mechanisms in schistosomosis - *Schistosoma mansoni* shares some antigens with intermediate (snail tropomyosin) as well as with definitive hosts (embryonic antigens, blood group antigens). Moreover, the receptors for some important host regulatory molecules (tumor necrosis factor) were found on the worm's surface. On the other hand, worms are able to produce and release into the host some immunoregulatory substances such as schistosomula-derived immunosuppressive factor, IgG-cleaving protease and even neuropeptides homologous to human endorphins.

More than 40 papers dealing with aspects of immune evasion were presented in different workshops. Many authors reported on certain immunosuppressive molecules released by parasites, which enable them to modulate the intensity and direction of host immune response, and consequently, protect parasites. A very interesting example of this kind of strategy has been described in *Trypanosoma brucei* model infection. Dr. Darji (Belgium) observed that macrophages pulsed *in vitro* with *T. brucei* lysate triggered lymphocytes to the elevated secretion of interferon-γ (IFN-γ), which has been shown to be responsible for the hyporesponsiveness of T-lymphocytes. Moreover, Dr. Olsson (Sweden) showed that IFN-γ supported the growth of *T. brucei in vitro* - the circuit is closed.

An important role in parasite protection is attributed to proteases produced by parasites. Congopain, a cysteinprotease released by *Trypanosoma congolense* (Dr. Authie, Kenya), as well as cathepsin purified from F*asciola hepatica* (Dr. Carmona, Uruguay) showed immunosuppressive activity both *in vitro* and *in vivo*. Another protease (gp63) released by *Leishmania major* and *L. donovani* (Dr. Hey, Denmark) specifically cleaved CD4-molecule (the main marker of T-helper subpopulation) on human T-lymphocytes, and proteolytic cytotoxins enable *Entamoeba histolytica* to penetrate the intestinal mucosa (Dr. Gamboa, Mexico). A possible role of the virus-like particles observed in metacestodes of *Taenia solium* and *T. crassiceps* in host-parasite interactions was proposed by Dr. Corella (Mexico).

2. Regulation of host immune response induced by parasites

The division of T-helper lymphocytes into two functionally distinct subpopulations (T_H1 and T_H2) has become one of the major advances in immunology of the host-parasite interactions in last few years. Whereas T_H1 cells producing IFN-γ and interleukin-2 (IL-2) mediate delayed-type-hypersensitivity response, T_H2 cells producing IL-4, IL-5, IL-9 and IL-10 mediate allergic type of response (associated with eosinophilia, mastocytosis and high IgE-antibody level). It has been proved that the outcome of many parasitic infections (i.e. resistance or chronic infection) is strictly based on the type of immune response elicited by parasite. This central role of T_H1/T_H2 regulatory mechanism was confirmed by the number of presentations concerning this problem.

A brief survey of the role of T_H1/T_H2 type of immune response in some important parasitic diseases was given by Dr. Perlman (Stockholm University, Sweden) in his opening lecture to the symposium "Immunology of tropical diseases". Whereas T_H2 type of immune response

associated with resistance dominated in most of the murine helminth infection, in the mouse model of *Plasmodium chabaudi* infection T_H1 type which dominated at the very early stages of infection (7-14 days post infection) has been switched to T_H2 type as the infection became chronic.

The most advanced understanding of T_H1/T_H2 regulation of immunity to parasites has been achieved in murine leishmaniosis. This research area was reviewed by Dr. Scott (University of Pennsylvania, Philadelphia, USA). It has been proved that the type of immune response (and, consequently, the outcome of infection) elicited by *Leishmania major* infection in mice depends on the genetic background of the host. Whereas mice of the susceptible BALB/c strain developed a chronic infection associated with T_H2 type of immune response, the resistant C57B1/6 mice displayed a self-limited infection associated with T_H1 response. In addition, it has been demonstrated recently that the type of immune response elicited depends also on the parasite species. Whereas *L. major* induced a self-limited infection in C57B1/10 strain of mice associated with T_H1 response, another species, *L. amasonensis*, induced a chronic infection accompanied by T_H2 response. The central role in the development of resistance/susceptibility in murine leishmaniosis belongs to IFN-γ because treatment of resistant C3H mice with anti-IFN-γ antibodies resulted in the development of chronic infection. Natural killer (NK) cells are probably the source of IFN-γ at the early stage of infection, because treatment of C3H mice with anti-sialo antibodies (which eliminated NK cells) resulted in the increased susceptibility of these mice to infection. Consequently, it has been suggested that activation of NK cells could improve the efficacy of a vaccination against *L. major* in susceptible (BAB/c) mice. This hypothesis was confirmed in the vaccination experiments, when the administration of *Corynebacterium parvum* (a potent NK cells activator) and IFN-γ significantly increased efficacy of immunisation with *L. major* antigens.

These findings concerning the key role of IFN-γ were further extended by numerous poster contributions. Dr. Stefani (Switzerland) reported on the possibility to render the susceptible strain of mice (BALB/c) resistant to *L. major* infection by treatment with anti-CD4-antibodies, which eliminate the T-helper subpopulation of lymphocytes. In such a situation, CD8+-T-cells can protect animals by production of IFN-γ. Moreover, the administration of anti-IFN-γ antibodies abrogated immunity to *Schistosoma mansoni* in mice vaccinated with attenuated cercariae (Dr. Smythies, England).

A good corelation between the experimental data concerning the role of T_H1/T_H2 regulation of immunity to parasites and the clinical findings were reported for leishmaniosis and trypanosomosis. The presence of T_H2-lymphokines (IL-5) and eosinophilia correlated negatively with the rate of *L. donovani* clearance in patients with visceral leishmaniosis (Dr. Jephtah-Ochola, Kenya). A similar correlation was described between T_H2-lymphokines (IL-10) production and the course of infection in *Trypanosoma cruzi* infection (Dr. Reed, USA). Some very surprising findings concerning the role of B-cells in the regulation of T_H1/T_H2 type of immune response were reported for *Plasmodium chabaudi* infection in severe combined immunodeficiency (SCID) mice (Dr. Weid, Germany). Whereas the normal BALB/c mice, as well as the SCID mice reconstituted with CD4+ (T-helper) cells, were susceptible to infection and displayed the switch from T_H1 to T_H2 type of immune response early in infection (2-3 weeks post infection), the B-cell-depleted BALB/c mice controlled the infection and retained the T_H1 phenotype.

The controversial results concerning the role of T-lymphocytes bearing the γ, δ-receptor (Tγ, δ-cells) in different parasitic infections were presented. Dr. Flynn and Sileghem (Kenya) reported on the central role of the Tγ, δ-cells in the resistance of West African cattle to *Trypanosoma congolense* infection. Whereas Tγ, δ-cells-which are able to recognise trypanosome antigens *in vitro* - were found in the resistant N'Dama cattle, no such response has been observed in the susceptible Boran cattle. In contrast, a significant increase in the number of Tγ, δ-cells was observed in both resistant (CBA) and susceptible (BALB/c) strains of mice early after infection with *Leishmania major* (Dr. Rossat, Switzerland). Whereas the percentage of Tγ, δ-cells declined in the healed CBA mice, in the chronically infected BALB/c mice it remained high throughout the experiment. Moreover, the administration of anti-γ, δ antibodies resulted in an increased intensity of infection in both strains. These findings were supported by the observation of *Plasmodium falciparum* antigen-specific Tγ, δ-cells in human individuals previously unexposed to infection, showing that these cells might play some role in the pathology of malaria, rather than in the protection (Dr. Goodier, Germany).

3. Immunodiagnosis

The key problem of immunodiagnosis of parasitic infections at the present time remains the isolation and characterisation of highly immunogenic parasite-specific antigens for more specific and sensitive detection of anti-parasitic antibodies. Several contributions dealt with this problem, but only limited progress toward highly specific immunoassays has been reported. Moreover, the numerous presentations described the serological cross-reactivity between certain parasites - for example 75 % homology between paramyosins isolated from *Taenia solium* and *Schistosoma mansoni* was reported (Dr. Landa, Mexico). A new interesting technique for purification of parasitic antigens for diagnostic purposes was introduced by Dr. Mountford and Wilson (U.K.) - the high performance electrophoretic chromatography (HPEC) combines the fractionation attributes of column chromatography with the resolving power of electrophoresis.

Very interesting data were presented in some contributions dealing with the correlation between the level of

parasite-specific antibodies of different isotypes and the susceptibility/resistance to infection. Dr. A. Capron (Institute Pasteur, Lille, France) reported in his lecture (symposium "Immunology of tropical diseases") on the correlation between the level of serum IgE (protective) or IgG4 (blocking) antibodies and the incidence of human schistosomosis. The age-dependent increase of the IgE and decrease of IgG4 antibody level in human sera correlated well with the declining incidence of *Schistosoma mansoni* infection. Moreover, the negative correlation between the serum antibody level to soluble egg antigens and the severity of infection has been described in *Schistosoma haematobium* patients (Dr. Magid, Egypt). In contrast, no correlation between serum IgA antibody to *Cryptosporidium parvum* antigens and the clinical status has been observed in healthy adults, healthy children, immunocompetent children with cryptosporidiosis and AIDS patients with and without cryptosporidiosis (Dr. Kassa, France).

4. Immunotherapy of parasitic diseases

At the present time, immunotherapy of parasitic diseases is becoming a rational development of vaccines, based on the latest advances in molecular biology of parasitic antigens and on the understanding of main regulatory mechanisms involved in the immune response to parasites.

This new complex approach has been documented by Dr. A. Capron (Institute Pasteur, Lille, France) on, probably, the best defined candidate for molecular vaccine against schistosomosis - 28kD-glutathion-S-transferase (Sm-28-GST). He briefly summarised the recognition of 28kD-protein from the worm's homogenate as the target molecule for the protective IgE-monoclonal antibody, as well as the cloning, purification and determination of the primary structure of Sm-28-GST during the past decade. Recently, more detailed analysis of this key molecule has been undertaken, including an investigation of the function of different peptide fragments. It has been shown that the major immunogenic part of Sm-28-GST is the peptide 115-131, whereas the peptide 24-43 is the major T-cell epitope, which is necessary for the induction of IgE production, and the peptide 190-211 is responsible for the anti-fecundity effect of immunisation with Sm-28-GST. *In vivo* vaccination trials showed that immunisation with Sm-28-GST resulted in a significant reduction of the worm burden in rats, hamsters and monkeys. Moreover, this vaccination resulted in a significant reduction of the fecundity of female worms, and consequently, in the number of eggs settled in the liver. In addition, the decreased viability as well as infectivity of *S. mansoni* eggs were observed in immunised animals. Hence the vaccination with Sm-28-GST led to a remarkable reduction in the liver pathology caused by *S. mansoni* infection. Similar results have been achieved in cattle immunised with *Schistosoma bovis*-derived GST. The first human trial with Sm-28-GST-based vaccine is in progress at the present time.

The possibilities for overcoming immune evasion by modern vaccines were shown by Dr. Lambert (WHO, Geneva, Switzerland) - the improved immunogenicity of antigens by using the appropriate carriers (liposomes, biodegradable microparticles, live virus vectors) and the modulation of the host immune response by cytokines and anti-cytokines. Dr. Louis (WHO, Geneva, Switzerland) reviewed the development of an antileishmanial vaccine based on the knowledge of T_H1/T_H2 regulatory mechanismus in resistance/susceptibility to leishmaniosis in mice. He demostrated that the protective effect of this antileishmanial vaccine depended, at least partially, on the efficacy of antigen-presentation by infected macrophages. Antigens from living parasite were presented more efficiently than antigens from lysate of leishmania and induced protective T_H1 type of immune response in susceptible BALB/c mice. Consequently, it has been concluded that an efficient vaccine against leishmaniosis should trigger T_H1 cells.

Very interesting data concerning the clinical trials of a new therapeutic vaccine against schistosomosis (*Schistosoma mansoni*) were presented in the posters of Dr. Nabih and his colleagues (Egypt). They isolated "chemically modified antigens" from adult infected *Biomphalaria alexandrina* snails previously exposed to "certain chemicals". A single intradermal injection of 0.5 ml of this vaccine showed 100 % therapeutic effect in patients with acute urinary schistosomosis as well as in patients with chronic schostosomosis, whereas previous chemotherapeutic treatments had failed. Unfortunately, the authors did not provide any further details concerning the preparation and composition of this vaccine. Therefore the presented results need further confirmation.

In conclusion, it can be expected that the rapid development of immunoparasitological research in this decade will be focused on the following problems:

a. overcoming the parasites' mechanisms for the evasion of host immunity

b. immunological basis of the hosts resistance/susceptibility (T_H1/T_H2-type of immune response) and its modulation?

c. rational development of molecular vaccines based on the role of different epitopes in the induction of protective immunity.

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Jiří Heřmánek