Chapter 7

Microbiome and Autoimmunity

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1. Introduction

Most of the currently known infections represent a persistent and stepwise development of the canonical chronic diseases of infectious origin (CDIO) associated with conditionally pathogenic microorganisms, i.e., viruses, intracellular parasites and other representatives of the endogenous microbiome, particularly, those manifesting with atypical properties. Pathogens are able to interact between themselves and to cause a disease, and the pathogens' genomes break the subtle regulation of microbial ecosystems (*microbiome*s) (Suchkov et al., 2007).

The aforementioned studies have led to a reappraisal of Koch's postulates to announce that he had shown theoretically more then a hundred years before: one microbe causes one disease. Interactions of microbial pathogens with specific tools of the patient's immune machinery in due the course of the infectious process give rise to different types of *micro-biocenosis* to manifest a broad range of activities of the microbiome-related pathogens including their ability to suppress the immune response.

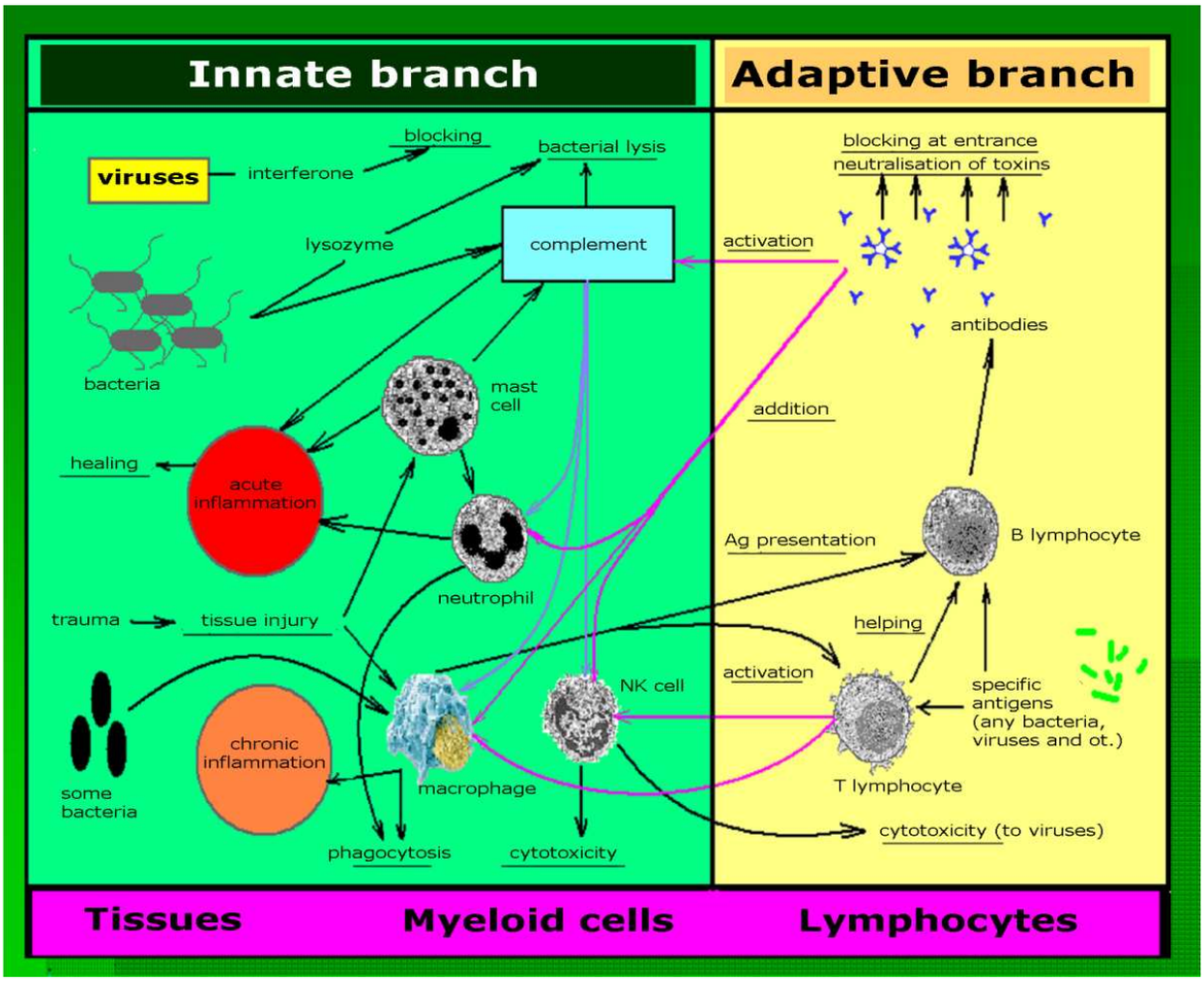
The key role of immune-related and microbial factor in CDIO pathogenesis is evidently proved today. However, a comparison of types of the patient's individual immune responses and the features of *microbial landscapes* with the clinical manifestations of the disease (*clinical pattern*) by singling out postinfectious clinical-and-immunological syndrome (PICIS) as a pathogenically oriented category and a fundamental term is appearing to be a more complicated objective to be cleared.

As many authors established, for CDIO-related specific form of PICIS has clinical and prognostic significance and informative and thus predictive value, because, for sure, PICIS determines to a considerable degree the extant of progressing and chronization of the underlying disease whilst determining risks of complications.

Postinfectious secondary immunodeficiency syndrome (PIFSI) is a *monosyndromal* and predominant form of PICIS in patients with CDIO.

More than in a third of cases another form of PICIS could be formed and thus observed, accompanying by postinfectious autoimmune syndrome (PIFA) reflecting the involvement of immune-mediated autoaggression, or PIFASID as an associated form of immune imbalance.

The susceptibility to one or another form of CDIO-associated PICIS depends on a number of genetically determined factors, which play a crucial role in formation of the patient's immune resources *via* cooperation between mechanisms of innate and adaptive immunity (Fig. 1).



Note: NK, natural killer

Figure 1. Main features of innate and adaptive immunity

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Unfortunately, the role of these mechanisms in the development and chronization of infectious diseases is still obscure, which deprives a doctor of the possibility to improve the currently available models of CDIO chronization with the ultimate goal to develop the most advanced treatment-and-rehabilitation in a package of the preventive treatment protocols, and their implementation into routine and daily clinical practice (Paltsev et al., 2009a).

The key role in the chronization and thus complications of such diseases, and thus the development of the associated immune disorders is played by:

i. properties of the infectious agent;

ii. type of a patient's immune response.

The microbial factor may promote development of a vast array of the associated immune disorders and thus forms of immune-mediated pathologies (PICIS), particularly, owing the microorganisms to gain, in the running course of the disease evolution, a large arsenal of intrinsic tools enabling microbes to escape from attacks of immune-mediated weapon, to attenuate and the latter whilst getting them weakened or to influence the dynamics of the clinical manifestations of PICIS itself. Actually, the severity and duration of CDIO depends on the interaction between the microbiome and the antimicrobial immunity machinery (Paltsev et al., 2009b).

2. PICIS and its role in the state-of-the-art model of immunopathogenesis of chronic infectious diseases

The PICIS variants include:

1. postinfectious secondary immunodeficiency syndrome (PIFSIS);

2. postinfectious autoimmune syndrome (PIFAS);

3. PIFAS coupled with PIFSIS (PIFASID) (Suchkov et al., 2004).

The occurrence and thus incidence of these syndromes in CDIO patients differs statistically depending on the form of a type of the primary infection and the stage of the destructive inflammatory process in the targeted organs or tissues. For example, the initial (including *subclinical*) stages of any clinical courses of CDIO are usually concomitant with a predominant (>50%) formation of PIFSIS, while the quotes of PIFAS and PIFASID do not exceed 20%.

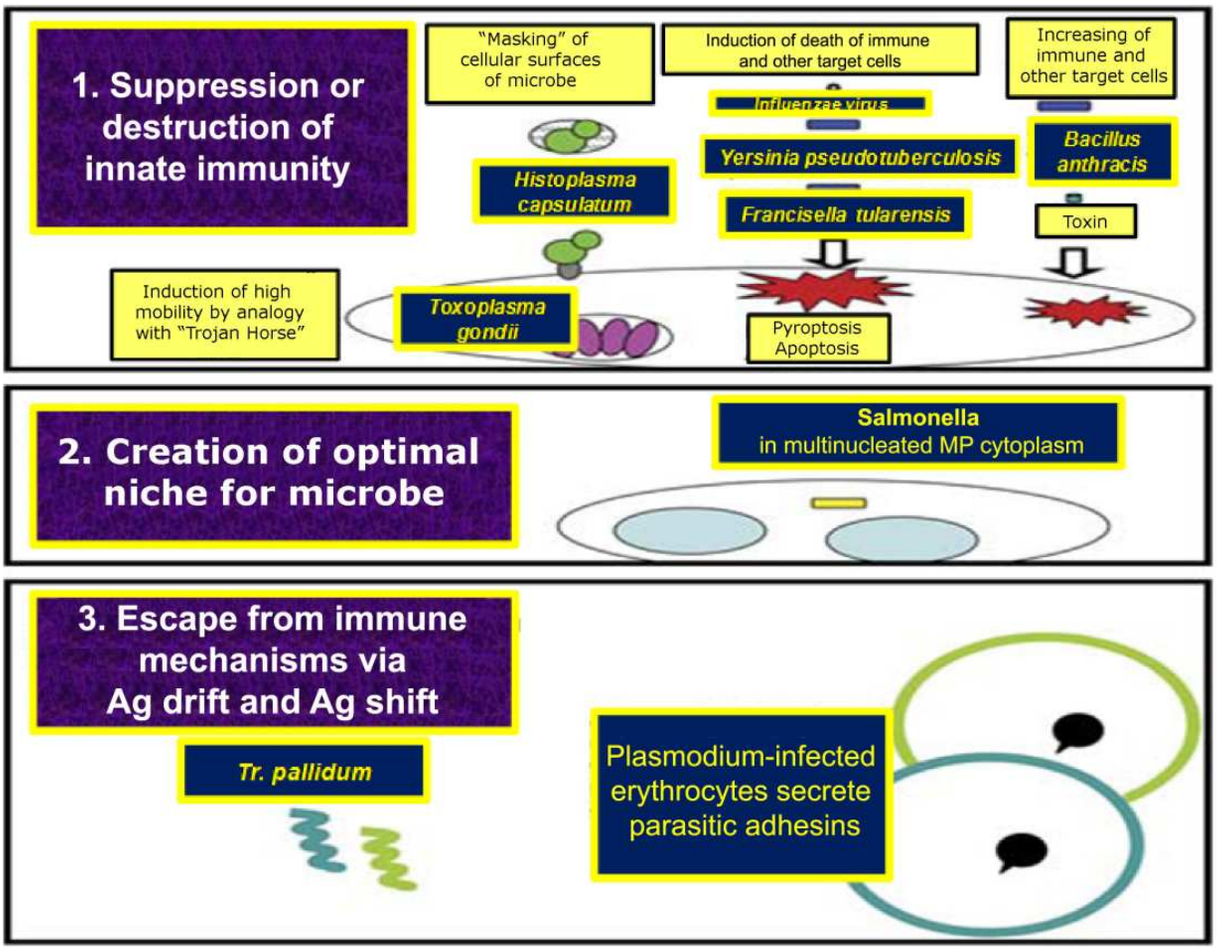
This situation changes with further development and chronization of the infectious process and its transformation from a subclinical into the clinical stage, viz., the incidence of autoimmune syndromes increases substantially. In intermediate stages of chronization, the quotes of PIFAS reach 50%, whilst in the final stages of chronization similar indices of PIFASID reach 60%.

It may thus be concluded that PIFSIS is not only the outcome of the infectious process, but, rather, the major factor responsible for provoking complications and raising thus a chronic

relapsing course. The role of *progression* and *chronization* of the disease is determined, in a large measure, by the form of PICIS or, rather, of PIFAS and PIFASID, which reflect the manifestations and thus a pattern of postinfectious autoaggression (Suchkov et al., 2004).

3. *Microbiome* and its role in the state-of-the-art model of CDIO pathogenesis

A crucial role in CDIO pathogenesis is played by primary and superinfectious factors endowed with the ability to generate large microbial associates. Therefore, the features of the patient's microbiome are key etiopathogenic links for realization of the infection-associated chronization phenomenon.



Notes: *Ag*, antigen

Figure 2. Scenarios of interactions between a microbial pathogen and the patient's antimicrobial immune response illustrating an escape from the immune supervision to survive

Moreover, in a course of their evolution microorganisms acquire a vast array of molecular and cellular tools enabling them to escape from the intrinsic control of the immune system

over the microbiome itself, to switch off mechanisms of the control over the microbiome, or to initiate changes underlying the *resistance* phenomenon (Fig. 2). As a result of the antagonistic interactions between a microbe and the antimicrobial immunity machinery, the immune response is either not elicited at all or is only partly activated giving rise to manifestations of PIFSIS, or progressing in a form provoking either PIFAS or PIFASID. This is concomitant with the formation of membrane films by clinical isolates of pathogenic microorganisms escaping from the control of antimicrobial agents.

In 30% of cases, the causative agent is not cultivated, but, rather, is converted into the *L*-form, which does not exclude the presence of an "invisible" pathogen in the course of the instrumental and laboratory diagnostics procedures, and implies the latent progress of the infectious process. The latter presents particular interest because the conversion of some microorganisms into the latent (*cryptic* or *sleeping*) form is one of the ways to chronization by escaping from the proper immune response.

4. Features of microbial spectra in CDIO patients

Conventional (predominantly, *gram*-negative) bacterial flora is detected in the majority of CDIO patients, though the results of the recent studies testify not only to the growth of *gram*-negative microorganisms, but also to a dramatic increase in the number of superinfectious pathogens of viral and parasitic origin.

The results of our recent studies suggest that the most frequently occurring human infections may conventionally be divided into two main categories:

1. susceptibility to relapsing infections provoked by pyogenic bacteria (*S. pneumoniae, S. aureus*, etc.) with a minimum *mimicking* resource increases dramatically in patients whose disorders are linked with antibody (Ab), complement and phagocytosis deficiency, PIFSI being the predominant form of PICIS;
2. a particular susceptibility to viral and intracellular pathogens endowing with a high *mimicking* potential increases in patients with disturbances in primary cell-mediated immunity (Fig. 3)

Fluorescence has been used to show that the process of intraintestinal hatching of *Trichuris muris* is critically dependent on the attachment of an enterobacterium to the polar operculum of the egg (*Panel A*). Hatched worms attach to the bowel wall and induce activation of type 2 helper T (Th2) cells, which in turn inhibit the proliferation and differentiation of type 17 helper T (Th17) and regulatory T (Treg) cells. In contrast, worm development was halted and specific immune responses were altered in mice that were depleted of gram-negative enterobacteria by antibiotics (*Panel B*), underscoring the influence of the intraintestinal environment on intestinal immune responses.

At the same time intracellular pathogens interfere in cell nucleus during DNA transcription. One of the key mechanisms by which microbes achieve the immunosuppressive ef-

fects is by subverting one of the body's most prolific nuclear receptors, the vitamin D receptor (VDR). Defects in VDR signaling transduction have previously been linked to bacterial infection and chronic inflammation. Each pathogen that decreases VDR expression makes it easier for other pathogens themselves to slow immune activity even further, creating a snowball effect.

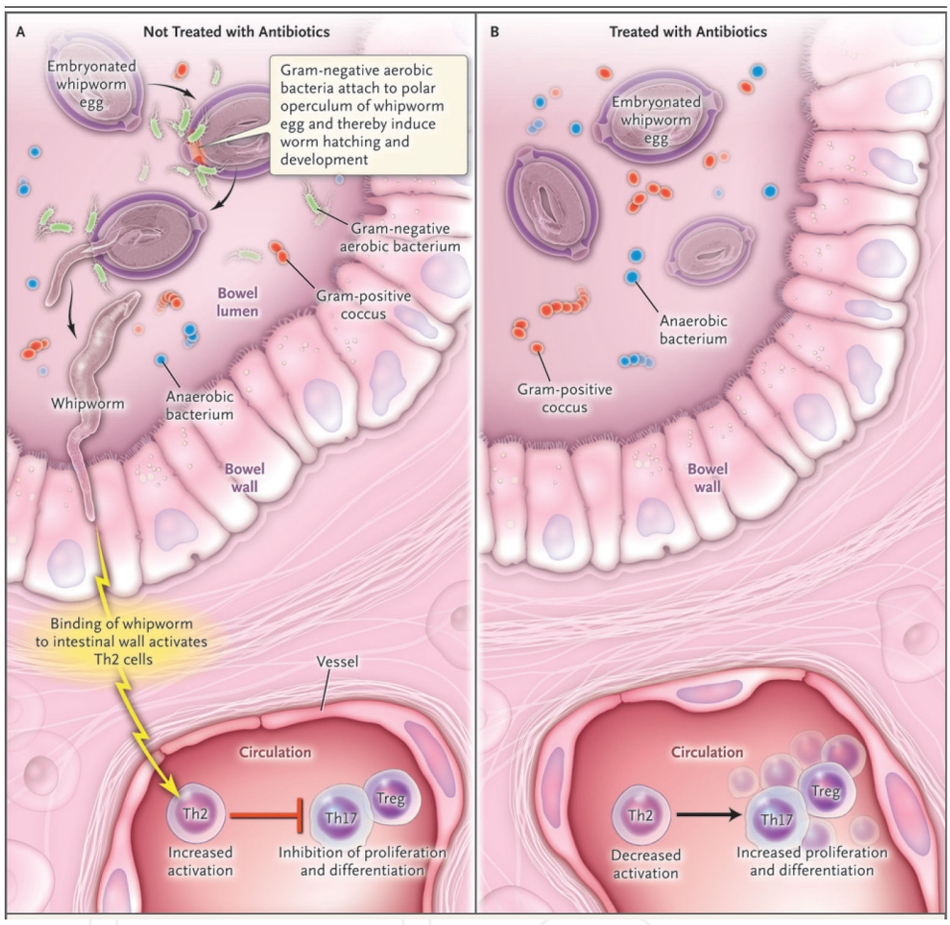


Figure 3. Hatching Parasites

However, a complete set of mechanisms by which persistent intracellular microbes slow innate immune activity has yet to be definitively determined (Proal A. D. et al. 2011). In such patients, these microorganisms provoke fast progressing infections associated with PIFA or moderate PIFSI with an impending transformation of PIFSI into PIFASID.

Microbiomes detected and properly assessed in the course of chronization and progression of CDIO are characterized by a high degree of multiplicity and variability, which have every right to be regarded as clinically important chronization criteria regardless of the nosological form of the disease. At the same time, the intrinsic architectonics of microbiomes varies widely depending on the microbial category:

1. in some cases (ICIIP and COPD/CP), the dominant is common to all microbial categories (including the total virulent resource/TVR);
2. for other categories (e.g., CPN), the bacterial dominant (which is TVR-limited) displays, contrary to ICIIP and COPD/CP, a "gap" in both specific ratio and virus variety;
3. in certain disorders (e.g., chronic myocarditis/CM), the specific ratio of bacteria and their TVR tend to minimum against the background of an absolute viral dominant.

5. Features of interactions between patient's antimicrobial immunity and etiopathogens during PICIS formation in the course of disease progression

The main feature of the defense immune response to the infective pathogen is formation of two subpopulations of regulatory T helper cells (Th cells). Effector CD4+ Th cells divide into Th-1, Th-2, Th-3 and Th-17 subpopulations depending on cytokines secreted, transcription factors and signal pathways. Th1 cells trigger effector mechanisms of cell-mediated immunity, and Th2 cells are responsible for antibody (Ab) formation (Mc Guirk et al., 2002) (Fig. 4).

Th3 cells (or regulatory Treg-cells) are the other clone of cells expressing CD4+ and CD25+. They are able to regulate functions of Th1/Th2 subpopulations and to maintain immune homeostasis (Sakaguchi, 2004; Shevach, 2002).

Th3 cells come from thymic CD4+ progenitor cells in the presence of IL-2 and TNF-β. Naive At the periphery CD4+ T cells can be converted by the signals transmitted through STATS in the presence of TNF-β into inducible Treg expressing transcription factor FoxP3 (Koenen, 2008). These cells are characterized also by low level of IL-2 and IFN-γ production and high level of IL-10, IL-35, TGF- β production. Two regulatory or proinflammatory cytokines, IL-10 and TNF-β, mediate suppression of the immune responses against autoAgs and thus prevention of autoimmune diseases.

Note: Ag, Lc, IL, NK, GM-CSF, TNF, IFN, LT, MP, antigen, leukocyte, interleukin, natural killer cell, granulocyte-monocyte colony-stimulating factor, tumor necrosis factor, interferon, leukotriene, macrophage, respectively; Th, T helper cell.

The development of autoimmune diseases was previously associated only with Th1 cells, but absence of IFN-γ not only prevents development of autoimmunity in mice, but accelerates process. This fact has lead to discovery of a separate subclone of T cells, differing from Th1 cells and capable of inducing local inflammation and autoimmunity.

This clone (Th17) is derived from naive CD4+ T cells in response to stimulation with IL-6, IL-23, IL-1β, TGF-β (Stochinger et al., 2007). IL-6 and IL-23 activate STAT3, which enhances the expression of transcription factors RORyt RORy, which in turn increase the expression of major cytokines of the clones - IL17A; IL17F; IL21; IL22 (Dyachenko & Dyachenko, 2010).

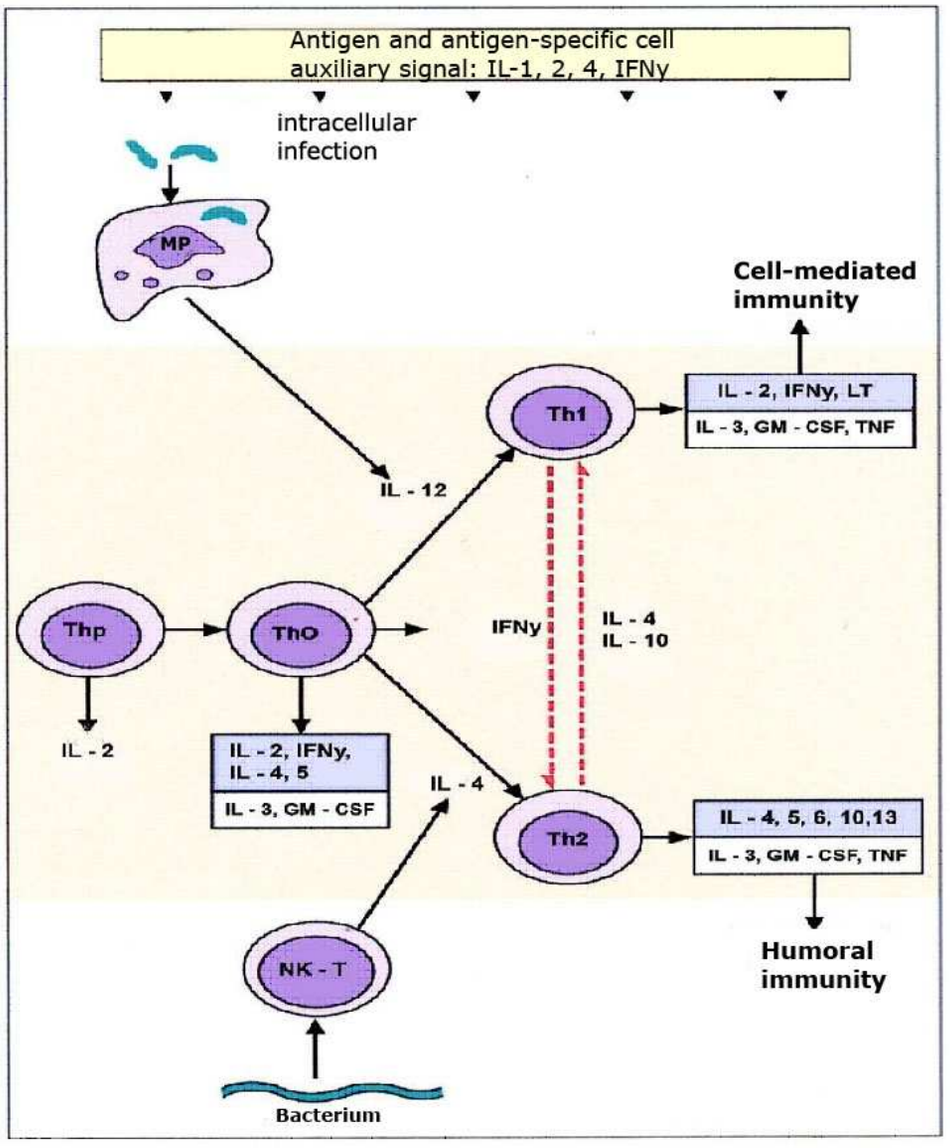


Figure 4. Ag-specific differentiation of T cells in two main-line directions and formation of regulatory Th1, Th2 cells

Thus, the differentiation of T cells is a result of the coordinated activity of cytokines and transcription factors. At the same time TGF-β produced by dendritic cells and macrophages may send differentiation of naive T cells both in the direction of Treg cells (CD4 + CD25 + FoxP3+), and in the direction of Th17 cells producing IL-17 (Aarvak, 2009; Chabaud et al.. 2001).. It occurs as a result of the expression of transcription factor FoxP3 and RORyt, which are important for the differentiation of Treg or Th17cells, respectively.

High concentrations of TGF-β stimulate production of FoxP3, which block the expression of genes associated with RORyt, resulting in the differentiation of naive CD4 + T-cells in ROR-yt, and it leads to the differentiation of Th17 cells and expression of IL-17 (Volpe et al., 2008; Zhou et al., 2008).. It is believed that FoxP3 rivals with RORyt through physical interaction,

while the inflammatory mediators IL-6 and IL-21 implement their inhibitory effect on post-translational level (Zhou et al., 2008).

Th17 cell line plays an important role in protection against a variety of microorganisms, have a strong proinflammatory effect by expressing IL-17. IL-17 promotes an expansion and recruitment of innate-related immune cells such as neutrophils enhances the inflammatory nuclear reactions together with TLR-ligands, IL-1β, TNF-α and stimulates the production of beta defensives and other antimicrobial peptides (Vojdani et al., 2006a, Vojdani et al., 2006b, Vojdani et al., 2006c, Chung et al., 2009; McGeachy et al., 2009). IL-17RA (its receptor) has common characteristics with classical receptors of innate immunity, and its intracellular tail domain transmits a signal over a general inflammatory transduction pathway, thus linking the innate and adaptive immunity.

The role of Th17 is not clear in case of viral and parasitic infections. Thus, for instance, Th17-induced response inhibits apoptosis of virus-infected cells and contributes to the persistence of the virus. Tissue infiltrated with activated Th17 lymphocytes producing significant amounts IL-17, IL-26, IL-21, IL-22, TNF-α and lymphotoxin-B in chronic inflammation (Yu et al;., 2009; Cho et al., 2004). Production of these cytokines is inversely related with the production of Th-1 and Th-2 cytokines.

Localization of etiopathogen, i.e., out-or intracellular, is a factor determining the development of a particular immune response and, therefore, one or other form of PICIS as a result of specific immune response (Mazo et al., 2007; Litvinov et al., 2008; Zhmurov et al., 2000; Rumyantsev & Goncharova, 2000).

The latter circumstance is important not only to the pathogenesis, but also from a clinical point of view, since much of the pathogens that have the ability to escape from immune response, also create unpredictable risks of complications and difficulties with the choice of treatment scheme. Herewith therapy should be personalized, taking into account the spectra of producing cytokines: IFN-y (Th1); IL-4, IL-5, IL-13 (Th2); IL-17 (Th17). The aim of such therapy may be the modulation effects caused in separate factors, cytokines, and transcription factors.

In so doing, the crucial factor responsible for the development of one or another type of the immune response and, accordingly, one or another form of PICIS is extra- and intracellular localization of the etiopathogen. The latter is important not only from the pathogenic, but also from the clinical point of view, because a considerable amount of pathogens escaping from the immune response involve unpredictable complications and difficulty in the choice of treatment strategies (Antonov & Tsinzerling, 2001; Borisov, 2000; Kukhtevich et al., 1997; Morozov, 2001 Paukov, 1996).

According to our original data, at least three forms of PICIS, viz., PIFSI, PIFA and PIFA-SID, are identified in the paradigm of immune pathologies associated with the underlying disease.

PIFSIS is a dominant monosyndromal form of associated immune pathologies. In other cases, we deal with the formation of a different clinical immunologic syndrome reflecting auto-

immune PIFA aggression. In some patients, a combination of PIFSIS and PIFAS gives rise to the appearance of the bisyndromal form of immunopathology (PIFASID).

6. Forms of PICIS

6.1. PIFSI

Abatement of antimicrobial protective mechanisms due to deficiency of innate immunity concomitant with imbalances in the adaptive branch is a crucial feature of PIFSIS, which manifests itself as a chronic disease (presumably, of bacterial and mixed origin). Suppression of the activity of its effector links markedly weakens the patient's response to the infecting pathogen resulting in the persistence of the pathogenic microorganism, or superinfection with conditionally pathogenic microorganisms maintaining low-intensity processes.

6.2. PIFAS

Many proteins from pathogens share structural similarities with human proteins, and those can also contribute to autoantibody (autoAb) production (Fig. 5). Lekakh et al. found that polyspesific autoAbs harvested from sera of healthy donors were able to cross-react with DNA and lipopolysaccharides of bacterial strains including *Escherichia coli, Pseudomonas aeruginosa, Shigella boydii, and Salmonella.* Furthermore, since human Abs are polyspecific, it is likely that some of them produced to target pathogens may mistakenly target human proteins, causing 'collateral damage' (Khitrov et al., 2007).

In the course of CDIO progression, a portion of autoreactive cytotoxic T lymphocytes (CTL) able to interact with cross-reacting microbial Ags associated with pathogen-conditioned infection undergo activation under the influence of various factors including molecular *mimicry* (Khitrov et al., 2007a; Fujinami et al., 2006; Rose & Mackay, 2000; Benoist & Mathis, 2001).

The consequences of this phenomenon manifest themselves during recognition of autoepitopes by autoreactive CTL as a result of which PIFAS acquires an ability to attack any organ or tissue in the infected host. The risk of development of this syndrome increases dramatically with increasing morbidity from infectious diseases and at high rates of pathogen flows, as, e.g. in mixed infections (Sanaev et al., 2007; Cherepakhina et al., 2010a).

At present, there exist three explanations for the associative interplay between the infection and the risks of PIFAS occurrence based on activation of autoreactive clones of T and B cells:

a. activation of microbial superAgs;

b. leakage of cryptic (intramolecular) autoepitopes;

c. molecular mimicry (Bauer et al., 2001; Bingen-Bidois et al., 2002; Blackwell et al., 1987; Carballido et al., 2003; Dantzer & Wollman, 2003).

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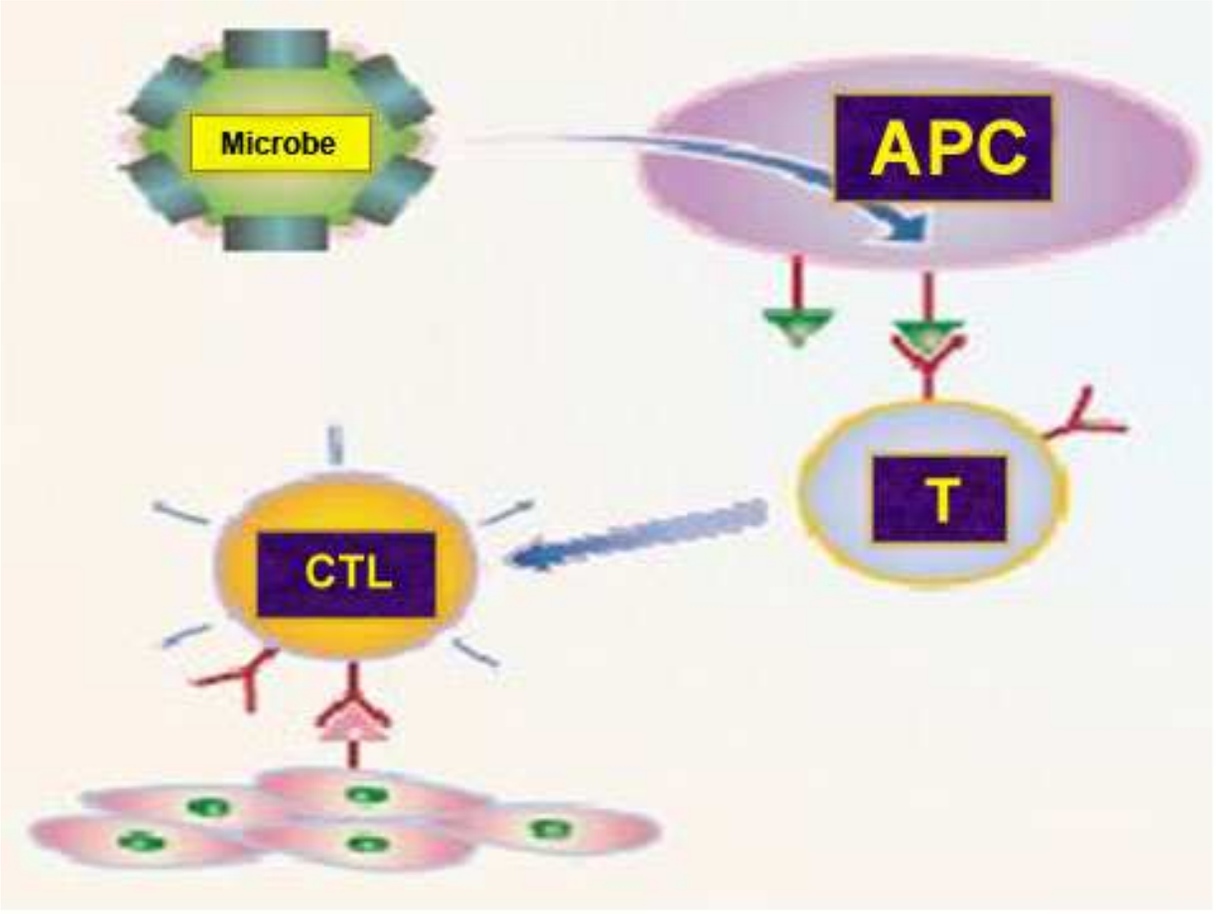

Note: The presence, in microbial pathogens, of Ags cross-reacting with or mimicking patient's Ags attenuates the patient's protective response by changing the direction of the infectious process. Activation of self-reactive CTL and production of Abs able to cross-react with both microbial epitopes and epitopes of the infected patient Abs in the paradigm of molecular/Ag mimicry underlies PIFA. Ag, antigen; Ab, antibody; APC, antigen-presenting cell; T, T lymphocyte; CTL, cytotoxic T lymphocyte; PIFAS, postinfectious autoimmunity syndrome

Figure 5. Molecular (Ag) mimicry and its role in PIFA induction

The aforementioned pathogenic mechanisms are not mutually exclusive and play an essential role in certain (early, as a rule) stages of the CDIO development as well as in PIFAS associated with the underlying disease. In other words, the induction stimuli for PIFA at the initiation point are as follows:

a. Ag features of the microbial pathogen;

b. tropism of the infectious pathogen to cells, organs and tissues against which the cytopathic effect is specifically directed (Sanaev et al., 2008; Cherepakhina et al., 2009).

Contrary to PIFSIS, in patients with PIFAS all the three categories of antimicrobial Abs (antibacterial, antiviral, antiparasitic) have high incidence. If the incidence and high titers of antibacterial and antiviral Abs are approximately equal in the majority of patients, antiparasitic Abs are present in maximum titers in some forms of the disease (e.g. CPN and CM), but are absent in others (ICIIP), most probably due to specific peculiarities of the underlying disease

rather than mechanisms of PIFA formation (Vinnitskij, 2002; Kolesnikov et al., 2001; Cherepakhina et al., 2010b).

Autoaggression provoked by an improper cooperation between both branches of immunity as a result of adaptive branch hyperfunction is a dominant feature of PIFAS (Shogenov et al.,2006).

Its key factors include a wide variety of anti-organ and anti-tissue auto-Abs able to promote multiple seropositivity and appearance of autoimmune inflammation markers (e.g., anti-B7-HI-auto-Ab). By illustration, the presence of antimyelin and antineuronal auto-Abs is typically specific for patients with ICIIP; anti-THG auto-Abs are specific markers of autoimmune inflammations in renal tissue of patients with CPN, while anti-CMC auto-Abs are typical of patients with CM (Shogenov et al., 2010).

The most informative PIFAS models include autoimmune myocarditis (AIM), autoimmune encephalomyelitis (AEM) and ICIIP, autoimmune hepatitis (AIH), autoimmune colienteritis (ACE), autoimmune pancreatitis (AIP), autoimmune gastritis (AIG), autoimmune (streptococcal) glomerulonephritis (AGN), etc.

6.3. PIFASID

This syndrome combines the abnormalities of the both branches of immunity and is clinically characterized by the presence of mixed immunopathology (PIFAS+PIFSIS). The associated disorders in effector and regulatory links of the adaptive branch are usually concomitant with this particular form of PICIS development (Manges et al., 2004; Cherepakhina et al., 2010c).

7. Clinical and immunological criteria of PICIS and state-of-the-art algorithms of immunogenetic diagnostics of CDIO

The recommended diagnostic ideology relies on the combination of two categories of screening procedures, viz.:

1. pathogenesis-oriented diagnosis of PICIS forms;
2. etiotropic diagnosis of microbial factors as the major PICIS provoker during chronization and progression of the infectious disease.

We have elaborated several criteria for substantiated clinical diagnosis of PICIS.

The following criteria should be taken into consideration during screening of abnormalities (immune complex test)

1. *innate branch:* selective phagocytosis and natural cytotoxicity (NCT) indexes, base functions of dendritic (DC) and Ag-presenting (APC) cells, in some cases, complement components;

2. *adaptive branch: selective* typing of effector and (in cases only) regulatory links of immunity combined with blood serotyping on antitarget auto-Abs and identification of Abs against mimicking Ag determinants (Khaitov & Pinegin, 2000; Bach, 2005).

The criteria for etiotropic diagnostics (construction/design of the microbial landscape map) taking account of newest advances in developing molecular and biological technologies, including achievements of metabolomics and metagenomics include the following:

1. spectrum and localization of microbial gene pools;
2. serological profile of antimicrobial Abs.

It may be inferred from the aforementioned that the therapeutic management of such patients should include not only eradication of the infectious agent, but also immunocorrection (in fact, the elimination of PICIS), which is especially important in patients with relapses and frequent alternation of exacerbation and remission periods.

8. Conclusion

Many currently known infectious pathologies are characterized by persistent growth of the CDIO link associated with conditionally pathogenic microorganisms, viruses, intracellular parasites and other endogenous pathogenic microorganisms, particularly those manifesting atypical properties (such as multiple resistance to antimicrobial drugs). At the same time, patients with such pathologies manifest not only low-level immune reactivity, but also inadequate immune responsiveness to the infectious process.

Numerous studies have shown that concrete forms of PICIS have clinical and prognostic significance for CDIO, because it is PICIS that determines, in a large measure, the progression and chronization of the underlying disease and predicts the risk of complications.

PIFSI is a *monosyndromal* and dominant form of PICIS in patients with chronic infectious pathologies.

At the same time, a different form of PICIS characteristic of immune autoaggression of PIFASID or an associated form of immunopathology was recorded in more than 30% of cases. Under these conditions, the form of PICIS and, correspondingly, the degree of immune disorders in patients with CDIO correlate, in an associative manner, with the severity of the clinical course of the disease and the specific peculiarities of *microbiocoenosis* and their interaction with the immune system of the patient. Therefore, any neglect of the results of the interaction between the microbial factor and the host organism implies the risk of appearance of novel specific resistant forms of microorganisms that weaken the immune responsiveness of the host organism and complicate the clinical course of the disease by promoting its chronization and by worsening prognosis. A certain contribution to aggravation and progression of the pathology is made by uncontrolled intake of antibiotics with a vast array of immunosuppressive properties and other pharmacological activities.

Recent progress in the study of the pathogenesis of autoimmune diseases may open up fresh opportunities for the recovery of lost or defective immune system functions, development and implementation of autoimmune diseases in the clinic qualitatively new treatment-and-rehabilitation technologies based on the use of the most advanced applied molecular biology and immunology strategies.

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