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Etiology of rheumatoid arthritis

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Summary. Definite genetic associations with immunological cooperative HLA-D(R) antigens have been demonstrated for rheumatoid arthritis (RA). Microbial etiology has not been proven, but some hope for the supporters of this view is still given by small viruses, plasmids of enteric bacteria or perhaps oncogen-like DNA-sequences. Yet, electrophoretical analysis of membrane proteins or surface glycoproteins of RA synovial cells does not show any differences compared to reference cells. Autoimmunity to several tissue elements has been demonstrated, but most of it is of secondary nature. Antigenicities of type II and III collagens are probably only contributory factors for HLA-DR4 positive individuals. Proteoglycans or minor cartilage collagens have not been extensively studied, so far. Endocrine, dietary or psychological influences might be triggering events for otherwise 'preloaded' individuals.
Key words. Arthritis, rheumatoid; cell membranes; etiology; immune regulation; membrane proteins.

Despite the failures to show a single specific cause of rheumatoid arthritis (RA) – perhaps it does not even exist – considerable knowledge has been obtained on the factors associated with the disease. This review aims at summarizing the knowledge available at present from various fields about the onset of RA, where several factors may be acting simultaneously, but with different relative strengths, to precipitate the clinical syndrome.

Genetic disease

Familial aggregation of RA has been thoroughly reviewed by Lawrence[62]. The risk for RA in the first-degree relatives is about two- to three-fold, but it is greatly affected by the severity of disease of the studied subjects: first-degree relatives of patients with seropositive erosive RA have a six to seven-fold excess of bone erosions as compared to the control population, but no excess is noticed in the relatives of seronegative patients. Monozygotic twins of seropositive RA patients have a 33-fold increased prevalence of erosive arthritis compared to the expected value. The figures are consistent with a polygenic inheritance with a threshold in penetrance[62].

In the earlier studies, RA could be correlated neither to ABH blood groups, nor to the transplantation antigens HLA-A, -B or -C, called class I molecules[53]. With the discovery of HLA-D region genes and class II antigens encoded by them, a new genetic link was demonstrated for RA: the allele HLA-D(R)4 was detected in about 46–77% of RA patients, while it occurred in about 14–34% of the control Caucasian population[34, 45, 81]. The relative risk for RA is about four-fold greater in individuals possessing the HLA-DR4 antigen. It is possible that even higher associations will be discovered, when the individual haplotypes of the polymorphic HLA-DR glycoprotein molecules are tested[74]. Also, the high level of IgM rheumatoid factor in the blood of RA patients coexists with the HLA-DR3 allele[81]. The juvenile form of RA differs from the adult disease in its HLA associations[104], indicating a different disease. Seropositivity, female sex and existence of rheumatic relatives tend to correlate positively with the HLA-DR4 appearance[34].

Since none of the genetic parameters correlate with seronegative RA and since that disease is usually milder, it has been postulated that no 'seronegative rheumatoid arthritis' exists, but that those who do not fulfill the classical ARA criteria represent cases of other presently undefined chronic arthritides[14].

Association of RA with other probably immunological diseases has been described: 13% of first or second degree relatives of RA patients have insulin-dependent diabetes and 13% have autoimmune thyreoiditis[110].

The exact biological roles of HLA-D-region coded molecules have not been established yet. At least, they act as stimulators in mixed lymphocyte reactions, as targets for cytotoxic T cells (in addition to the HLA-A, -B and -C molecules) and as controlling elements in antigen presentation[46]. They are expressed by B lymphocytes, activated T lymphocytes and antigen presenting cells (e.g. monocytes, macrophages, dendritic and related cells), i.e. cells involved in the immunological co-operation.

T-lymphocytes of patients with the HLA-DR4 allele react to collagen, while the cells of other patients do not[103]. Additional evidence for the involvement of major histocompatibility complex (MHC) genes in the peripheral arthritis is demonstrated by the strong HLA-B27

association of reactive arthritis, although the exact mechanism of this has not yet been resolved[60,64]. Clearance of foreign antigens by macrophages has also been connected with HLA-antigens: intracellular degradation of sheep erythrocytes by human peripheral blood monocytes was slower in those cells which possessed the HLA-DR3 allele[63]. This would lead to quite new areas in the functions of MHC products.

Microbial disease

Infection has commonly been suggested to be the cause of rheumatoid arthritis throughout the history of the disease. The more popular considerations of this theme have been summarized by Bennett[11] and Marmion[67]. The postulated pathogens include viruses, bacterial plasmids as a subgroup of them, mycoplasmas and bacterial constituents. More hypothetical agents might be viroids or activators of cellular proto-oncogen-like DNA sequences[12].

Viruses

Virus infection would nicely explain the many pathological phenomena appearing in RA. That is why it has remained one of of the most popular hypotheses on the etiology of RA[127]. Exhaustive studies searching for classical infective virions, their nucleic sequences or antibodies against them have, however, given either negative or conflicting results[67]. As possible targets of infection, the synovial fibroblasts[76,77], macrophages[43] and lymphocytes[42,75] have been investigated.

Candidates to be involved in RA have been suggested to be e.g. rubella[20,29], measles[48,97] and Epstein-Barr(EB) virus[4,30]. Rubella virus is the most arthritogenic of them and has been isolated from peripheral blood lymphocytes of patients with rubella arthritis even for six years after the primary infection[17]. Also, some arthritic syndromes of unknown origin have later been proven to have been caused by rubella virus isolated from synovial fluid of patients[33]. However, lack of seropositivity and symmetrical joint erosions is discordant with RA[61].

Present opinion mostly attributes to these ubiquitous viruses an immune response modulating rather than a simple causative role in RA, in a genetically susceptible host. An illustrative example of this is given by EB virus, which has the capacity to induce transformation and neoantigen production in infected B lymphocytes[16]. About 85% of both rheumatoid and control populations have been infected with EB virus. After infection, both populations exhibit equally antibodies to EB virus capsid antigen and EB nuclear antigen (EBNA, B lymphocyte neoantigen), but 67–90% of the RA patients and only 8–25% of the controls have antibodies against a soluble B cell nuclear neoantigen, called RANA = RA-associated nuclear antigen[100]. Anti-RANA titers of RA patients correlate with the disease activity in about ⅔ of cases, while antibodies against other EB virus-determined antigens do not[5]. The mean anti-RANA titers are higher in Pima Indians known to be prone to RA than in Caucasians, indicating a probable genetic hyperresponsiveness to this antigen[100]. Some evidence suggests that it could be mediated by a defect in EB virus-specific suppressor T cell function[111]. So, evidence for a causative role of EB virus is lacking, but RA patients may have a genetic difficulty in suppressing the proliferation of some EB virus-infected B lymphocytes, leading to increased amounts of some antibodies. The biochemical nature of RANA remains to be clarified, in addition to its biological significance.

Unequivocal alterations of cultured rheumatoid synovial cells

Parameter	Change	Reference
Mol. wt of hyaluronic acid	Decreased	15, 119
Acid hydrolase activities	Increased	32
Neutral protease activity	Increased	44
Response to cortisol in vitro	Reduced	15
Endogenous CTAP[a] concentration	Increased	15
Expression of HLA-DR antigens[b]	Increased	51
Reactivity in autologous MLR[b,c]	Increased	51

[a]CTAP, connective tissue activating peptide. [b]Changes observed in RA macrophage-like synovial cells. [c]MLR, mixed leukocyte reactions.

Since the discovery of persistent, slow virus infections as human pathogens, they have also been postulated as the cause of RA[23]. At presently, we know of mechanisms by which viruses may establish persistent infections, escaping the immune surveillance of the host e.g. by shedding the viral protein from the plasma membrane of host cells or changing gene expression after an antibody attack[78]. In addition to altered plasma membrane structures, viruses might modify only internal cell membranes or nucleic acids[27]. The abnormalities of synovial fibroblasts cultured from RA patients compared to those from controls have been considered to indicate a persistent, hiding infection: if the controversial reports are neglected, the principal changes observed in RA cells include increased degradative activity and elevated immunological reactivity (table). Decrease in the mol. wt of hyaluronic acid complexes secreted by RA synovial fibroblasts is as nonspecific as the other changes mentioned in the table[120]. No consistent protein differences have been noticed in the membrane structures of RA synovial fibroblasts[55–57]. The separation of antigenic proteins occurred, however, according to their mol. wts only. It is possible that the putative changes are not reflected in mol. wt aberrations. As synovial macrophage-like cells or invading lymphocytes have also been implicated as the primary sites of persistent infection[67], it might be relevant to note that the appearance of some new proteins and increased synthesis of several others has been shown in the peripheral blood leukocytes of RA patients, correlating with the disease activity[123]. It is not clear whether these reflect regulatory changes only.

Recently, small DNA-viruses called parvoviruses were detected in some synovial specimens of RA patients by electron microscopy[99]. They cannot be cultivated. Confirmation by other laboratories is needed before any causative role can be accepted for them.

Other organisms

Mycoplasmas have been suggested to cause RA, mainly because some mycoplasmal arthritides occuring in animals closely resemble the human RA[22]. Even the immune response-escaping mechanisms and immune complex-mediated tissue destruction could be consistent with the human disease. It is also possible that the site of infection is extraarticular, e.g. respiratory or in the

genital tract, giving rise to an immune complex-mediated joint disease[22]. In view of the lack of evidence, it might be considered that some RA patients develop their disease after mycoplasmal infection, but this is not sure.

Peptidoglycans of bacterial cell walls are relatively non-degradable in human cells, since they are composed of polymers of unfamiliar molecules: N-acetylmuramic acid and (also appearing in eucaryotic cells) N-acetyl glucosamine heteropolymers connected with peptide bridges of D-amino acids[11]. In rats, sonicated bacterial cell walls injected i.p. have been found to cause arthritis[40]. In humans, immunogenic peptidoglycans, which are common to a wide range of bacteria, could originate from bacteria of the digestive tract, e.g. pharyngeal streptococci or enteric species. An immune response could be elicited by peptidoglycan dimers forming haptenic antigens with IgG[11]. Streptococcal cell wall sonicated have been shown to elicit monocytes, leading to synovial cell activation and tissue destruction by secreted plasminogen activator[40]. Reactive arthritides after e.g. Yersinia or Salmonella infections give additional importance to the bacterial antigens as possible causative agents of RA[64]. Nevertheless, no definitive demonstrations of the involvement of bacterial antigens in RA exist[86]. In ankylosing spondylitis, it has been speculated that a plasmid of Klebsiella bacteria transmits the elements needed for the cell surface alteration of HLA-B27 positive lymphocytes, which is followed by a deviant immune response[107]. Related mechanisms are not ruled out in RA either.

Autoimmune disease

Immunohistology of rheumatoid synovium

Cellular infiltration in RA synovium consists of lymphocytes, macrophages, plasma cells and some granulocytes[54]. 70% of the lymphocytes are T cells[54]. The architecture of the infiltrate may be divided into lymphocyte-rich, often nodule-like areas, plasma cell-rich areas with scanty amounts of lymphocytes and intermediate = transitional areas[59]. Immunohistochemical techniques have shown that a great majority of the T cells in lymphocyte-rich areas stain with the OKT4 antibody, i.e. they are helper/inducer cells. These tend to accumulate around blood capillaries and reside in close contact with activated HLA-DR positive macrophage-like cells, called ID (interdigitating) cells[26, 47, 68]. This microanatomical interrelationship is similar to that seen in the initiation of immune responses, where macrophages present foreign antigens to helper T lymphocytes, using also a cellular contact with HLA-DR antigens. The abundance of ID cell/helper T lymphocyte clusters would imply that regulation of immune response is impaired in RA[47]. The increased potential of macrophage-like cells from RA patients to activate autologous T lymphocytes has been demonstrated in vitro as well[51]. Some investigators have pointed out that the overrepresentation of OKT4 positive lymphocytes is seen only in follicular areas, whereas transitional areas contain more OKT8 positive (suppressor/cytotoxic) lymphocytes than helper cells[59]. They stress the importance of the latter areas in the pathogenesis of RA, since T lymphocytes of transitional areas are more often transformed to blasts than those of lymphocyte-rich follicular areas[59]. The immunohistology of rheumatoid synovium is not disease-specific, since similar cell infiltrates are seen e.g. in immunological skin diseases[52].

Part of the lymphocyte-activating effect of macrophages is mediated by soluble factors, mainly interleukin 1, which has been found in RA synovial fluid as well[28]. It has the capacity to multiply the immune response by stimulating T cell proliferation. The vicious circle of chronic inflammation may be worsened by T lymphocyte factors, which in turn are able to activate macrophages[6, 47]. Interleukin 1 also stimulates synovial fibroblastic cells to release collagenase and prostaglandin E2, which mediate destruction of cartilage and resorption of bone[70].

Immunopathogenic mechanisms of diseases

This presentation follows the classification of Coombs and Gell as described by Wager[121]. Type I or anaphylactic response is probably not involved in RA and is not discussed further. Type II reactions are cytotoxic responses initiated by antibodies binding with cell or tissue antigens. Effector mechanisms leading to cell or tissue destruction may include nonspecific killing of 'labeled' cells (antibody-dependent cell-mediated cytotoxicity = ADCC), phagocytosis of opsonized cells or binding of complement components to antibodies. Humoral mechanisms of type II mediate the majority of injuries caused by autoantibodies.

Type III reactions are caused by immune complexes. Type IV reactions comprise cell-mediated responses leading to target cell killing without antibody opsonization. Effector cells include sensitized killer T lymphocytes or activated macrophages trimmed by lymphokines of helper T cells. Secretion of soluble mediators, e.g. factors inhibiting leukocyte or macrophage migration (LIF or MIF) belong to type IV reactions. Moreover, natural killer cells (NK cells) destroy the targets without prior immunological sensitization.

Humoral autoimmunity in RA (type II reactions)

It has often been speculated that a new antigen on synovial cells or in the extracellular matrix, altered by host metabolism or an infecting microbe, is eliciting host defence mechanisms, which leads to chronic inflammation. The sequence of cellular interactions operating in the production of antibodies – antigen presenting immunomacrophages, helper T lymphocytes and B lymphocytes/plasma cells – has been demonstrated in rheumatoid synovia[26, 68]. There is also a relative lack of suppressive T lymphocytes[18]. However, in addition to the F_c part of native IgG, no major knowledge exists about the target antigens.

Cartilage is relatively isolated in the body, because it is not vascularized. This has lead to speculation on its potential autoantigenicity, due to false 'foreign' recognition by lymphocytes. Antibodies against type II cartilage collagen appear in RA patient sera[21, 105, 113]. Native type II collagen, injected with Freund's incomplete adjuvant, causes arthritis in about 40% of immunized rats[114]. However, careful studies using sophisticated techniques have shown that antibodies to native human type II collagen exist only in about 3–13% of patients[10, 21]. Antibodies to other collagen types exist in RA patient sera as well, and also in sera of other patient groups, suggesting that anti-

bodies are formed mainly as a secondary reaction to tissue injury[106].

RA patients have antibodies against at least intermediate filaments[58], fetal liver antigens[95], histones[108] or RANA[100]. The immunopathogenic significance of these is open to discussion. They might reflect polyclonal B lymphocyte activation (e.g. EB-virus-induced anti-RANA antibodies) or helper T cell circumvention due to neoantigen structures[109]. A secondary scavenger cell aid by antibody opsonization is possible, too. Moreover, anti-F_{ab} antibodies appear in 70% of RA patients. These include anti-allotypic and anti-idiotypic antibodies and may interfere with the idiotype-anti-idiotype network, regulating antibody production[71].

Antibodies against nondefined synovial cell antigens have been sought by in vitro tests, detecting either bound IgG on synovial cell layers or using ADCC[35,37], with negative results. Peripheral blood monocytes of RA patients exhibit increased[122] or decreased ADCC[9], depending on the technique used.

Immune complexes in RA (type III response)

Rheumatoid factors (RFs) are the main antibodies occuring in RA patients, though they are not specific for RA. The role of IgM RF may even be protective[121], but IgG class RFs are most probably pathogenic. In synovial tissue, about half of the plasma cells secrete IgG of anti-IgG specificity[72], leading to IgG RF-IgG RF complexes, which bind complement in synovial tissues[124] and might cause tissue injury. This is reflected by decreased complement levels in RA synovial fluids[121]. Circulating levels of neither IgG RF nor IgM RF correlate with disease activity, but are associated with systemic vasculitis[3] or with the stage of disease[1]. The reason for the synthesis of RFs remains obscure.

Complement can also be activated by type II collagen[41] or synovial cell intermediate filaments[66] without any preexisting antibody-antigen complex. The pathogenic importance of these mechanisms remains to be evaluated.

Cell-mediated immunity in RA (type IV responses)

A beneficial effect of lymphapheresis in RA[49] and preponderance of T lymphocytes in synovial infiltrates has been attributed to the involvement of cell-mediated immunity in RA[80]. Synovial reaction in RA resembles classical skin delayed-type hypersensitivity reactions, where HLA-DR positive macrophage-like cells have been shown to play a role[52]. Compared to skin reactions, HLA-DR expressing macrophages in RA synovia are more abundant, probably because of perpetuating inflammation.

Sensitized T lymphocytes are important killers of virus-infected cells. Hyporesponsiveness to PPD, mycoplasmal and viral antigens by RA lymphocytes has been observed, as measured wit the LIF test, possibly indicating a defective eradicating capacity in vivo[19]. Cellular sensitivity to autologous synovial cell components has been shown by the LIF test, but not against allogeneic RA cells[92]. Most probably nonspecific autologous HLA antigen cooperations are responsible for this reaction, and not RA-related antigenic changes, since there is no cell-mediated cytotoxicity against autologous synovial cells of RA patients[73].

Cellular immunity against type II and type III collagens has been reported in about 75% of RA patients, but only in 10–20% of control subjects, as measured by the LIF test[112]. Isolated synovial T lymphocytes of RA patients (three out of the four tested) have been shown to react with bovine type II collagen[52]. Denatured type I collagen also transforms lymphocytes in about 60% of RA patients[101]. It is notable that T cells react against the primary or secondary structure of the collagen molecule, while the B cell specificity lies in the tertiary or quaternary structure, giving rise to different humoral and cellular immune responses[102]. It as been shown that all humans respond to collagens via their T cells, but the response is usually suppressed. HLA-DR4 positive individuals (with or without RA) exhibit the cellular response because of lack of respective suppressor cells[103]. This could lead to overactivation of helper T lymphocytes during the physiological degradation of joint collagens. Reactions to minor cartilage collagens, i.e. types 1α, 2α, 3α or short chain collagens[13,96] have not been studied with RA patients cells, so far. Positive LIF test results, and lymphocyte transformation have been observed in RA, other arthritic and relapsing posttraumatic synovitis patients, when tested against various cartilage proteoglycan antigens[31]. This would imply that antigenic components released in inflammation or even after a single trauma might initiate vicious circles of RA in susceptible individuals.

Natural killer (NK) cell activity of RA patients' peripheral blood against K-562 erythroleukemia cell targets equals that of controls[24,98], while that of synovial fluid has been suggested to be either equal[89] or decreased compared to peripheral blood[24,98], reflecting differences in techniques used. Synovial fluid NK cells are also probably activated and bear no F_c receptors[98]. Reinitz et al.[89] have demonstrated an increased NK cell activity of mononuclear cells in RA synovial membrane, too. The NK cell activity of RA peripheral blood cells against synovial fibroblast targets has been reported to be increased[84], but this might be due to alloantigenic differences only[36]. Significance of these changes remains uncertain, but may reflect both activation of NK cells and increased possibility of persistent viruses in RA synovia[24].

Endocrine disease

Some well-known clinical data show that hormones regulate the activity of rheumatoid arthritis: ¾ of the patients are females, suggesting some role for estrogens. When patients with RA become pregnant, the symptoms disappear in about 75% of cases, followed by worsening of the disease at puerperium[79]. RA can also begin after delivery. Oral contraceptives prevent joint symptoms to some extent[117]. The protective effects are mediated by pregnancy associated α_2-glycoprotein[116], which has at least immunosuppressive properties[85]. Other endocrine influences have been recently reviewed[2].

Metabolic or nutritional disease

Evidence for a primary metabolic defect in RA does not exist. Usually, the metabolic alterations are connected with activated or altered cell functions. Those of cultured synovial cells were discussed previously. Here, the

changes reflecting functions of phagocytes are briefly mentioned.

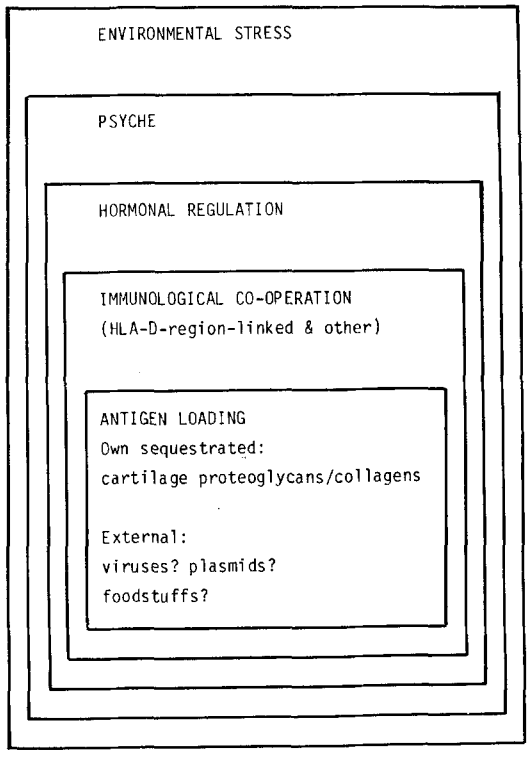
For the most part, the oxygen-derived free radicals liberated by neutrophils and macrophages during phagocytosis oxidize the free thiol groups of serum proteins[39]. That is why serum sulphydryl levels are decreased in RA[38], reflecting activation of phagocytes. The lowered level even has prognostic significance in early synovitis[39]. Superoxide dismutases are detoxicating enzymes produced by cells to abolish harmful superoxide anions ($O_2 \cdot^-$) created during phagocytosis. The activity of superoxide dismutase, the main copper-containing enzyme of cells, is elevated in polymorphonuclear and mononuclear leukocytes of RA patients[125], but depressed in their red cells[8]. Serum and synovial fluid copper and ceruloplasmin levels are elevated and zinc levels depressed in RA, but within the red cells the values are normal[8]. Increased copper levels in serum might also result from increased ceruloplasmin synthesis of the liver, stimulated by interleukin 1 from synovial macrophages[87].

Public opinion often considers dietary constituents to be etiological factors in RA, because of beliefs in diet therapies, and their occasional success; e.g. Dr Dong was cured of his arthritis by returning to Chinese food, rich in seafoods, vegetables and rice[25]. He attributed the arthritogenic effect of a conventional diet to chemical additives and to allergy to certain foodstuffs. The role of prostaglandin precursors and eicosapentaenoic acid in the diet has also been discussed[126]. Beneficial effects of total fasting on RA activity parameters has been demonstrated in a controlled study[115]. The effect of Dong's diet in an unselected RA patient group was not verified, but the disease of two patients improved markedly[83]. Obviously, careful critical studies of specified dietary regimens should be performed, until this topic is resolved[126].

Psychological disease

RA has classically been held to be a psychosomatic disease. The influence of psychic factors could be on disease onset or on the course of the disease, even though specific personality traits do not exist[69]. Rimón interviewed 100 RA patients, and could identify a major conflict group (55 patients) with emotionally important events prior to the onset of disease and a nonconflict group (33 patients) with more heredity factors for RA[91]. An increase in stressful life events before the onset of RA has been reported later, too[7]. In rats, stress in the form of exposure to a cat has been shown to decrease the occurrence of type II collagen-induced arthritis[94]. Possible immunoregulatory, endocrine or other mechanisms involved in this link have been discussed[93].

Families of RA patients are more disturbed than those of neurotic patients and come close to those of schizophrenics in the level of psychiatric problems[90]. Yet, in the interviews, despite the more problematic background, RA patients show lower scores of psychopathology than osteoarthritic patients, except depressiveness[82]. However, in psychological tests, the rigid character of a typical patient is evident, comprising e.g. static anxiety, rationalizations, dependency and infantile aggression problems[50]. Reduced ability to express emotions openly or even to recognize them comes close to the alexithymic concept of psychosomatic disease development[65, 118].



Etiological levels of rheumatoid arthritis.

Integrated model

The picture of the etiology of RA is far from complete. However, a multilevel model of various coexisting etiological factors can be derived from the information mentioned, applying the concept of the bio-psycho-social monism of man (fig.). It is noteworthy that the different elements are definitely of varying relative importance in different individuals[88]. Although the principal microbe or antigen may be the same, some people develop their disease mainly because of genetic background, others due to emotional inadequacy and still others perhaps because of unsuitable dietary loading.

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Mini-Reviews

Methanogens: a short taxonomic overview

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Key words. Methanogenic bacteria; *Archaebacteria;* classification; physiology; taxonomy.

Introduction

Scientific interest in methanogenic bacteria began in 1776, when the physicist A. Volta described the formation of some sort of 'combustible air' in the sediments of lakes and ponds rich in organic matter. Famous scientists like Béchamp, Popoff, Soehngen and Omelianski studied the microbial origin of methane gas, a development extensively described by another pioneer of the metabolism of the methane formation, Barker[4]. Methanogens live in strongly anaerobic habitats; they are found in two main natural ecosystems, in sediments of lakes and ponds that are rich in organic material, and in the intestines of various animals, among which ruminants and termites may be the most important. In the methane fermentation, unlike other fermentations, no complex substrates are degraded to methane by one single bacterial species, but methane formation needs the cooperation of at least two different bacterial populations. The first one degrades complex organic substrates to low mol.wt. organic acids, CO_2 and hydrogen, and the methanogens use the latter two of these products and eventually acetate to form methane.

All morphological forms found among bacteria, e.g. cocci, rods and spirilla, are also observed among methanogenic bacteria; the unique property of methane formation has been used since the first description of methanogens as the main taxonomic characteristic of this group to distinguish them from the other bacteria.

The findings of novel structures, components and pathways in certain bacterial groups led some years ago to the proposal of the new kingdom of the *Archaebacteria*[42]. *Archaebacteria* have been clearly separated from other procaryotes on the basis of distinct biochemical properties and of differences from all other organisms, e.g. with respect to cell wall composition, structure of lipids, tRNA and RNA-polymerase and the presence of new coenzymes. Besides methanogens, several other organisms have been placed in this new kingdom; the extreme halophiles which form a 1st group together with the methanogens, the *Thermoacidophiles* with *Sulfolobus* as a 2nd one and the genus *Thermoplasma* as a 3rd group[14]. Very recently the latter two groups have been separated from the *Archaebacteria* to form a new kingdom of *Eocyta*[22a].