



Review

Inflammation as “common soil” of the multifactorial diseases

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ABSTRACT

Inflammation is classically recognized as an essential step for the control of microbial invasion or tissue injury as well as for the maintenance of tissue homeostasis under a variety of noxious conditions. One of the most intriguing aspect of studying inflammation is the plurality of the inflammatory mediators that are continuously discovered (microRNAs, adipokines, inflammasomes and the danger signals, etc.) and their effects on target tissues. Several studies have demonstrated that inflammatory response represents the “common soil” of the multifactorial diseases, encompassing both chronic inflammatory rheumatic disorders and a wide variety of conditions including type 2 diabetes, cardiovascular and neurodegenerative diseases, obesity, cancer, asthma, and ageing. While the inflammatory response observed in the rheumatic disorders seems to be triggered by infection and injury, i.e. the main inducers of inflammation, in the other conditions mentioned it appears to be supported by tissue malfunction or homeostatic imbalance. In the present review, we discuss the data emerged from research on inflammatory mediators sustaining multifactorial diseases.

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1. Introduction

Pathways of systemic inflammation have been recognized as an essential component in the pathogenesis of different multifactorial diseases encompassing chronic inflammatory rheumatic disorders, as well as a wide variety of conditions including type 2 diabetes,

cardiovascular and neurodegenerative diseases, cancer, obesity, asthma, and ageing. While the rheumatic diseases have become prototype entities for defining the pathological basis of chronic inflammation, there are differences between these diseases and the other conditions mentioned. Indeed, the inflammatory response observed in this latter group does not seem to be triggered by infection and injury, classically recognized as the main activators of inflammation, but it appears to be supported by tissue malfunction or homeostatic imbalance. This type of response exhibits a lower

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magnitude of inflammation than the classic reactions and their mediators remain largely unknown [1].

In the present review, we focus on the role of inflammation in the pathogenesis of several chronic disorders and provide evidence of how the inflammatory response represents the unifying force driving the progression of these heterogenic multifactorial diseases. We will consider the data emerged from research on rheumatic disorders separately, dwelling upon those in which relevant information has been recently uncovered, and those related to other conditions (Fig. 1).

2. Inflammatory rheumatic diseases

The multifaceted phenotype of chronic inflammatory rheumatic diseases, labeled as immune-mediated disorders, is probably endorsed by the complex underlying pathogenetic network of molecular and cellular mediators matching with environmental factors in genetically-primed individuals. As a matter of fact, the pathogenesis of rheumatic diseases often evokes the concept of an inflammatory response leading to autoimmunity: yet, Witebsky's postulates [2] are rarely fully satisfied and, furthermore, since some patients do not respond to immunosuppressive treatment, the hypothesis of additional inflammatory mechanisms causing tissue damage is being widely accepted. In this view, targeting cellular and molecular effectors of tissue destruction is considered a new prerequisite for a successful treatment of joint diseases.

2.1. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disease, affecting approximately 1% of the adult population. Overwhelming evidences indicate that both innate and adaptive immunity participate to disease pathogenesis: the role of T and B cells, macrophages, mast cells and fibroblast-like synoviocytes has been widely described [3], but new inflammatory mediators are constantly arising.

For instance, anti-citrullinated protein/peptide antibody (ACPA), a disease-specific marker of RA, are associated with more aggressive disease and their levels correlate with radiological damage and disease activity [4]. Thus, ACPAs are most likely involved in the pathogenic inflammatory mechanisms of RA.

Interestingly, it is remarkable to note that the presence of autoantibodies and gene expression profile in healthy first-degree relatives (HFDRs) resemble those found in individuals with autoimmune disorders [5], confirming that interactions with environmental factors lead to the induction of the disease.

Our group analyzed the presence of ACPAs in HFDRs of patients with RA (manuscript in preparation). Interestingly, of 83 sera from HFDRs of ACPA-positive RA patients, only two (2.4%) were positive for ACPAs, while only four of 53 sera (7.5%) from HFDRs of ACPA-negative RA patients were positive for ACPAs. This low prevalence confirms a high specificity of ACPAs for RA, suggesting that these autoantibodies, in contrast to findings in other autoimmune diseases, are probably directly involved in the pathogenesis of RA.

In recent years, apart from ACPAs, interest has been captured by the discovery of novel mediators of inflammation, such as microRNAs and adipokines. MicroRNAs (miRNA) are a class of small noncoding RNAs that operate in different cells as post-transcriptional repressors of gene expression, and are considered to be key negative regulators of inflammation. Their expression appears dysregulated in different inflammatory diseases, including RA, where several inflammatory stimuli, such as Toll-like receptor (TLR) ligands and cytokines, induce their expression, although questions remain on how they may be implicated in RA pathogenesis [6].

Adipokines are soluble proteins secreted by the adipocytes of white adipose tissue (WAT), a highly dynamic organ with huge functions in physiological and metabolic processes. In fact, apart from its well known roles (regulating energy balance, haemostasis, and metabolism), WAT, through the secretion of adipokines, also modulates immune and inflammatory responses. Adipokines comprise a very heterogeneous group of factors, including adiponectin, leptin, resistin, visfatin, and omentin. They are all pro-inflammatory proteins, except for adiponectin, which shows anti-inflammatory effects in obesity and vascular diseases, while being pro-inflammatory within joints [7]. In particular, adiponectin has been demonstrated to promote inflammation through cytokine synthesis, attraction of inflammatory cells to the rheumatoid synovium and recruitment of pro-destructive cells via induction of chemokines [8]. Also leptin may play a role in RA, considering that circulating levels of this adipokine were shown to be high in patients [9].

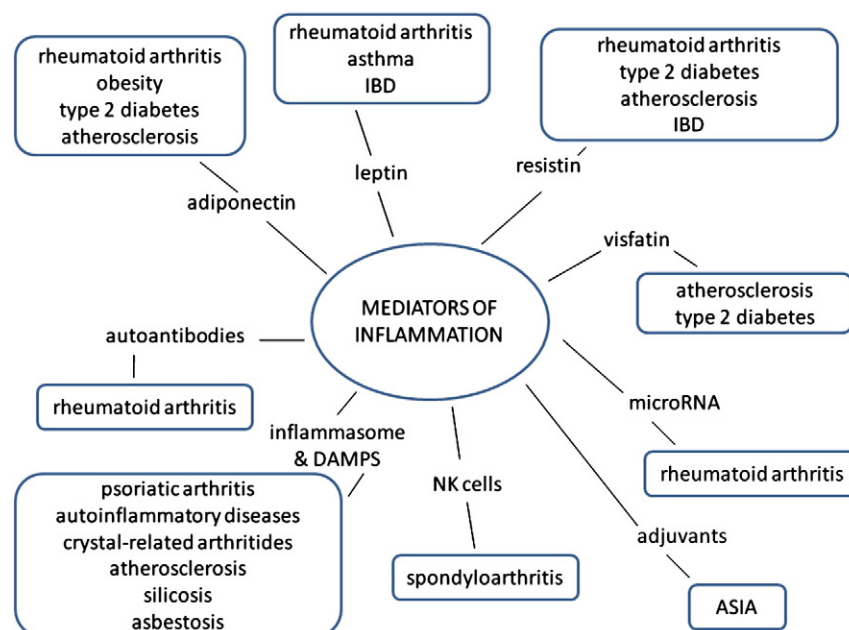


Fig. 1. Inflammatory mediators shared by the multifactorial diseases. (IBD: inflammatory bowel disease; ASIA: Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants; NK: natural killer; DAMPs: damage-associated molecular patterns).

Table 1 summarizes the main features of the best-characterized adipokines.

2.2. Psoriatic arthritis

Psoriatic arthritis (PsA) is an inflammatory arthropathy belonging to spondyloarthritis (SpA) and occurring in approximately 25% of patients with psoriasis, characterized by an infrequent seropositivity for RF and ACPA both in serum and in synovial fluid [10]. Up until approximately a decade ago, T lymphocytes were thought to play an important role in the pathogenesis of the disease, the most convincing argument being the demonstration of infiltrates of clonal CD8+ T cells in the synovial tissue and the skin [11]. Accordingly, the inflammation associated with PsA was supposed to be caused by autoimmunity against a common antigen in the skin and joints targeted by activated T cells. The pathogenetic role of T lymphocytes has recently been reinforced by the observation that T helper type 17 (Th-17) may be an important effector in SpA: levels of interleukin 17 (IL-17), a pro-inflammatory cytokine secreted by Th-17 [12], were found elevated in synovial fluid and serum from patients with SpA [13]. The cytokine network appears to be also amplified by different macrophage subtypes, identified by the CD163+ and the CD68+ phenotype respectively, producing different pro-inflammatory cytokines, such as tumour necrosis factor α (TNF), IL-1, and IL-18 [14, 15]. All these features heavily outline the belief that a persistently altered innate immune response drive the pathologic changes observed in PsA synovium. This hypothesis is supported by the observation that PsA susceptibility may be conferred by the expression of killer immunoglobulin-like receptors (KIRs), a multigene family of both inhibitory and activating receptors, on natural killer (NK) cells [16], an important arm of innate immunity. Our group, by means of flow cytometry, confirmed a higher frequency of NK cells expressing KIR3DL1 [17], an inhibitory receptor binding HLA class I alleles bearing the Bw4 motif, including HLA-B27, that is strongly associated with the development of SpA. We also observed an impaired IFN- γ intracellular production in stimulated NK cells from SpA patients as compared to healthy controls [17]: since it has been demonstrated that some types of peptides promoting HLA-B27 binding to KIR3DL1 inhibit NK cell IFN- γ production [18], it is conceivable that similar mechanisms may explain the abnormal NK cell cytokine production observed in our study.

The relevant role of innate immunity in PsA pathogenesis has introduced a new concept on the pathophysiology of the disease, centered on the knowledge gained from anatomic and magnetic resonance imaging studies, which have demonstrated that enthesitis underpins most of the manifestations of PsA [19]. Because a prime feature of entheses is stress dissipation, and since even normal

insertions are sites of microdamage and tissue repair responses, it has been hypothesized that tissue-specific factors realize an autoinflammatory damage privileging the entheses, and distinct from autoimmunity, which is instead principally played out in the primary and secondary lymphoid organs [20]. Interestingly, an association between joint injury and PsA, but not RA, is well reported [21]. This model is supported by the recognition of the anatomic unit called “the synovio-enthesal complex” (SEC), emphasizing that entheses are often functionally and anatomically linked to the adjacent synovium. Microdamage and microinflammation in the SEC may be the forerunner of frank enthesitis and enthesal erosion and, subsequently, inflammation in adjacent synovial structures in PsA patients. Indeed, tissue damage leads to the release of many endogenous self-danger pro-inflammatory molecules, grouped under the name of damage-associated molecular patterns (DAMPs). Access of these molecules to the synovium may trigger and perpetuate inflammation, especially in the presence of intercurrent infections and fortuitous HLA gene associations [20].

To summarize, given that PsA represents inflammation at two different target tissues that cannot be explained adequately by traditional autoantibody and autoimmune paradigms, the SEC concept supports the importance of joint-specific factors serving as danger signals. These may trigger innate immune responses and consequently involve the mediators of adaptive responses, configuring PsA as a disease more similar to autoinflammatory disorders than to autoimmune conditions.

2.3. Inflammasome-related diseases

Autoinflammatory diseases (AIDs) cover a wide spectrum of syndromes caused by primary dysfunction of the innate immune system, expressing with seemingly unprovoked and recurrent attacks of fever, serositis, arthritis, rash, and lymphadenopathy. These manifestations occur together with a dramatic elevation of acute-phase reactants, in the absence of infectious causes or the typical features of autoimmune diseases such as high-titer autoantibodies or autoreactive T cells [22]. The main pathogenetic pathways implicated in the development of AIDs are driven by DAMPs, that are recognized by TLRs on the surface of macrophages, thus activating different intracellular sensors [23]. Unlike PsA, in AIDs the DAMPs interact with an intracellular multiprotein complex of over 700 kDa, called the inflammasome. This is composed of an assembly of units including one sensor (NALP3, also known as cryopyrin), two connecting proteins (ASC and cardinal), and one effector (ICE, interconvertin enzyme), though the total number of units remains indefinite and several types of inflammasomes have been identified. After activation by DAMPs, the inflammasome induces the activation of caspases,

Table 1

Main features of the best-characterized adipokines.

Adipokine	Characteristics	Functions	Diseases	Reference
Adiponectin	244-residue protein, also called GBP28 and Acrp30; three oligoforms (trimer, hexamer, and high molecular weight)	<ul style="list-style-type: none"> • pro-inflammatory (RA) • anti-inflammatory (obesity, type 2 diabetes, atherosclerosis) 	<ul style="list-style-type: none"> • RA • obesity • type 2 diabetes • atherosclerosis 	[8, 30, 36]
Leptin	16 kDa—class I cytokine superfamily	<ul style="list-style-type: none"> • pro-inflammatory (RA) • decreases food intake, increases energy consumption • increases bronchial epithelial cell proliferation 	<ul style="list-style-type: none"> • RA • IBD • asthma 	[9, 33, 36, 40]
Resistin	12.5 kD cysteine-rich protein	<ul style="list-style-type: none"> • pro-inflammatory: activates TNF and IL-12 in monocytes, activates NF-kB 	<ul style="list-style-type: none"> • RA • type 2 diabetes • atherosclerosis 	[7, 33, 36]
Visfatin	52 kDa protein, also called pre-B colony enhancing factor (PBEF)	<ul style="list-style-type: none"> • pro-inflammatory: up-regulates production of IL-1β, IL-6, and TNF-β in monocytes • activates insulinic receptor 	<ul style="list-style-type: none"> • atherosclerosis • type 2 diabetes 	[7, 33]

RA: rheumatoid arthritis; TNF: tumour necrosis factor; IL: interleukin; NF-kB: nuclear factor-kappa B; IBD: inflammatory bowel disease

which then process and release IL-1 β , and afterwards other potent pro-inflammatory cytokines [24].

Most surprisingly, it has recently been discovered that the inflammasome may be activated by various stimuli, establishing an unexpected link between AIDs and other diseases such as gout. Via this link, mechanisms by which monosodium urate (MSU) crystals, the causative agent of gout, promote joint inflammation, can be in part explained. In fact, MSU crystals behave like DAMPs and are capable of activating the inflammasome [25]. The same Authors demonstrated that calcium pyrophosphate dehydrate (CPPD) crystals, responsible for CPPD crystals deposition disease, also engage the cryopyrin inflammasome to release active IL-1 β [25], providing us with several lines of evidence on the pathogenetic mechanisms of crystal-induced acute inflammation. In addition to MSU and CPPD crystals, other crystalline substances can sensitize the inflammasome, including cholesterol crystals [26], crystalline silica, and asbestos dust [27], leading to assume that NALP3 activation may be therapeutically exploited in such pathologies. Hence, these substances resemble the effect of adjuvants, since they may elicit an immune-mediated response in genetically-susceptible subjects. Interestingly, exposure to several adjuvants has been documented in a group of peculiar conditions presenting similar complex of signs and symptoms, namely siliconosis, the Gulf war syndrome, the macrophagic myofasciitis syndrome, and post-vaccination phenomena, suggesting that they share a common causative denominator, i.e. a trigger entailing adjuvant activity. To emphasize this aspect, it was proposed to include these conditions under a common syndrome entitled “ASIA” (Auto-immune/Autoinflammatory Syndrome Induced by Adjuvants) [28].

Table 2 lists the inflammasome-related diseases identified so far.

3. Non-rheumatic inflammatory diseases

Chronic inflammation underlies various slowly disabling illnesses that affect a large part of the population, such as atherosclerosis, diabetes mellitus, hypertension, metabolic syndrome, cancer, asthma, neurodegenerative diseases, and many others.

Considering the epidemiologic relevance of these disorders, current research efforts are focusing on dissecting the molecular

and cellular mechanisms behind the inflammatory response, in order to provide an extensive array of targets for the development of anti-inflammatory drugs.

3.1. Atherosclerosis

For a long time, atherosclerosis has been mainly considered to be a disorder of lipid metabolism, but nowadays it is especially deemed as an inflammatory disease characterized by endothelial dysfunction [29]. We have already mentioned the capability of cholesterol crystals to activate inflammasome, but numerous other mediators interacting through complex networks in the atherogenesis process have been identified, which include adhesion molecules, cytokines, proteinases, reactive oxygen species, adipokines. In particular adiponectin is able to inhibit both the inflammatory process and atherogenesis by preventing the migration of monocytes/macrophages, the most important cell type leading to atherosclerosis, and suppressing their transformation into “macrophage foam cells” in the vascular wall [30]. Among adipokines, we have evidences that also resistin and visfatin affect atherosclerotic processes (Table 1).

3.2. Metabolic syndrome and type 2 diabetes

The metabolic syndrome is a condition characterized by increased waist circumference, decreased serum high-density lipoprotein, increased serum triglyceride levels, hypertension and insulin resistance (IR) [31]. It is accompanied by endothelial cell activation, adipocyte hypertrophy, macrophage infiltration, and free-fatty acid accumulation in adipose tissue, all leading to a low-grade inflammatory state [32]. These changes are relevant since in the lean state adipose tissue secretes elevated levels of adiponectin and other anti-inflammatory adipokines and is insulin responsive; conversely, increased energy intake is followed by adipocyte hypertrophy/death and chemotactic adipokine release. As a consequence, macrophages infiltrate into the tissue and exacerbate the inflammatory response, thus leading to IR, hypoxia, decreased adiponectin release and endothelial dysfunction [33]. Increased levels of inflammatory

Table 2
Inflammasome-related diseases hitherto identified.

Disease	Clinical features	Response to anakinra
<i>Cryopyrinopathies</i>		
Muckle–Wells syndrome	Recurrent or sub-chronic urticaria-like lesions, sensorineural hearing loss, amyloidosis	Yes
Familial cold autoinflammatory syndrome	Rash, fever and arthralgia after cold exposure	
Chronic infantile neurological cutaneous and articular syndrome (CINCA)	As MWS, plus mental retardation, chronic aseptic meningitis, bone deformities	
Familial Mediterranean syndrome	Short duration of fever episodes (24–48 h), abdominal and chest pain, erysipelas-like erythema, high incidence of renal amyloidosis in untreated patients	Possible
Pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA) syndrome	Pyogenic sterile arthritis, pyogenic gangrenosum, cystic acne	Yes
Hyperimmunoglobulin D syndrome (HIDS)*	Arthralgia, abdominal pain, lymphadenopathy	Yes
Tumour necrosis factor receptor-1-associated syndrome (TRAPS)*	Prolonged fever episodes (1–3 weeks), periorbital edema, monocytic fasciitis, renal amyloidosis	Yes
Systemic juvenile idiopathic arthritis (SOJIA)*	Chronic joint inflammation	Yes
Adult-onset Still's disease (AOSD)*	Arthralgia, fever	Yes
Behcet's disease*	Arthralgia, uveitis, ulcers	Yes
Schnitzler's syndrome*	Urticaria, fever arthralgia	Yes
Gout	Arthritis	Possible
Pseudogout	Arthritis	Possible
Contact dermatitis	Urticaria	Unknown
Fever syndrome*	Fever	Unknown
Hydatidiform mole*	Hydatid mole	Unknown
Vitiligo*	Skin depigmentation	Unknown
Blau syndrome	Arthritis, dermatitis, and uveitis (noncaseating granulomatous inflammation)	Unknown
Crohn's disease	Inflammatory bowel disease	No
Essential hypertension*	Variable complaints related to elevated pressure or hypertensive vascular disease	Unknown

MWS: Muckle–Wells Syndrome; anakinra: antagonist of the interleukin-1 receptor.

*The involvement of the inflammasome is only hypothesized.

mediators and acute-phase reactants are also a frequent finding in patients with incident type 2 diabetes [34].

3.3. Inflammatory bowel diseases

The hallmark of inflammatory bowel diseases (IBD) is an exaggerated response of the mucosal immune system to dietary factors and commensal bacteria in genetically predisposed individuals. Recent data indicate an altered local expression and serum levels of some adipokines with immune-modulating capacities in IBD: several Authors found a decreased production of leptin at site of the involved tissue, and an increased production of adiponectin, with a parallel increase in the serum. Also resistin serum levels were increased, while a decrease was observed after anti-TNF treatment [35]. In patients with enteropathic arthritis, an interesting *ex vivo* study provided evidence of T cell clonality, finding identical clonal expansion in the colon and in the joint [36].

3.4. Cancer

Clinical and epidemiologic studies have suggested a strong association between chronic infection, inflammation and cancer. There are two different pathways linking the inflammation with tumorigenesis: an extrinsic pathway mediated by chronic inflammation (inflammation-induced cancer) and an intrinsic pathway in which genetic alterations, in the absence of an underlying inflammation, initiate a tumour-driven host immune response leading to a microenvironment composed of inflammatory cells (cancer-induced inflammation) [37].

3.5. Inflammaging

The term “inflammaging” has been coined to explain the phenomenon that ageing is accompanied by a low-grade chronic, systemic up-regulation of the inflammatory response and these features are also common to most age-associated diseases. In the setting of inflammaging, it is important to include Alzheimer's and Parkinson's diseases, in which the innate immune system participates to neurodegeneration. In particular, in Alzheimer's disease pro-inflammatory cytokines can be toxic on neurons, favouring the increased concentrations of amyloidogenic peptides by neuronal cells and astrocytes [38]. In Parkinson's disease there is an overproduction of inflammatory mediators that may easily trigger neurodegeneration, since dopaminergic neurons in the substantia nigra are highly sensitive to various forms of disturbance [39].

3.6. Asthma

Probably leptin plays also a role in asthma. That comes from several observations: human bronchial cells constitutively express leptin and its receptor *in vitro*, the constitutive expression of leptin receptor is decreased by transforming growth factor (TGF)- β 1, a fibrogenic factor, and increased by steroids *in vitro*, and finally leptin decreases the spontaneous release of TGF- β 1 and increases bronchial epithelial cell proliferation through its receptor [40].

4. Conclusions

Inflammation is classically recognized as an essential step for the control of microbial invasion, but, following a more modern view, it especially represents an important process for maintenance of biological homeostasis. An aberration of these mechanisms may favor the development of various illnesses, in which a relevant role is mediated by the molecular and cellular components of the innate immune system. Apart from the classic mediators, novel elements belonging to the innate immunity are continuously discovered which

synergistically enhance inflammatory responses through the integration of a multiplicity of pathways. Among the most intriguing are autoantibody systems, microRNAs, adipokines, inflammasomes and the danger signals, NK cells, since all of them have allowed to establish unexpected links among seemingly different chronic diseases.

These studies have demonstrated that inflammatory response represents the “common soil” of the multifactorial diseases, and are particularly significant since they offer the potential to define new molecular targets for the therapy of such disorders burdened with a high epidemiologic impact.

Take-home messages

- Inflammatory response represents the “common soil” of the multifactorial diseases, including chronic inflammatory rheumatic disorders as well as a wide variety of conditions such as type 2 diabetes, cardiovascular and neurodegenerative diseases, inflammatory bowel diseases, obesity, cancer, asthma, and ageing.
- The inflammatory response observed in the rheumatic disorders seems to be triggered by infection and injury, i.e. the main activators of inflammation, while in other conditions, it appears to be supported by tissue malfunction or homeostatic imbalance.
- A plurality of inflammatory mediators has recently been discovered (microRNAs, adipokines, inflammasomes and the danger signals, etc.) and their effects on target tissues are currently being investigated.

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BCG Vaccination: A Role for Vitamin D?

BCG vaccination is administered in infancy in most countries with the aim of providing protection against tuberculosis. There is increasing interest in the role of vitamin D in immunity to tuberculosis. **Lalor MK, et al. (PLoS One 2011;6:16709)** determined if there was an association between circulating 25(OH)D concentrations and BCG vaccination status and cytokine responses following BCG vaccination in infants. Blood samples were collected from UK infants who were vaccinated with BCG at 3 (n=47) and 12 (n=37) months post BCG vaccination. These two time-points are denoted as time-point 1 and time-point 2. Two blood samples were also collected from age-matched unvaccinated infants (n=32 and 28 respectively), as a control group. Plasma vitamin D concentrations (25(OH)D) were measured by radio-immunoassay. The cytokine IFN γ was measured in supernatants from diluted whole blood stimulated with M.tuberculosis (M.tb) PPD for 6 days. 58% of infants had some level of hypovitaminosis (25(OH)D <30 ng/ml) at time-point 1, and this increased to 97% 9 months later. BCG vaccinated infants were almost 6 times (CI: 1.8–18.6) more likely to have sufficient vitamin D concentrations than unvaccinated infants at time-point 1, and the association remained strong after controlling for season of blood collection, ethnic group and sex. Among vaccinees, there was also a strong inverse association between IFN γ response to M.tb PPD and vitamin D concentration, with infants with higher vitamin D concentrations having lower IFN γ responses. Vitamin D may play an immuno-regulatory role following BCG vaccination. The increased vitamin D concentrations in BCG vaccinated infants could have important implications: vitamin D may play a role in immunity induced by BCG vaccination and may contribute to non-specific effects observed following BCG vaccination.

Does HLA-DR7 differentiate the overlap syndrome of auto-immune hepatitis-primary biliary cirrhosis (AIH-PBC) from those with auto-immune hepatitis type 1?

Autoimmune hepatitis (AIH) and overlap-syndrome (OS) are autoimmune liver diseases of unknown etiology. Although HLA-DR3/DR4 plays susceptibility role in AIH but there is limited information in regard to OS. As regards, **Coss Adame E, et al. (Ann Hepatol 2011;10: 28-32)** determined the genetic expression of HLA-DR among patients with AIH versus OS in order to establish susceptibility alleles in comparison to healthy controls (HC). 26 patients with AIH and 15 patients with OS were studied. Ninety-nine healthy historical controls without autoimmunity were evaluated. Patients had at least one liver biopsy. Characterization of HLA-DR was extracted from peripheral blood leukocytes. Alleles were obtained for AIH, OS and HC and comparisons were made between groups. There was a significant increase in HLADR3 and DR1 in AIH compared with the HC group (p=0.04, OR 2.6, 0.87–7.9, 95% CI). In the AIH group there was a decreased frequency in allele HLA-DR8 when compared with HC (p=0.04, OR 3.2). There were no statistical differences between the genetic frequencies in the OS group compared with HC. However, HLA-DR7 was able to distinguish between OS patients from those with AIH (p=0.02, OR 9.8, 1.02–233.6, 95% CI). HLA-DR1/DR3 is increased in AIH, but contrary to data reported in AIH, HLA-DR7 frequency was increased in OS, suggesting increased susceptibility which distinguishes patients with AIH from those with OS.