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REVIEW

Chronic inflammation as a manifestation of defects in immunoregulatory networks: implications for novel therapies based on microbial products

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Abstract Based on a unifying theory presented here, it is predicted that the immune defects resulting in chronic inflammation rather than effective immune responses could be rectified by the therapeutic use of agents prepared from micro-organisms. With appropriate molecular patterns, these should be able to induce protective immunoregulatory networks or to reprogramme defective ones. In contrast to acute inflammation, chronic inflammation appears to have no beneficial role, but is a state of sustained immune reactivity in the presence or progression of a disease process. This results in an escalating cycle of tissue damage followed by unproductive tissue repair, breaks in self-tolerance, malignant transformation or deleterious changes in tissue morphology and function. Such inappropriate immune reactivity is an underlying characteristic, either in initiation or maintenance, of a diverse range of disease states including chronic infection, autoimmunity, allergy, cancer, vascular disease and metabolic alterations. Evidence is presented that the inappropriate immune reactivity is due, at least to some extent, to failures in the establishment of immunoregulatory networks as a result of hygiene-related factors. Such networks are the result of activation of antigen-presenting cells, principally dendritic cells, by molecular patterns of micro-organisms encountered sequentially during life and establishing the 'biography' of the immune system.

Keywords Inflammation · Infection · Immune regulation · Immunopathology · Autoimmunity · Cancer · Metabolism · Hygiene hypothesis

"Pluralitas non est ponenda sine necessitate." William of Occam (c.1285–c.1349)

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Introduction

Acute inflammation is usually regarded as a temporary and self-limiting response to infection or trauma and, though inducing discomfort, is essential for the restoration of tissue homeostasis and subsequent healing processes. By contrast, the much less well understood chronic inflammation appears devoid of any physiological role. Instead, it is a harmful condition that plays a central maintaining role in a number of disease conditions and opposes, rather than facilitates, normal healing processes (Medzhitov 2008). In this context, there is growing evidence that chronic inflammation is the expression of immune dysregulation. We propose a definition of chronic inflammation as a state of sustained immune reactivity in the presence of persistence and/or progression of a disease process. Such chronic inflammation is characterized by an escalating cycle of tissue damage, followed by attempts at tissue repair, resulting in breaks in self-tolerance (autoimmunity), malignant transformation (tumours) or deleterious changes in tissue morphology and function (fibrotic change or replacement).

Chronic inflammation, as thus defined, is characteristic of diseases as distinct as chronic infection, cancer, autoimmunity in its diverse forms, type 2 diabetes, obesity, allergy and vascular disease. The challenge is to determine whether there is a common underlying basis to the chronic inflammation seen in these very diverse conditions that points to a unified therapeutic approach. Thus, Mantovani et al. (2008) state that, among the many unanswered questions in the field of oncology, the most difficult ones concern the best way to treat such inflammation. They conclude that a therapeutic re-alignment of the tumour microenvironment from one that promotes the tumour to one that inhibits it 'could be the start of an exciting new era for anticancer therapies'. By similar reasoning, we could be at the start of an exciting new era of treatment for the other diverse conditions listed above.

It appears counterintuitive to link obesity and type 2 diabetes with the diseases associated with immune dysregulation, as, although both are very common in the industrially developed nations, the predisposing factors appear to be diet related rather than hygienic factors. There is, however, evidence that immune dysregulation is involved in the maintenance of these metabolic disorders, as described below (Bensinger and Tontonoz 2008).

Immune responses, whether associated with resolution of disease processes or with chronic inflammation, are induced and maintained by numerous cellular and soluble mediators which are controlled by regulatory networks. Many of the mediators are the same for the two phenomena: notably, complement components, antibody, chemokines, cytokines and cells, especially T lymphocytes and macrophages. Cells of the monocyte/macrophage series play a key role in the resolution of inflammation and tissue repair, but, as a result of inappropriate signalling under conditions of chronic cellular stress, they can contribute to tissue damage and maintenance of a chronic disease state (Gordon 2003). In addition to their well-described roles in immune reactivity, cells of this series are involved in the regulation of several metabolic processes that may well provide clues to the link between tissue regulation, immunity and chronic inflammation that seem to be central to the diseases under discussion.

A classic example of the functional diversity of macrophages is seen in tuberculosis, in which, by forming granulomas, they lead to quiescence in most primary cases. But in post-primary tuberculosis, they release proteolytic enzymes, which contribute to massive tissue necrosis and pulmonary cavity formation (Rook and Zumla 2001). Also, as described below, inappropriate recruitment of macrophages by tumours may mediate their growth and spread.

Accordingly, components of the immune system, both cellular and soluble, are pleiotropic in nature, having quite different effects depending on context, with observed responses resulting from the interplay of many different components favouring either resolution or progression of a pathological process. Thus, the terms 'pro-inflammatory' and 'anti-inflammatory' applied to cytokines and other mediators may frequently be misleading.

Changing paradigms in immunology relevant to immune modulation

In order to understand current concepts relevant to chronic inflammation and immune modulation, it is necessary to consider the many recent paradigm shifts that have occurred in the discipline of immunology.

- Traditionally, the immune system is regarded as distinguishing 'self' and 'foreign', but emphasis is now placed on its ability to detect 'danger', flagged up by changes in cells induced by infection, stress or malignant transformation (Matzinger 2002).
- The importance of the innate immune system as the first line of host defence during infection has recently become much clearer. It mostly relies on physical and chemical barriers to infection, as well as on different cell types that recognize invading pathogens and elicit antimicrobial responses. Physical and chemical defence mechanisms are represented by epidermis, ciliated respiratory epithelium, vascular endothelium and mucosal surfaces with antimicrobial secretions, while the cellular components include dendritic cells (DCs), macrophages, granulocytes, natural killer cells and $\gamma\delta$ T lymphocytes (Basset et al. 2003). Innate mechanisms rely on recognition of evolutionarily conserved structures on pathogens as described below. On this early recognition, clearance of pathogens is achieved through relatively nonspecific effector mechanisms, such as complement activation, phagocytosis, autophagy and acute inflammatory response. By contrast, the adaptive immune system is characterized by a broad repertoire of antigen-specific receptors on lymphocytes and mediates the elimination of pathogens in the late phase of infection and the generation of immunological memory (Iwasaki and Medzhitov 2004). As described below, innate and adaptive responses are intimately interrelated, with the former being involved in the activation and further shaping of adaptive immunity.
- Antigen presenting cells (APCs), including DCs and certain macrophages, do not 'see' individual epitopes in isolation, but as part of the challenging macromolecule or whole organism. The overall pattern of molecules encountered by the APC critically determines the nature of the ensuing immune responses. The APC,

therefore, performs 'a mini taxonomic exercise' on an encountered micro-organism (Rook 1991).

- The target-specific molecules that drive the qualitative nature of the immune response, termed adjuvants, are widely distributed among micro-organisms and include molecules from Gram-positive and -negative bacteria, DNA and RNA viruses, fungi and protozoa. The complement of adjuvants on a given micro-organism is termed the pathogen-associated molecular pattern (PAMP), although this is a misnomer as such patterns are found on avirulent saprophytic organisms as well as pathogens. Components of PAMP include bacterial cell wall lipopeptides, lipopolysaccharides (endotoxins) and lipoglycans, unmethylated CpG-islands of bacterial DNA, double-stranded viral RNA and bacterial heat-shock proteins (Hobohm et al. 2008).
- PAMP is recognized by various evolutionarily conserved 'gatekeeper' molecules in the APCs, collectively termed pattern recognition receptors, which provide early detection and elimination of invading microbes via innate immunity mechanisms and modulate subsequent adaptive immune responses to the pathogens (Ishii et al. 2008). There are four main classes of pattern recognition receptors: toll-like receptors (TLRs), retinoic acid-inducible gene I-like helicase receptors, cytoplasmic nucleotide-binding oligomerization domain-like receptors (NOD-like receptors) and C-type lectin receptors (Medzhitov 2007).
- Toll-like receptors represent the first line of host defence against microbial infection and play a pivotal role in both innate and adaptive immunity. TLR-ligand binding triggers a signalling cascade that leads to the induction of key mediators that contribute to an immune response. Additionally, by their ability to augment antigen presentation or induce the expression of target molecules, activation of TLRs results in the shaping of the adaptive immune reaction and they have thus been identified as potential therapeutic targets.
- This complex recognition system determines the regulatory activity of the APCs, especially DCs, and thereby the qualitative nature of T helper cell activation, proliferation and maturation induced by the APCs (Steinman and Hemmi 2006). Depending on the nature and the intensity of the stimuli, DCs can achieve different levels of maturation and activation (Sher et al. 2003; Pulendran 2005), which determine their capacity to affect polarized T helper (Th) cell responses. Thus, depending on the initial maturation signal, DCs can prime Th cells to differentiate toward the Th1, Th2, Th17 or regulatory T cells (Treg) types as shown in Fig. 1 (Sher et al. 2003; Cools et al. 2007; Rutella et al. 2006; Mortellaro et al. 2008). The Th1 and Th2 cells produce or induce type 1 and type 2 cytokines, respectively. Until recently, it was thought that patterns of immune reactivity were determined by a 'balance' between Th1 and Th2 cells and their respective cytokines. The situation is now seen as much more complex with other cell types and cytokines involved. In particular, a range of Tregs and a lineage of effector T cells, termed Th17 cells, have been described.
- Activation of pattern recognition receptors is a double-edged sword, leading in some cases to the pathogenesis of autoimmune, chronic inflammatory and infectious diseases (Cook et al. 2004). Thus, for example, the PAMP of some members of the genus *Mycobacterium*, such as *M. tuberculosis*, induce immunopathology and disease progression, whereas certain saprophytic species drive protective responses that can overcome the harmful effects of the former species (Dlugovitzky et al. 1999).
- The key effector cells of the immune system, the macrophages, may be activated by the 'classical' and the 'alternative' pathways, resulting in M1 and M2 macrophages, though these may well be polar forms in a spectrum of phenotypes. The classical pathway is IFN-γ-dependent and mediated by Th1 T cells, while the alternative pathway is mediated by the type 2 cytokines interleukin-4 (IL-4) and IL-13 (Gordon 2003). The predominant macrophages type determines the qualitative nature of immune responses. Studies on mycobacterial immunity showed that M1 macrophages secrete IL-23, a cytokine closely related to IL-12, which promotes Th1 or Th17 T cell immunity, depending on additional cytokines and perhaps the tissue in which these cells are elicited. Whereas, M2 macrophages predominantly secrete IL-10, which down-regulates Th1 responses (Verreck et al. 2004).
- In addition to being driven by PAMP, the APCs, particularly the DCs, are affected by metabolic stress-related signals, as described below. Also, pattern recognition receptors are activated by certain host-derived ligands released by various cell types during stress responses.

The link between metabolism, immune responses and chronic inflammation

Regulation of the genome is essential for homeostasis of the body, and key mediators include a highly conserved superfamily of proteins termed nuclear receptors. These contain domains that are linked to the operator parts of genes and those that are ligand receptors. In the absence of ligands, nuclear receptors repress gene expression. The best known are the hormone receptors and, in this context,

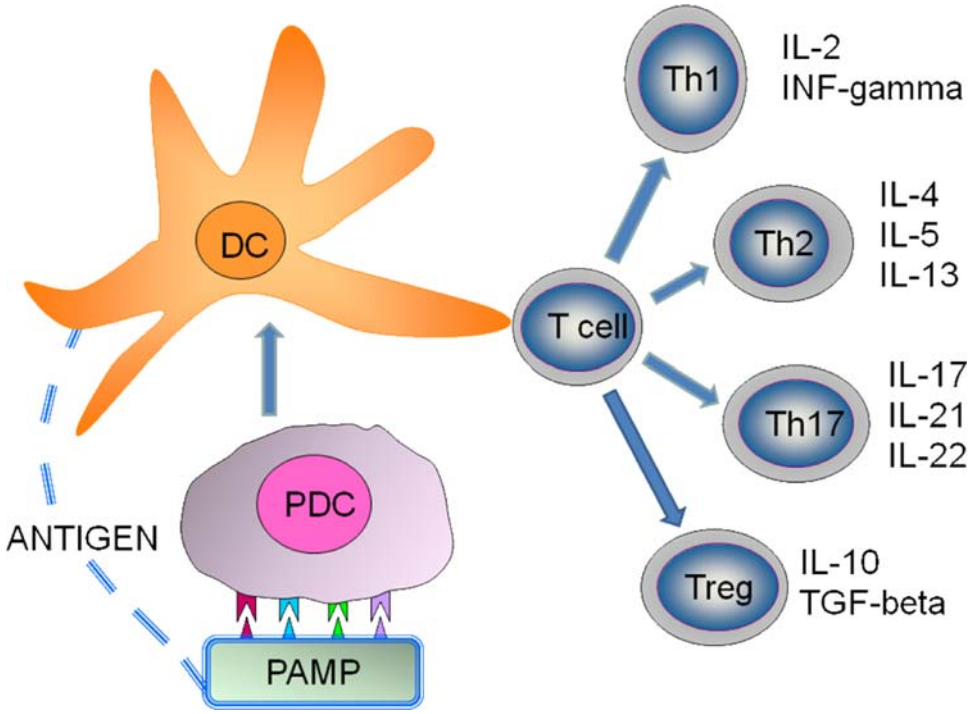

Fig. 1 Pathogen-associated molecular pattern-driven programmed maturation of the dendritic cell (*DC*) from the pre-dendritic cell (*PDC*) and subsequent induced differentiation of naive antigen-specific T cells into the functional types (colour figure online)

hormonal factors affect patterns of immune responsiveness and provide a means for the higher centres in the brain to modulate immune reactions. Thus, for example, the balance between dehydroepiandrosterone and corticosteroids affects maturation of helper T cells along the Th1 and Th2 pathways, respectively (Rook et al. 1994; Bottasso et al. 2009).

Peroxisome-proliferator-activated receptors (PPARs) and the liver X receptors (LXR) are also important classes of metabolite-activated nuclear receptors. Ligands for the PPARs include various lipids, such as unsaturated fatty acids and low- and very low-density lipoproteins, as well as certain pharmacological agents. There are three related PPAR proteins, PPARα, PPARδ and PPARγ, with both overlapping and complementary properties. The most extensively studied of these nuclear receptors, PPARγ, has regulatory effects on obesity, peripheral insulin sensitivity, muscle function and wound healing, as well as contributing to the pathogenesis of atherosclerosis (Zandbergen and Plutzky 2007).

In addition to regulating genes involved in metabolism, PPARs and their ligands repress target genes involved in a range of immune functions, including those of the transcription factor nuclear factor kappa-B (NFκB) and the nuclear factor of activated T cells (NFAT). It has, to date, not been easy to define a unified pattern of immune repression by PPARs (Bensinger and Tontonoz 2008), possibly because, as discussed below, certain PPAR ligands, such as oxygenated low-density lipoproteins, rather than the PPARs themselves, determine patterns of immune reactivity. Thus, the association of the level of PPAR expression and the qualitative nature of immune reactivity (Odegaard et al. 2007) may be secondary to an underlying regulatory series of immune reactions.

The LXR also affect the expression of genes involved in immune regulation and play a previously unexpected role in innate immunity by mediating macrophage responses to modified lipoproteins and intracellular pathogens (Joseph et al. 2004).

The involvement of these nuclear factors in immune reactivity establishes an association between lipid metabolism and inflammation and this is fundamental to the pathogenesis of atherosclerosis and to the peripheral insulin resistance characteristic of type 2 diabetes.

Inflammation and immunity in type 2 diabetes and obesity

Although the degree of immune activation seen in type 2 diabetes is far below that in acute infections, abnormalities in many systemic indicators of inflammation have been reported in this disease, and prospective studies have revealed subtle inflammatory changes in patients many years before the diagnosis of type 2 diabetes (Schmidt et al. 1999; Pradhan et al. 2001; Thorand et al. 2003). The pathogenesis of type 2 diabetes is attributed to the toxic effect of excess glucose, non-essential fatty acids and triglycerides, probably mediated by increased oxidative stress. On the other hand, the concept of an immune origin of type 2 diabetes is based on the role of immune mediators

in determining insulin resistance, beta cell function, glucotoxicity and lipotoxicity. In this context, TNF-α and IL-6 can directly interfere with insulin signalling and the induction of an intracellular response in muscle cells or hepatocytes that interferes with the ability of the insulin receptor to phosphorylate its intracellular targets (Ruan and Lodish 2003; Senn et al. 2003; Dandona et al. 2004).

In the case of obesity, functionally active immune cells within adipose tissue exert potent effects on adipocyte metabolism and endocrine function. In the obese state, there is an increase in macrophage accumulation in adipose tissue, which correlates with increased expression of a range of cytokines and chemokines (Xu et al. 2003). This expression of cytokines has been implicated in various forms of metabolic dysfunction, including decreased insulin sensitivity (Hotamisligil et al. 1993), increased lipolysis (Feingold and Grunfeld 1992) and increased leptin production (Trujillo et al. 2006). Thus, cytokine expression in adipose tissue contributes significantly to the pathogenesis of the metabolic syndrome associated with obesity, and with direct and indirect effects on non-adipose tissues (Uysal et al. 1997). The teleological reason for a close link between the immune system and energy stores is unknown, although some explanations may be considered.

Energy reserves in living organisms must serve a wide variety of often competing physiological functions. The current view of adipose tissue is that it is an active secretory organ, sending out and responding to signals that modulate appetite, energy expenditure, insulin sensitivity, endocrine and reproductive systems and bone metabolism, as well as immune function. There is, accordingly, an important biological link between energy balance and immune function and, as a consequence, susceptibility to disease. Immunity, like all other physiological processes, requires adequate energy to sustain optimal functioning, in which context several studies describe the energetic costs of immune reactivity induced by a variety of antigenic stimuli and across several vertebrate and invertebrate species (Moret and Schmid-Hempel 2000; Bonneaud et al. 2003). Thus, increased energy dedicated to immune responses, although beneficial in the short term, can ultimately come at the cost of decreased fitness, especially if immune activation is prolonged or excessive. The risk of infection and death is highest, however, when insufficient energy reserves are available to sustain optimal immunity.

Chronic inflammation and cellular stress

Another metabolic phenomenon with implications for inflammation and immune regulation is stress of the endoplasmic reticulum by metabolic overload, resulting in its failure to fold nascent protein chains correctly (Zhang and Kaufman 2008). Endoplasmic reticulum stress is particularly likely to occur in cells with high metabolic activity, such as macrophages, β-cells in the pancreatic islets and adipocytes, and is characteristic of obesity and type 2 diabetes (Gregor and Hotamisligil 2007). To protect the affected cells, the unfolded protein response is mediated by stress sensors, located in the endoplasmic reticulum, which in the healthy cell are maintained in the inactive state by chaperone molecules. When activated, the sensors limit further protein synthesis by inhibiting ribosomal function and enable the cell to adapt to chronic stress. But, if the stress is too severe, the unfolded protein response induces apoptosis of the affected cell to protect the organism against the harmful effects of misfolded proteins (Rutkowski and Kaufman 2007).

In some situations, destruction of cells by apoptosis may be beneficial, such as in the case of tumour cells and redundant cells of the immune system after successful resolution of an infection; but in other situations, essential cells may be irrevocably lost. In many cases of type 2 diabetes, cellular resistance to insulin is an early feature resulting in excessive insulin production. This exerts great stress on the β-cells in the pancreatic islets with induction of unfolded protein response, which, if it leads to apoptosis, sets up a vicious circle resulting in disintegration of the islets, undetectable endogenous insulin and the need for large amounts of exogenous insulin to maintain energy production and normal blood glucose levels.

The increased protein folding activity by endoplasmic reticulum in metabolically stressed cells requires oxygen and generates reactive oxygen species which, if they escape limiting mechanisms, accumulate and induce cell and tissue damage. A clue to a possible immunological limiting mechanism comes from studies on malignant transformation in melanocytes, which also, at least in part, is the result of excessive generation of reactive oxygen species. A postulated repair mechanism of oxidatively stressed melanocytes involves populations of T cells and, possibly, macrophages that transfer soluble factors to the target cells by direct cellular contact (Krone et al. 2005). Prime candidates for these factors are the gangliosides, especially LM1, which have several important effects on cell function, including repression of transcription, induction of enzymes and co-enzymes involved in regulation of the intracellular redox potential and restoration of a normal phenotype in various pre-malignant cell lines. The excess generation of reactive oxygen species in the pre-malignant melanocytes has been attributed to blockage by HERV-induced protein sharing, homologous amino-acid sequences with the oxygen-responsive element-binding protein, which is essential for redox regulation within the cell, and is also known as the nuclear factor for activated T cells (NFAT) (Krone et al. 2005).

The generation of excess reactive oxygen species in a cell leads to disturbed mitochondrial function due to leakage of calcium ions from the endoplasmic reticulum, in turn leading to further reactive oxygen species generation and direct induction of NFκB. The latter induces a range of inappropriate immune responses, including a dysregulated array of cytokines and to the acute phase response. Thus, although in principle a protective mechanism, the unfolded protein response is, when not properly regulated, a harmful response leading to a vicious circle resulting in further endoplasmic reticulum stress. From the limited number of studies on the subject, it appears that endoplasmic reticulum stress and conditions leading to over-expression of heat-shock proteins and related stress proteins are mostly distinct and unrelated phenomena (Liao et al. 2006).

The unfolded protein response is also involved in the pathogenesis of atherosclerotic lesions, as the accumulation of free cholesterol in the endoplasmic reticulum of macrophages induces unfolded protein response and the events leading to inflammation as described. Oxidized lipids and phospholipids generated by the inflammatory process lead to damage of endothelial cells of the arterial wall.

Mechanisms linking innate immunity to cholesterol metabolism and atherogenesis, and the long-suspected aetiological link with infections, are poorly understood. Interference with the expression of the LXR class of metabolite-activated nuclear receptors referred to above may provide an explanation, as pathogens have been shown to interfere with macrophage cholesterol metabolism through inhibition of the signalling pathway of the LXR (Hong and Tontonoz 2008; Korf et al. 2009). Activation of TLR3 and TLR4 by microbial ligands blocks the ability of LXR to induce the appropriate target genes in cultured macrophages and in aortic tissue, thereby strongly inhibiting cholesterol efflux from cells (Castrillo et al. 2003). It would be of interest to determine whether activation of alternative TLRs, such as TLR2 by phosphoinositol-capped lipoarabinomannan, a major adjuvant of many non-pathogenic mycobacteria (Doz et al. 2007), would have the opposite and beneficial effect.

A link between metabolism, chronic inflammation and immune reactivity

It is clear that an interplay between type 1 and type 2 cytokines and, as a consequence, between M1 and M2 macrophages has a pivotal place in the pathogenesis of obesity, peripheral insulin resistance and atherosclerosis, as well as chronic infections. In this context, PPARγ has a key regulatory role in determining patterns of immune reactivity, as it affects the maturation and differentiation of DCs (Gosset et al. 2001). Thus, the application of PPARγ ligands to immature DCs stimulated by lipopolysaccharide resulted in a markedly decreased secretion of IL-12 and other chemokines involved in promotion of Th1 maturation, showing that activation of PPARγ in DCs favour a Th2 response. This, through the type 2 cytokine IL-4, leads to M2 differentiation. It is possible that an abnormally sustained PPAR expression leads, at least in part, to a 'Th2 drift' characteristic of the diseases under discussion, and certainly observed in several forms of cancer (Ito et al. 1999; Jarnicki et al. 2006; Nevala et al. 2009). This would explain why sustained PPAR signalling antagonizes protection in infection by *Leishmania major*, an intracellular parasite requiring classically (Th1) activated M1 macrophages for its destruction (Adapala and Chan 2008).

A unifying explanation of the link between metabolism and immune reactivity operating at the level of the DCs is provided by one common feature of these conditions: the induced activity of lipoxygenase enzymes in APCs, including those in the monocyte/macrophage series, notably 12/15-lipoxygenase, which oxygenates fatty acids linked by ester bonds to lipids and lipoproteins in cell membranes (Conrad et al. 1992). Altered membrane lipids, such as the oxidized forms of low-density lipoprotein, cause damage to intracellular organelles, disrupt normal cell function and play a key role in inducing chronic inflammation, as for example in atherosclerotic lesions.

Expression of 12/15-lipoxygenase is related to the maturation pathway of T helper cells, being induced by the type 2 cytokine IL-4 and inhibited by the type 1 cytokine IFN-γ. Thus, production of PPARγ ligands, such as oxidized low-density lipoproteins in macrophages is IL-4 dependent (Huang et al. 1999). More fundamentally, 12/15-lipoxygenase may be involved in the pattern of T helper cell maturation from the precursor cells. It is usually assumed that maturation of Th1 and Th2 cells from their precursors is due to the direct effects of cytokines, but an indirect monocyte-dependent determinant of maturation has been described (Yang et al. 2002).

Th17 cells: new players in the immunological orchestra

In addition to the now classical Th1 and Th2 T cells, a third class known as Th17 cells, so named as they produce the cytokine IL-17, have been a focus of attention over the last few years (Tato and Cua 2008). As mentioned above, studies on mycobacterial immunity showed that classically activated (M1) macrophages secrete IL-23, a cytokine closely related to IL-12. In response to *M. tuberculosis*, DCs synthesize IL-23, which, in addition to stimulating IFN-γ-producing Th1 cells, also induces Th17 cells (Khader et al. 2005). Differentiation of Th17 cells also

requires the presence of transforming growth factor beta (TGF-β) in combination with other cytokines, particularly IL-6 (Mangan et al. 2006; Bettelli et al. 2006). Study of the generation of human Th17 cells in vitro has proven even more challenging than the mouse system. Human Th17 cells probably do not rely on TGF-β for their generation, but on the presence of IL-1, IL-6 and IL-23 (Wilson et al. 2007; Acosta-Rodriguez et al. 2007).

The physiological role of Th17 cells is not fully understood, but they appear to be involved in immunity, including mucosal immunity, to infection. In experimental tuberculosis, for example, IL-17-producing T cells play an important role in the recall response to *M. tuberculosis*, favouring the expression of chemokines that serve to recruit protective IFN-γ-producing T cells into the lung (Khader et al. 2007). In addition, $CD4^+$ cells secreting IL-17 and IL-22 are involved in the adaptive immune response against *M. tuberculosis* of tuberculosis patients and exposed individuals (Scriba et al. 2008).

On the other hand Th17 cells are potent inducers of inflammation with major functions in facilitating infiltration of other cells of the immune system into the target organ. These have been implicated in the pathogenesis of autoimmune processes, including type 1 diabetes, psoriasis and Crohn's disease (Cooke 2006). This has led to Th17 cells being regarded as the 'inflammatory cells', but this view has been cautioned against as their induction and involvement in chronic inflammation and immunopathology may reflect an underlying immune dysregulation (Cooke 2006; Fouser et al. 2008).

Chronic inflammation, allergy and cancer

The link between chronic inflammation and allergy is well exemplified by allergic or extrinsic asthma; a condition characterized by airway hyper-responsiveness, a chronic inflammatory leukocyte infiltration in the bronchial wall and elevated serum IgE. Th2 lymphocytes are thought to play a key role in the initiation and perpetuation of this condition. TLR receptors are ubiquitously expressed by alveolar epithelial cell type II, alveolar macrophages, airway and vascular smooth muscle cells, mast cells and DCs (Soong et al. 2004; Morris et al. 2005). The status of TLR4 activation may determine the onset and severity of allergic asthma, possibly by modulating the balance between Th1 and Th2 responses (Constant et al. 2002). The engagement of TLR4 or TLR9, in conjunction with IL-6 production, by airway DCs and macrophages, releases effector T cells from the inhibitory effect of $CD4^+CD25^{+-}$regulatory T cells (Eder et al. 2004), which exacerbate asthma. This effect may, however, be counterbalanced by the production of IL-10 by the pulmonary DCs that induce antigen-specific tolerance in effector T cells and, therefore, may prevent airway reactivity to inhaled antigens.

Recurrent or chronic inflammation has been implicated in the development of up to a quarter of human cancers, especially those of the prostate, bladder, large intestine, liver, oesophagus and stomach (Palapattu et al. 2005). Thus, Balkwill and Mantovani (2001) remarked that genetic damage is the 'match that lights the fire' of cancer, but some types of inflammation provide the 'fuel that feeds the flames'. In some, but certainly not all, cancers, chronic inflammation promotes tumour development by creating a microenvironment that promotes cell survival, angiogenesis and metastasis, and suppresses antitumour immune responses. Once a cancer is established, some degree of chronic inflammation is seen in most, if not all, cases and has been termed 'the other half of the tumour' (Mantovani et al. 2008).

The inflammation-associated factors favouring carcinogenesis and tumour development include those induced by immune reactivity, especially reactive oxygen and nitrogen species and free radical derivatives (Beckman and Koppenol 1996). In addition, as described above, the inflammatory microenvironment contains many cellular and soluble factors associated with immune reactivity, which can have adverse as well as beneficial effects. Thus, macrophages may be recruited by tumours and serve as a source of factors that promote tumour growth, angiogenesis and metastatic spread (Condeelis and Pollard 2006).

Inflammatory reactions in cancer may be driven by intrinsic (oncogene) or extrinsic (microenvironment) factors. Alternatively activated (M2) macrophages, together with suppressor T cells, contribute to chronic smouldering inflammation and favour progression of the disease, while classically activated (M1) macrophages mediate killing of cancer cells. Thus it has been postulated that agents that are able to shift the macrophage balance from M2 to M1 would have therapeutic potential (Allavena et al. 2008).

On the other hand, as mentioned above, the division of macrophages into M1 and M2 types may be an oversimplification and there may be a spectrum of types, with 'typical' M1 and M2 being at opposite poles of the spectrum. There is evidence that tumour-associated macrophages are driven by tumour and T cell factors towards a polar M2 phenotype that causes dysregulated immune and inflammatory reactions, resulting in tumour progression (Mantovani et al. 2002; Sica et al. 2006). There is also, paradoxically, evidence that M1 macrophages mediate inflammation-driven carcinogenesis in, for example, gastric, colonic and liver cancer associated, respectively, with *Helicobacter pylori* infection, inflammatory bowel disease and hepatitis. The paradox may be explained by the findings that the relative abundance of M1 and M2 tumour-associated macrophages may depend on

the stage of tumour progression, with 'switching' occurring at different stages (Biswas et al. 2008) and that tumour-associated macrophages do not fit clearly into the M1/M2 division and appear to secrete mediators that favour both protection and tumour progression (Van Ginderachter et al. 2008). It is possible, however, that the M1/M2 balance, and indeed the Th1/Th2 balance, in cancer and other conditions characterized by chronic inflammation are superficial reflections of immune dysregulation at a more basic level, perhaps at the level of the DC as described above.

In an experimental mouse model of mammary and colon cancers, a combination of intralesional injection of a chemokine (CCL16), to cause the accumulation of DCs and macrophages in tumours, a TLR9 ligand (CpG) and systemic injection of an antiinterleukin-10 receptor antibody caused a rapid switch of the phenotype of the tumour-associated macrophages from M2 to M1 and an induction of diffuse hemorrhagic necrosis of the tumour within 16 h (Guiducci et al. 2005). Furthermore, such treatment restored the function of DCs and induced their migration to draining lymph nodes where they generated tumour-specific immune responses, which cleared up residual tumour cells. In this context, a key escape mechanism utilized by tumours to escape immune destruction is blockage of normal DC function (Vicari et al. 2002).

Immune dysregulation, chronic inflammation and the hygiene hypothesis

The diseases listed above are all associated with chronic inflammation of which inappropriate and dysregulated immune reactivity, either primary or secondary, is a key promoter. Accordingly, the cause of such dysregulation requires consideration. Notably, all of these conditions are increasing in prevalence in the industrially developed nations and there is growing evidence that this increase in risk is the result of 'improvements' in living standards that isolate children from sources of such infections, resulting in compromised development of immunoregulatory networks and an increased risk of certain diseases. This concept, frequently but inappropriately called the hygiene hypothesis, postulates that the overall maturation of the immune system, and the development of complex regulatory networks, is affected by antigenic challenges, principally resulting from repeated infection early in life that evolution had led the developing immune system to 'expect' (Strachan 1989; Karmaus and Botezan 2002; Martinez and Holt 1999; Stanford et al. 2001). The pattern of antigenic challenges that occur during life has been termed the 'biography' of the immune system (Krone et al. 2009), and microbes that induce normal immunoregulatory networks have been named 'old friends' (Rook et al. 2004).

The immunological implication of contact with the environment has undoubtedly changed with time. This is especially the case in the industrially developed countries where the early influences of contact with environmental bacteria, viruses and possibly other substances, which mould the developing immune system, both innate and adaptive, have changed under sociological pressures. This is reflected in the changing prevalence of several of the diseases listed above. While most studies have focused on the impact of reduced environmental contact on those living in the developed nations, relatively little attention has been paid to excessive environmental influences in other parts of the world, such as the massive contact with environmental mycobacteria that accounts for the poor performance of Bacille Calmette–Guerin (BCG) vaccination against tuberculosis in south India and Malawi (Fine 1995). Therapeutic strategies based on immune modulators to combat immune dysregulation due to both excessive and diminished environmental influences are therefore required.

A consequence of the hygiene hypothesis is that the temporal sequence of infections may be changed, with certain encounters with micro-organisms that once occurred in infancy now being delayed until later in life. The pattern of immune reactivity to antigenically related micro-organisms is heavily influenced by the first one to be encountered, a concept termed 'original antigenic sin'. Thus, for example, immune responses to the Epstein–Barr virus and ensuing manifestation of disease differ according to whether infection occurs in infancy, as it usually does in many parts of the world, or in early adult life as in the industrially developed nations. It has been postulated that alterations in immunoregulatory networks due to changes in the sequence of infections may be risk factors for autoimmune processes such as multiple sclerosis (Krone et al. 2009).

The impact of environment-related factors on risk of chronic infectious diseases such as tuberculosis is not easily determined, as the socio-economic factors that lead to improved hygiene, together with the introduction of effective anti-microbial therapy, also diminish exposure to the causative organisms. There are, however, interesting data from Scandinavia in the 1960s showing that the risk of progression from infection by the tubercle bacillus, indicated by tuberculin reactivity, to overt tuberculosis was significantly lower in farming communities than in town dwellers (Magnus 1966). At the time it was concluded that those in the urban environment had been predominantly infected with *M. tuberculosis* and those in rural settings with the supposedly less virulent *M. bovis*, but this hypothesis is not supported by bacteriological data and an environment-based explanation is a plausible alternative.

Hygiene-related factors affecting the risk of allergic disorders and certain forms of cancer have been well described in recent years. In the case of cancer, several studies confirm that exposure of infants to infection by, for example, attending day-care centres or living on farms affords significant protection against leukaemia (Perrillat et al. 2002; Ma et al. 2002), and similar factors protect against allergic disorders (Martinez and Holt 1999). Likewise, certain infections early in life afford significant protection against melanoma (Krone et al. 2003). In both leukaemia and melanoma, vaccination with BCG affords similar levels of protection to natural infections (Grange and Stanford 1990; Krone et al. 2003). These observations raise hopes for the introduction of vaccination strategies to prevent these and other diseases associated with hygiene-related factors. They also raise the possibility of harnessing the PAMPs of bacteria and other micro-organisms, individual components of PAMP or their synthetic analogues for the treatment of the same range of diseases. Examples of the successful use of such agents are listed in Table 1 and references to recent use of synthetic TLR agonists in the treatment of cancer and other conditions are cited by Zeromski et al. (2008).

Table 1 Examples of claimed successful clinical use of agents based on PAMP, either as whole bacteria, bacterial extracts or single TLR agonists

Agent	Clinical or experimental use
Whole bacteria and crude extracts	
BCG, intravesical	Superficial bladder cancer
Mycobacterium chelonae ('Turtle vaccine')	Tuberculosis
Mycobacterium vaccae, heat killed	Cancer, tuberculosis, psoriasis, allergy
Extracts of *Streptococcus pyogenes* and *Serratia marcescens* ('Coley toxins')	Cancer, especially sarcoma
TLR agonists	
Bleomycin (TLR 2)	Pulmonary fibrosis
MALP-2 (TLR 2,6)	Pancreatic carcinoma
Polyinosinic:polycytidylic acid (Poli I:C) (TLR 3)	Herpes virus infections, viral infections, LPS-induced inflammation and liver injury, murine colitis
Monophosphoryl lipid A (TLR 4)	Ischaemic myocardial injury
Flagellin (TLR 5)	Experimental colon tumours, damage by chemicals and ionizing radiation, allergic airway disease
Imidoazoquinoline (TLR 7)	Skin malignancies, genital warts
Imiquimod (TLR 7)	Basal and squamous carcinoma, melanoma
CpG B-type oligodeoxynucleotide (CpG-ODN, PF3512676) (TLR 9)	Metastatic melanoma, enhancement of various vaccines

The relevant TLRs, when applicable, are shown in parentheses

Conclusions

By the application of Occam's razor, a common pattern of immune dysregulation, related at least to some extent to the 'biography' of the immune system, has been postulated. This hypothesis sheds light on observations that, at first view, appear paradoxical. At the basic level, the regulatory faults appear in many cases to be due to inadequate stimuli for the induction of DCs to assume a regulatory role by means of encounters with infectious agents, our 'old friends'. The challenge, therefore, is to determine whether our 'old friends', especially those with appropriate and powerful PAMP-related adjuvant activity, could be used as immunotherapeutic agents to prevent and treat a diverse and increasingly common range of diseases that cause a high proportion of human suffering.

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