4

IL-22 Induces an Acute-Phase Response Associated to a Cohort of Acute Phase Proteins and Antimicrobial Peptides as Players of Homeostasis

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1. Introduction

Upon different external *stimuli* including bacteria and virus infection, and internal *stimuli* including both self-damaged products from trauma, burn injury, surgery, cancer mediated inflammatory disorders, exhausting exercises, child delivery and stroke as well as different immune diseases, an organism need to react in order to continuously preserve an equilibrated thermodynamic state, namely homeostasis. This process is highly conserved in living beings. The absence of this global state generates pathological processes and ultimately, the death.

1.1 Acute phase response

In mammals, a complex network of intercellular and intracellular signaling participates to the maintain of homeostasis after stimulus by recognizing non-self elements in the body, involving pro-inflammatory processes, including cytokines, cytokine modulators, and hormones associated to a number of systemic changes referred as the acute-phase response (APR). Moreover, APR occuring quickly after *stimuli*, is a transient modulation of physiological process favoring innate defense of organisms during this early phase of physiological perturbed situation or illnesses (infection or trauma) involving modulation of production, mostly by the liver, of some blood proteins namely acute phase proteins (APP) to resolve the local inflammation, repair the injured tissue, and re-establish homeostasis. Thus, both pro- and anti-inflammatory responses are initiated almost at the same time, with a little delay of anti-inflammatory responses and concomitantly signals act synergistically (Adib-Conquy & Cavaillon, 2009).

Inflammation is key in homeostatic processes elicited by microbial components or by tissue damage products. The outcomes, **either tissue repair or persistent inflammatory damage and degeneration**, strongly depend of the local cell death profile and its associated molecules as well as on the features of infiltrating antigen cell presenting cells. Monocytes, platelets and endothelial cells participate in vascular inflammation that regulates the

humoral innate immunity and participates in homeostatic processes by activating, for example, anti-inflammatory regulators.

The acute-phase response is resolved as soon as stimulation disappears. These APR regulation is due to the expression of inflammation regulators including IL-10, SOCS, soluble receptors of inflammatory cytokines (IL-1ra) as well as due to short span of APP and their mRNA half-lives. In cases where inflammation becomes deregulated, the acute-phase response become chronic, and local inflammation potentially becomes systemic.

Not only pathogenic, but also, in a lesser extent, non-pathogenic microorganisms harbor the highly conserved non-self molecules which are critical for their survival or for their pathogenicity. During infectious processes cells, including macrophages respond to exogenous danger signals induced by the pathogens associated molecular patterns (PAMPs) or Microbe-associated molecular patterns (MAMPs) that are not found as a part of eukaryotic cells. This response is amplified by endogenous mediators released and by co-factors or concomitant stressful events, and molecular mechanisms involved in the vicious circle destruction-reconstruction of vessels and tissues, act through injury-associated signals known as Damage-Associated Molecular Patterns (**DAMPS or Alarmins)** and **acute phase proteins**.

Among PAMPs, Gram-negative and Gram-positive bacteria respectively express at their surface LPS and peptidoglycan as well as lipotechoic acid. In addition, molecules found in microorganisms include mannose (almost absent in humans), bacterial unmethylated CpG DNA, bacterial flagellin, the amino acid *N*-formyl-methionine found in bacterial proteins, double-stranded and single-stranded RNA from viruses, and glucans, mannans, and zymosan from fungal cell walls. More than 1 000 recognition elements have been identified and designated by soluble pattern-recognition receptors.

Damage-associated molecular patterns (**DAMPs**) or **alarmins**, are released by stressed cells and act as endogenous danger signals promoting and enhancing the inflammatory response. The following molecules: **S100A8** and **S100A9** participate in migration and cytoskeletal metabolism. Cell damage or activation of phagocytes triggers their release into the extracellular space where they become danger signals that activate immune cells and vascular endothelium. S100A8 and S100A9 seem to interact with RAGE4 and TLRs (Vogl et al., 2007); the nuclear, high mobility group box-1 (**HMGB1**) protein that is not characterized by having pro-inflammatory activity but it binds LPS, DNA or IL-1β and induces signaling pathways leading to NF-κB activation thereby enhancing inflammatory pathways; and Serum amyloid A (**SAA**) released by **necrotic cells** are the major DAMPs increased in serum of **several inflammatory diseases**, including cancer, sepsis, atherosclerosis, and arthritis. Several receptors appear to mediate the effect of SAA, including FPRL1, RAGE, TLR2 and TLR4. The downstream signaling pathways triggered by SAA include ERK and p38 activation induces chemotactic for neutrophils and the production of proinflammatory cytokines and NO(He et al., 2009; Sandri et al., 2008). DAMPs activate innate immune response through pattern recognition receptors (PRRs) (Bianchi, 2007) such as Receptor for advanced glycation end products (RAGE) found in endothelial cells and macrophages and activate MAPkinase-dependent inflammation upon interaction with one of the following factors HMGB1, S100 proteins and β-amyloids (van Beijnum et al., 2008). Some DAMPs engage TLRs to induce and amplify the inflammatory response. **TLR2** and **TLR4** signaling have been shown to mediate NF-κB activation initiated by HMGB1 (Park et al., 2006), S100A8 (Vogl et al., 2007) and SAA (He et al., 2009; Sandri et al., 2008). Different signaling

pathways are involved that may cross-talk at several levels, but all culminate in the activation of NF-κB.

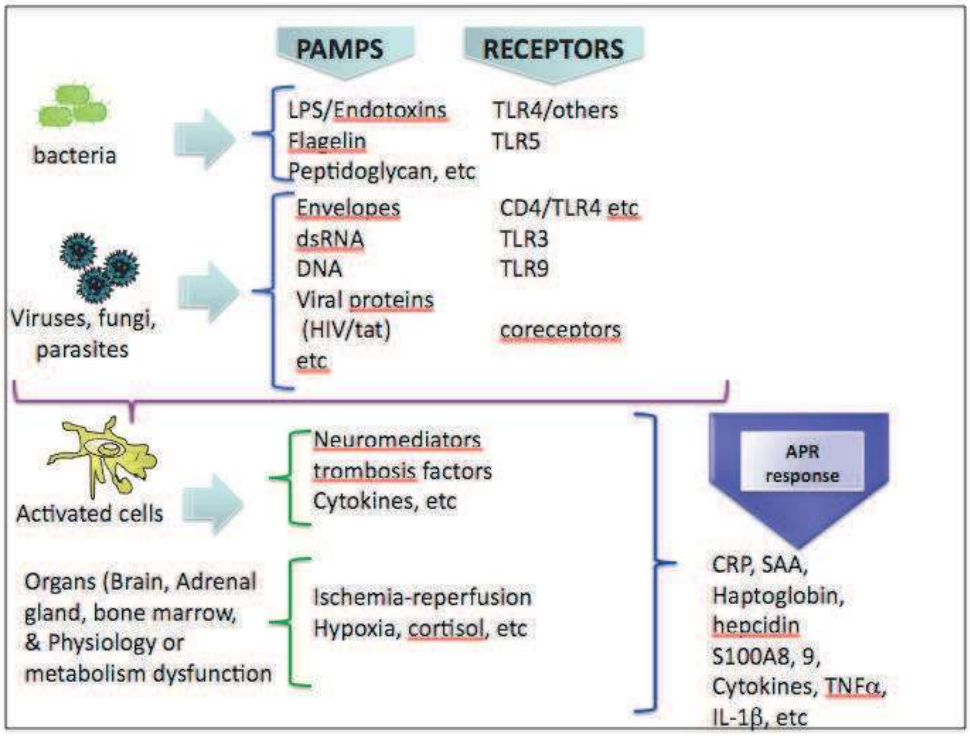

Fig. 1. PAMPS as inducers of the APR.

2. Organs involved in the APR

Organs involved in the APR include: **brain**, (involved in fever, anorexia, somnolence and increased synthesis of CRH and ACTH); **liver**, (increased amounts of metallothionein and antioxidants and which re-orchestrates its pattern of plasma protein synthesis); **bone marrow**, (erythropoiesis is suppressed and thrombocytosis induced, and loss of bone substance occurs; **the adrenal gland**, (cortisol production is enhanced by both direct and indirect stimulation); **muscle**, (decreased protein synthesis and proteolysis may occur); and **fat cells**, (alterations in lipid metabolism)(Kushner, 1993).

2.1 Acute phase proteins

A change of approximately 25% in plasma concentration has been suggested as the definition of acute phase proteins (APP, (Morley & Kushner, 1982)). Changes in plasma protein concentrations mainly depend of their synthesis by liver cells in response to circulating inflammation-associated cytokines.

CRP present at high concentrations in a patient with pneumonia allowed its discovery in 1930. CRP is one of the major APP, which increase in response to sudden homoeostatic

disequilibrium. More generally, during the acute-phase response, circulating levels of plasma proteins increase (positive APPs) or decrease (negative APPs).

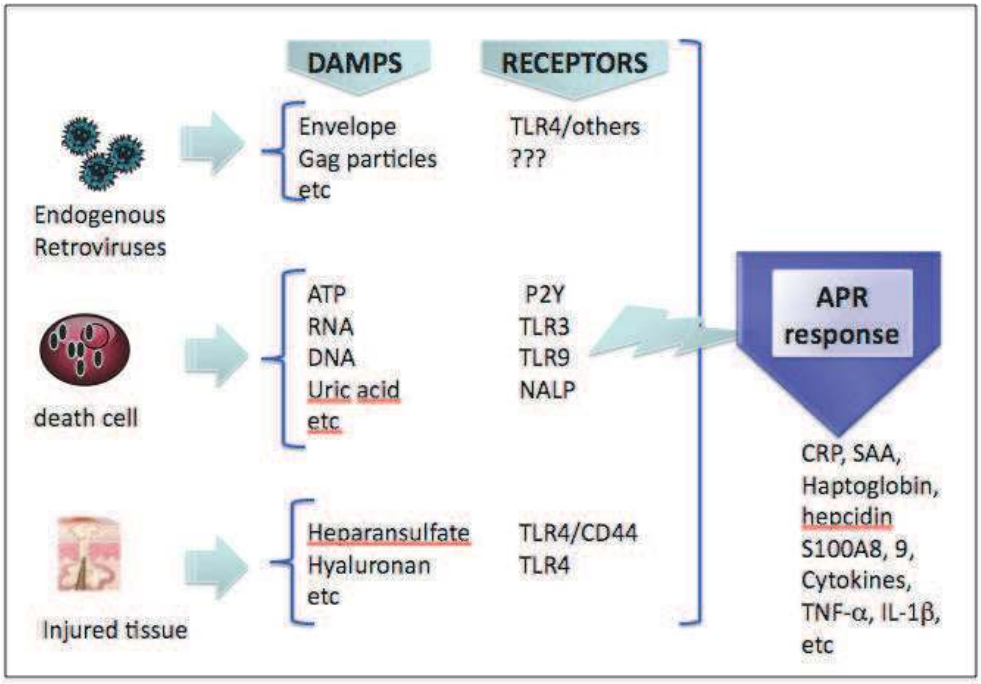

Fig. 2. DAMPs as inducers of the APR

Thus, upon stimuli, amount changes of different proteins are observed. In normal situations, the major positive APP, CRP and SAA, are present in only very low amounts, but they are able to rapidly increase by around of 1000-fold upon infection for example. In a similar situation, haptoglobin, α-acid glycoprotein, α_1-protease inhibitor, α-antichymotrypsin and fibrinogen, increase about 2–5-fold. Whereas, only a modest elevation, of about 50%, is exhibited by both, ceruloplasmin and the complement components C3 and C4. In contrast, the negative APPs, such as albumin, transferrin, transthyretin, α_2 HS glycoprotein, α-fetoprotein, insulin-like growth factor-1 (IGF-1) and coagulation factor XII, typically decrease during the acute-phase response.

Even if not possible for all APP, most of them have been classified in functional categories as illustrated here with some examples: **Antiproteases**: α_1-protease inhibitor, α_1-antichymotrypsin, pancreatic secretory trypsin inhibitor and inter-a-trypsin inhibitors; **Molecules of coagulation and fibrinolysis**: plasminogen, tissue plasminogen activator (tPA), urokinase, protein S, vitronectin and plasminogen activator inhibitor 1 (PAI-1); **Complement molecules**: complement factors C3, C4, C9, C-1 inhibitor, C4b-binding protein, factor B, and mannose-binding lectin (MBL); **Transport proteins**: ceruloplasmin, haptoglobin and hemopexin. This is the case of the major APP, CRP, SAA, a1-acid glycoprotein, fibronectin, angiotensinogen, ferritin and beta2-glycoprotein I. It is to be noteworthy that the expression level of APP could be specie-dependent, such as APP in

alpha-macroglobulin that is highly expressed in rat but not in humans (Gabay & Kushner, 1999).

Certain APPs are involved in the regulation of the inflammatory response. These include secreted phospholipase A2 (pLA2), lipopolysaccharide (LPS)-binding protein, and interleukin 1 receptor antagonist (IL-1Ra) (Gabay et al., 1997). In response to the non-self antigen exposure, a healthy host must rapidly interact with it to initiate an antigen-non-specific recognition *via* innate immunity mechanisms controlling and maintaining homeostasis. This response helps **the organism not only to eliminate microbes and/or** preventing infection, but also eliminates all defective self-molecules.

Most of the APP play a protective role, such as haptoglobin (Cid et al., 1993),Thus, for example, hemopexin exhibits an anti-oxydant activity as well as certain anti-proteases including α1-antichymotrypsin suppresses superoxide anion production, vitronectin inhibits cell lysis complement-mediated (Kilpatrick et al., 1992). Among the main acute phase proteins, two of them are hyper-reactive, the C-reactive protein (CRP) and the mannose-binding lectin (MBL) that act as soluble pattern-recognition receptors. The CRP binds to membrane phospholipids of microorganisms such as phosphorylcholine from bacteria and phosphatidylethenolamine from fungus. It allows binding of microorganism to phagocytes, and activates the classical complement pathway (Ahmed et al., 1996; Cermak et al., 1993; Jiang et al., 2006). Most of the effects of the other main acute-phase protein in humans, the serum amyloid A (SAA), are still unknown. SAA rapidly bind to high-density lipoprotein and influence cholesterol metabolism during inflammatory states. SAA mainly induces lymphocytes and phagocytic cells adhesion and chemotaxis may increase the oxidation of low-density lipoproteins (Banka et al., 1995; Berliner et al., 1995; Malle & De Beer, 1996)

Mostly, these molecules play a role of scavenger proteins by transporting microorganism up to cells (mainly macrophages) in charge of the non-self evacuation. Beta2-glycoprotein I (Agar et al., 2011), also known under the name of Apolipoprotein H (ApoH) is one of the acute phase proteins exhibiting the most striking scavenger properties, strikingly is able to catch early apoptotic cells in a Ca2+-independent manner(d'Angeac et al., 2005). This protein traps every kind of pathogenic microorganisms, including parasites (examples: *Leishmania donovani, Plasmodium falciparum,* etc), Gram + or Gram - bacteria (*Escherichia coli, Salmonella, Listeria monocytogenes, Staphylococcus aureus*, etc) and RNA or DNA enveloped or non-enveloped viruses (Hepatitis B, Hantaviruses, HIV, Rotaviruses, and others viruses) (Godoy et al., 2009; Stefas et al., 1997; Stefas et al., 2001). In addition, products of the complement pathways, in turn, promote inflammation; chemoattract phagocytes to the infected zone, also attach microbes to phagocytes, and finally induce cytolysis of infected cells.

During the acute-phase response, in addition to plasma proteins changes induced by or associated to pro-inflammatory cytokines, other kinds of changes are observed, such as those associated with neuroendocrine, including somnolence (may reduce energy requirements), anorexia, fever, etc. that are related with an increased secretion of corticotrophin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH), cortisol and arginine, vasopressin, insulin serum levels and decreased insulin-like growth factor 1 (IGF-1). Haematopoietic changes include the anaemia of chronic disease, leucocytosis and thrombocytosis. Metabolic changes include, loss of muscle with decreased nitrogen, gluconeogenesis, increased leptin, osteoporosis and cachexia. Intrahepatic changes include increased synthesis of metallothionein, inducible nitric oxide synthase (iNOS), a haeme oxygenase (HO), manganese superoxide dismutase (mSOD), hepatocyte growth factor

activator (HGFa), glutathione and tissue inhibitor of metalloproteinase 1 (TIMP-1). In addition, changes in lipid metabolism occur, including increased hepatic lipogenesis, lipolysis in adipose tissue, decreased lipoprotein lipase activity in muscle and adipose tissue, increased plasma levels of triglycerides. Fever may stimulate chemotaxis, cytokine production, complement-mediated opsonization, and T-cell function. Increased hepatic production of the antioxidant agents, haeme oxygenase and manganese superoxide dismutase may be required for the limitation of oxidant mediated-tissue injury. Hypercortisolaemia can modulate the immune and inflammatory responses and play a major role in the maintenance of haemodynamic stability in patients with severe illness.(Gabay & Kushner, 1999).

Lipids produced in excess circulate and are also used as nutrients by immune cells from inflammation to rebuild their damaged membranes. A lipid excess that could enhance inflammatory processes. Some of these circulating lipoproteins, such as leptin, are able to bind LPS and decrease its inflammatory effects, moreover, may play a direct or indirect a role in host defense against different microbial agents such as the scavenger role of Apoliproprotein H.

As for inflammatory processes, the APR is beneficial for the host when this response happens in within very short kinetics. In contrast, a persistence of the acute-phase response due to chronic stimulation, in chronic diseases, metabolic disturbances strongly inducing a loss of skeletal muscles, adipose tissue and osteoporosis, frequently leads to cachexia. This persistence associating cytokines activity with the acute-phase response could become fatal, as observed in septic shock.

In some patients with chronic inflammatory conditions, chronically cleaved SAA could induce amyloidosis with deleterious consequences forming plaques in brain that could enhance neurological diseases, such as Alzheimer disease.

3. APR and Antimicrobial activities

Thus, cells receiving PAMPS and/or DAMPS (or alarmins) *stimuli* through corresponding molecular interactions, will, in turn, initiate APR by modulating the expression of pro-inflammatory cytokines and APP. Some of these APPs exhibit antimicrobial activities similarly to antimicrobial peptides (AMP).

Gene-encoded anti-microbial peptides (AMPs) are widespread in nature, as they are synthesized by microorganisms as well as by multicellular organisms from both the vegetal and the animal kingdoms. These naturally occurring AMPs form a first line of host defense against pathogens and are involved in innate immunity. Depending on their tissue distribution, AMPs ensure either a systemic or a local protection of the organism against environmental pathogens. They are classified into three major groups: (i) peptides with an alpha-helical conformation (insect cecropins, magainins, etc.), (ii) cyclic and open-ended cyclic peptides with pairs of cysteine residues (defensins, protegrin, etc.), and (iii) peptides with an over-representation of some amino acids (proline rich, histidine rich, etc.). Most AMPs display hydrophobic and cationic properties, have a molecular mass below 25-30 kDa, and adopt an amphipathic structure (alpha-helix, beta-hairpin-like beta-sheet, beta-sheet, or alpha-helix/beta-sheet mixed structures) that is believed to be essential to their anti-microbial action. Interestingly, in recent years, a series of novel AMPs have been discovered as processed forms of large proteins. Despite the extreme diversity in their primary and secondary structures, all natural AMPs have the in vitro particularity to affect a

large number of microorganisms (bacteria, fungi, yeast, virus, etc.) with identical or complementary activity spectra. This review focuses on AMPs forming alpha-helices, beta-hairpin-like beta-sheets, beta-sheets, or alpha-helix/beta-sheet mixed structures from invertebrate and vertebrate origins. These molecules show some promise for therapeutic use (Bulet et al., 2004).

AMP are cationic small proteins involved in host innate immune defense by mainly binding negatively charged (acidic) phospholipids (Fig. 3), even other different mechanism remain to be elucidated. The presence of cholesterol and the absence of acidic phospholipids in normal human cells avoid that AMP could attack the self cells.

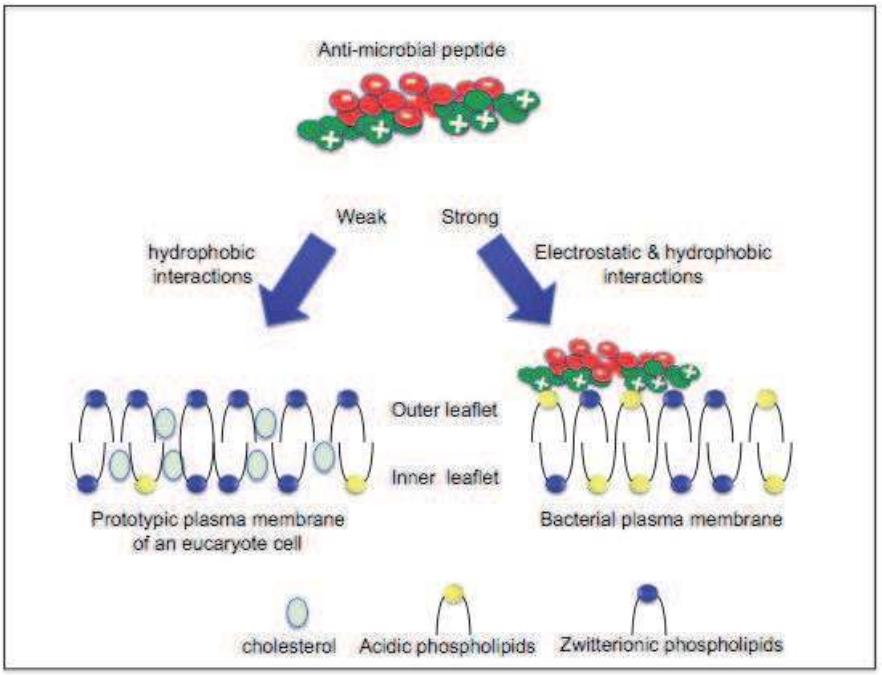

Fig. 3. Antimicrobial peptide activity on membranes from eukaryote and prokaryotes cells.

AMPs are highly conserved in within organism's evolution, thus they are present from bacteria, amoebas up to Humans. In vertebrates, they are abundant in mucosal tissues (eyes, mouth, genitourinary, skin, lung, trachea), some patrol cells (neutrophils, platelets, etc), intestinal tract (duodenum). In humans, Paneth cells are an important source, that mainly secrets alpha-defensins, when stimulated by bacterial PAMPs (lipopolysaccharide, muramyl dipeptide and lipid A). In addition to defensins, these cells secrete lysozyme and phospholipase A2 that also exhibit an antimicrobial activity. These secretory molecules show a broad anti-infectious spectrum of agents, (bacteria, fungi and viruses) protecting the gut as a gastrointestinal innate barrier.

Then, upon bacteria killing by AMP, bacteria release inflammatory mediators (LPS, LTA), that will induce the cell (monocytes, macrophage) responses, adherence of PMN and chemotaxis, histamine degranulation of mast cells, fibroblast growth as well as the induction

of adherence, apoptosis of viral- or bacteria-infected host cells, inhibition of fibrin clot lysis (to limit bacterial spread) and inhibition of proteases (to limit tissue injury). If inflammation becomes chronic AMP will participate in both T cell recruitment as well as enhancement of monocyte chemotaxis and macrophage response.

A rich literature has reported results directly or indirectly demonstrating the efficiency of AMP. Mice carrying a genetically engineered metalloproteinase deficiency showed an increased susceptibility to bacterial infection generating an absence of soluble α-defensins to protect mice against bacteria due to the absence of their extracellular cleavage and activation (Wilson et al., 1999). In a mouse model of septicemia, LL-37 binds to and neutralizes LPS and protects against endotoxic shock (Bals et al., 1999). Histatins protect from periodontal disease by inhibiting the *B. gingivalis* protease (Nishikata et al., 1991).

Due the efficiency against microbes the use of AMP, some AMP have been extracted from species different of those where effects are needed. This is the case of dermaseptin (DS), a 34 amino acid residue cationic peptide isolated from *Phyllomedusa sauvagii* skin, has been incubated *in vitro* with promastigotes of *Leishmania mexicana*. Immunocytochemical, and electron microscopic observations have shown that the amphipathic peptide generates disrupt the lipid bilayer leading of the surface membrane and death of the parasite (Hernandez et al., 1992).

Hepcidin (gene name, *HAMP*), an IL-6-inducible acute phase protein that also exhibit antimicrobial properties, is the key negative regulator of iron metabolism. Liver is the primary source of *HAMP* synthesis, but it is also produced by other tissues such as kidney or heart and is found in body fluids such as urine or cerebrospinal fluid. Hepcidin is a stress-inducible peptide of the biliary epithelia. In the bile, hepcidin help to protect against bacterial infections (Strnad et al., 2011).

Studies in transgenic mice confirmed that **C-reactive protein** is protective against microbial pathogens thru its *in vitro* ability to bind microbes, activating the complement classical and alternative pathways as well as FcγRII (Szalai, 2002).

SAA is the major acute phase protein in man and most mammals. Recently, it was demonstrated that SAA binds to many Gram-negative bacteria including *Escherichia coli* and *Pseudomonas aeruginosa* through outer membrane protein A (OmpA) family members. At normal concentrations of SAA, the SAA-*E coli* opsonization increase, both the rate of neutrophils with bacteria as well as the number of bacteria. The amount of neutrophil reactive oxygen intermediate production and phagocytosis by both neutrophils and IL-10 and TNFa-producers macrophages are enhanced in a SAA-dependent manner (Shah et al., 2006).

CRP have both properties to induce proinflammatory cytokines and tissues factor and anti-inflammatory for example inhibiting superoxide anions secretion by neutrophils as well as inducing IL-1ra synthesis by PBMC. Serum amyloid A consists rapidly bind to high-density lipoprotein and influence cholesterol metabolism during inflammatory states (Banka et al., 1995). SAA could contribute to the inflammatory state by inducing chemotaxis and adhesion (Malle & De Beer, 1996).

4. Cytokines and acute phase response

A complex network of intercellular signaling involving cytokines, cytokine modulators and hormones regulates the acute-phase response (APR). Inflammation-associated cytokines, produced by both cell in the inflammatory site circulating immune cells, induce changes in expression of APP by liver cells. Liver is one of the primary organs required for the

constitutive production of blood proteins and one of the major sources of acute-phase proteins. Thus, liver in uncontrolled local tissue inflammation processes produce, IL-6 and other family members, TNF-α, and IL-1β leading the production of these acute-phase proteins, mainly SAA, fibrinogen, CRP that are indicative of an APR.
APR participate at a very early stage after stimulus by recognizing non-self elements in the body, **quickly after infection**, preceding both the complete activation and the setting up of immune responses. Also, the acute-phase response is resolved as soon as stimulation disappears. These APR regulation is due to the expression of inflammation regulators including IL-10, SOCS, soluble receptors of inflammatory cytokines (IL-1ra) as well as due to short span of APP and their mRNA half-lives.
Activated immune cells including monocytes and lymphocytes release pro-inflammatory cytokines to stimulate hepatocytes; subsequently induce synthesis and secretion of acute phase proteins. Tumor necrosis factor-alpha (TNF-alpha), interleukin-1 beta (IL-1beta), and interleukin-6 (IL-6) following their pattern-recognition receptors (PRRs) bind pathogen associated molecular patterns (PAMPs). IL-22 is a more recently discovered cytokine that is also produced by liver cells.

5. IL-22 expression and functions

A study on HepG2 hepatocellular carcinoma-derived cell line allowed to identify an IL-22–dependent induction of APP gene expression (Dumoutier et al., 2000). Wolk et al. subsequently reported increased levels of circulating SAA as a consequence of IL-22 addition (Wolk et al., 2004).
Interleukin-22 (IL-22), a cytokine from the IL-10 family but exhibit low homology with IL-10, produced by several immune cell subsets, mainly including (IL-6, TNFa)-stimulated Th-22 that will produce the largest amounts (37 up to 65% of the total depending on the tissue) in the absence of IL-17 production, IL-12-stimulted or activated (CD3) Th-1/Tbet+ (35%), (IL-1b, IL-6, TGFb, IL-23)-stimulated Th-17/RORgt+ (10%) that in addition will produce IL-17A&F IL-21 and IL-28. Innate lymphocytes NK22/NKp44+ (Duhen et al., 2009; Eyerich et al., 2009; Trifari et al., 2009) and NK cells (Wolk & Sabat, 2006) and γδ T and LTi-like cells that are IL-22 producers (Zenewicz et al., 2008). Other T cell subset have been shown an IL-22 production such as the T8 /Tc22 in atopic dermatitis (Nograles et al., 2009) and in psoriasis where also Tc17-Il-17A production was associated (Res et al., 2010).
It has been demonstrated that IL-22 does not act on immune cells as compared with other T or NK cells secreted cytokines. Direct effects of IL-22 are restricted to non-hematopoietic cells carrying IL-22 receptors that are expressed on the surface of only epithelial cells and some fibroblasts in a large variety of organs, including parenchymal tissue of the gut, lung, skin, and liver.
The expression of the IL-22R1 chain determines cells and organs exhibiting an IL-22 target profile (Boniface et al., 2005). Thus, the main IL-22R1 and IL-10R2 expressers are epithelial and fibroblast cells (Wolk et al., 2004; Wolk et al., 2005) excluding to the immune monocytoid or lymphoid cells and they are carriers of both IL-22R and IL-10R2 (Kotenko, 2002; Langer et al., 2004; Pestka et al., 2004; Sabat et al., 2007)
Depending on local inflammatory processes in its targeted tissues, this cytokine is quickly over-expressed in its source cells and exhibit three main documented activities (Fig 4): (i) **antimicrobial** by inducing AMPs (SAA, A-antitrypsin, haptoglobin, hepcidin, S100A7, S100A8 S100A9, β-Def-1 & 2, RegIII β, γ, etc), (ii) **tissue-damage protection** *via* induction of

APR (IL-6, TNFa, CXCL1, S100A7, S100A8 S100A9, β-Def-1 & 2, IL-20, etc) and (iii) **tissue repair and remodeling** by enhancing expression of MMP-1,2 as well as Muc-1, 3 10, 13 and some survival genes (Bcl-2, Bcl-X_L).

Thus, a localized production of IL-22 in the liver seems to promote hepatocyte survival and proliferation, but could primes the liver to be more susceptible to tumor development without significantly affecting liver inflammation (Park et al., 2011). Damaged cultured keratinocytes become repaired after IL-22-dependent remodeling (Eyerich et al., 2009). AAT that has been reported as a potential biomarker for hepatitis B in diagnosis (Tan et al., 2011). IL-22 contributes to regenerate tissues following liver surgery (Ren et al., 2010) or alcool-cirrhotic damages (Ki et al., 2010).

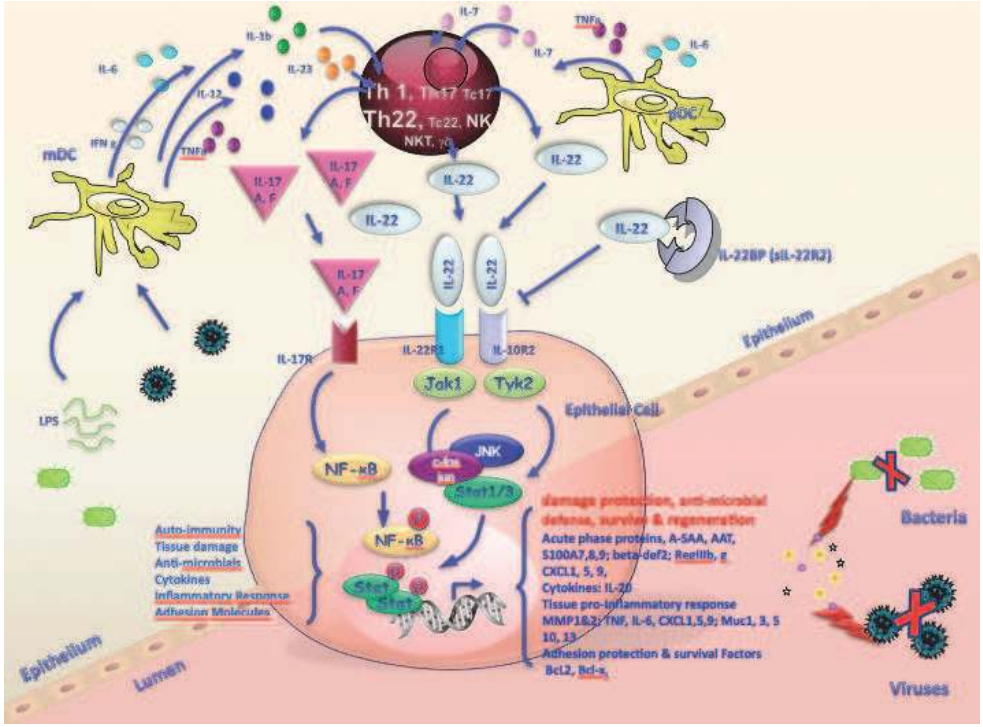

Fig. 4. Mucosal innate protection and tissue damage, the double game of IL-17 & IL-22 cytokines is determined by the local environment situation. Main IL-22 pathways playing a pivotal role in the protection of mucosal tissues against intracellular and extracellular infectious agents such as extracellular bacterias or sexually transmitted viruses. In vivo or ex vivo data these localized anti-infectious activities could involve several possible pathways including both different mode of action of anti-microbials and the infectious pathways used by pathogens. In addition IL-22 will play an important role in both tissue damage protection through APP induction and regeneration.

In the aim to understand the factors that impede immune responses to persistent viruses is essential in designing therapies for HIV infection, Pellegrini *et al* (Pellegrini et al., 2011) have

done a study on mice infected with LCMV clone-13 that exhibit persistent high-level viremia and a dysfunctional immune response. Interleukin-7, a cytokine that is critical for immune development and homeostasis, was used here to promote immunity toward clone-13, enabling elucidation of the inhibitory pathways underlying impaired antiviral immune response. IL-7 downregulated the critical repressor of cytokine signaling, Socs3, resulting in amplified cytokine production, increased T cell effector function and numbers, and viral clearance. Additionally, IL-7 promoted production of IL-22 that abrogated liver pathology.
Recently an improvement intestinal inflammation in a mouse model of ulcerative colitis by IL-22 was mediated by enhanced mucus production has been reported. A local gene delivery was used to inhibit IL-22 activity through overexpression of IL-22-binding protein. Treatment with IL-22-binding protein suppressed goblet cell restitution (reparation) during the recovery phase (Sugimoto et al., 2008).
Aging is characterized by a progressive alteration of **homeostatic** mechanisms modulated by environmental and genetic factors. It is associated with a pro-inflammatory status. Cytokine dysregulation is believed to play a key role in the proposed remodeling of the immune-inflammatory responses accompanying old age. Centenarians displayed significantly higher circulating IL-22 levels compared to control population (Basile et al., 2011). This pro-inflammatory condition is probably not only protective against infections, but also it contributes to a better predisposition to preserve homeostasis, thus promoting the longevity of these subjects.
Once the IL-22 expression is set up, the biological activity of this cytokine will be mainly regulated by two factors: (i) the expression level of its appropriated receptor, IL-22R1 on its target epithelial cells (Li et al., 2004; Xie et al., 2000) and (ii) the expression level and localization of the soluble IL-22 binding protein (IL-22 BP) (Dumoutier et al., 2001).

6. IL-22 induces expression of an acute-phase response

Liang et al assessed effects of IL-22 in mice (Liang et al., 2010). By utilizing adenoviral-mediated delivery of IL-22 and systemic administration of IL-22 protein, we observed that IL-22 modulates factors involved in coagulation, including fibrinogen levels and platelet numbers, and cellular constituents of blood, such as neutrophil and RBC counts. Thus, IL-22 induces effects on systemic biochemical, cellular, and physiological parameters as well as thymic atrophy, body weight loss, and renal proximal tubule metabolic activity. These cellular and physiological parameters are indicative of a proper APR (Gabay & Kushner, 1999) in systemic inflammatory state. AdIL-22 mouse infection induces sustained high levels of circulating SAA and fibrinogen respectively on days 3, 7, and 14 and on Days 1 3, and 7 in blood. These observations demonstrated that exposure IL-22 for 2 wk resulted in the modulation of acute-phase proteins of the acute phase response (Liang et al., 2010).
Following the interaction between IL-22 and its receptors, several observations report that IL-22 induces **APP, anti-microbial peptides gene expression**, cytokines, chemokines, and matrix metalloproteinases (Boniface et al., 2005), from **skin, gut, lung, or liver** epithelial **cells**. IL-22 modulates local inflammation, through **mucosal barrier integrity** and generating a protective inflammatory response against mucosal entry pathogens including viruses (Misse et al., 2007)and extracellular bacteria (Aujla & Kolls, 2009; Zheng et al., 2008).
The majority of IL-22 effects are benefic or **protective** (gut, vagina, lungs, liver) for the host, but in some situations of chronic inflammation, it has been reported that this cytokine could have **pathogenic** effects (skin, joints) including in noninfectious inflammatory disease states.

In rheumatoid arthritis, IL-22 play an inflammatory role, may result in bone damage (Geboes et al., 2009). Thus, IL-22 alone has been reported to be able to induce skin hyperplasia and epidermal wound healing (Boniface et al., 2005; Eyerich et al., 2009). The effect of IL-22 signaling will depend on the local cellular situation. Surprisingly, it has been shown *T. trichiura* colonization of the intestine may reduce symptomatic colitis by promoting goblet cell hyperplasia and mucus production through Th2 cytokines and IL-22 (Broadhurst et al., 2010).

7. IL-22 induces antimicrobial responses is depending of the "niche" circumstances

Zheng et al. reported that *in vivo* IL-22 induced the anti-microbial peptides **named the RegIII** proteins in intestinal epithelial cells. An intestinal infection *Citrobacter rodentium* in IL-22-deficient mice induced death (Zheng et al., 2008). Moreover IL-22 in intestine is differentially generated by a subset of NK cells, NKp46+(Satoh-Takayama et al., 2008). Aujla et al. reported that in a mouse model IL-22 upregulated the expression of lipocalin 2 in lung tissue and increased the transepithelial resistance to bacteria, and consequently, and here also the IL-22 neutralization during pulmonary *Klebsiella pneumoniae* infection death of these animals is observed (Aujla & Kolls, 2009). During pulmonary *K. pneumoniae* infection, it seems that both IL-22 and IL-17A cytokines produced by T cells were necessary for the host defense. Whereas for intestinal infection with *C. rodentium*, IL-22 was produced earlier than IL-17A and this latter was dispensable. Also, independently of IL-17, IL-22 can protect against *Salmonella enteritica* that induces systemic infections (Schulz et al., 2008), due to IL-22 increased levels upon intraperitoneal mice contamination (Siegemund et al., 2009). In contrast, multi-microbial sepsis can be avoided by inhibiting IL-22 with IL-22BP-Fc 4 h before sepsis induction leading to enhanced accumulation of neutrophils and mononuclear phagocytes and a reduced bacterial load at the site of infection. In addition, IL-22 blockade led to an enhanced bacterial clearance in liver and kidney and reduced kidney injury. These results imply an important proinflammatory role of IL-22 during septic peritonitis, contributing to bacterial spread and organ failure(Weber et al., 2007). IL-22 therefore, appears to play an important role in the regulation of inflammatory processes *in vivo*.

Analysis of Th1, Th2, and Th17 cytokine responses in cultured PBMCs from individuals of a cohort of subjects infected with *Leishmania donovani* having developed a visceral disease Kala Azar (KA) or having been protected against KA showed that IL-17 and IL-22 were strongly and independently associated with protection against KA. These results suggest that, along with Th1 cytokines, IL-17 and IL-22 play complementary roles in human protection against KA, and that a defect in Th17 induction may increase the risk of KA(Pitta et al., 2009). However mechanisms of protection in this case remain unclear.

Some clinical reports on *Candida albicans* state that IL-22 is associated to the presence of IL-22 (Liu et al., 2009), and some established correlations tend to show that IL-22 could play a role in controlling this infection (Puel et al., 2010). In animal models the role of IL-22 seems related to IL-17 environment (De Luca et al., 2010), IL-22 will show positive effects if IL-17RA is deficient but in an IL-17-independent manner. Another report from mouse model studies on *C. albicans* state that IL-17 and IL-23 but not IL-22 and IL-12 are required (Kagami et al., 2010).

These contradictory results must be taken into account, because would IL-17 and IL-22 certainly do not exhibit the same behavior in humans and in mouse, consequently,

physiopathological observations in animal models do not allow to extract conclusions extendable to humans.

IL-22 could synergize with other cytokines such as IL-7, a cytokine that is critical for immune development and homeostasis, to protect mouse organs from pathogenic effects of a LCMV (clone-13). Mice infected with have persistent high-level viremia and a dysfunctional immune response. IL-7 was used to promote immunity toward clone-13, enabling elucidation of the inhibitory pathways underlying impaired antiviral immune response. Mechanistically, IL-7 downregulated a critical repressor of cytokine signaling, Socs3, resulting in amplified cytokine production, increased T cell effector function and viral clearance. IL-7 enhanced thymic output to expand the naive T cell pool, including T cells that were not LCMV specific. Additionally, IL-7 promoted production of cytoprotective IL-22 that abrogated liver pathology (Pellegrini et al., 2011). This example is not far from the observations reporting that the IL-22 expression was increased in the presence in viral hepatitis C cases but didn't show in vitro models a direct effect on HCV (Dambacher et al., 2008). In contrast, IL-22 alone could be considered to treat Theiler's virus-induced encephalomyelitis, a mouse infection characterized in susceptible animals by chronic inflammation and demyelination (Levillayer et al., 2007).

Means to avoid the HIV mucosal entry is a crucial objectives to fight against this viral dissemination. The earliest responses to acute HIV-1 infection (AHI) will be due to the action of the mucosal epithelial cells, macrophages and DCs, NK cells as well as antimicrobial factors such as beta-defensins, activated complement. We have shown that natural constitutive higher IL-22 levels of transcripts and proteins are found in repeatedly HIV-1-exposed, uninfected individuals (ESN) as compared with "normal healthy individuals at an approximative ratio 3/1. These higher quantities of one of the major innate inducer protection systems permit an absence of infection in ESN. IL-22 induces A-SAA that, in turn, will agonistically bind to formyl peptide cell receptor (FPR) and therefore induce indirect down modulation of CCR5 in the same immature myeloid dendritic cells, which consequently will drastically reduce HIV-1 infection (Misse et al., 2007). In addition, IL-22-mediated antiviral effects include the stimulation of the production of beta-defensins 2 and 3 by ectocervix epithelial cells as well (F. Veas, M. Clerici, unpublished observations). Some of these individuals could exhibit other complementary HIV protection systems such as APOBEC, or anti-CCR5 IgA antibodies (Miyazawa et al., 2009), as well as the over expression of CCL28 in ESN that helps massive migration of anti-viral IgA secretory B cells up to mucosal tissues (Castelletti et al., 2007).

It has been recently reported that in HIV infected persons, an induction of acute phase protein serum amyloid A (A-SAA) occurred as early as 5-7 days prior to the first detection of plasma viral RNA, considerably prior to any elevation in systemic cytokine levels. Furthermore, a proteolytic fragment of alpha-1-antitrypsin (AAT), was observed in plasma coincident with viremia. Both A-SAA and AAT fragment have anti-viral activity *in vitro* and quantitation of their plasma levels indicated that circulating concentrations are likely to be within the range of their inhibitory activity (Kramer et al., 2010).

IL-22 is a potent inducer of AAT and MMP then mucosal or topic treatments could be beneficial to avoid the HIV mucosal entry and therefore can be crucial to fight against this viral dissemination.

High systemic levels of IL-10, CRP and IL-22 in HIV-1C-infected Indian patients were associated with low viral replication *in vitro*. Whereas using healthy-donor PBMC *in vitro*, these isolates exhibited a high replication capacity.in *In vitro*, pretreatment of virus cultures

with IL-10 and CRP resulted in a significant reduction of virus production, whereas IL-22, which lacks action on immune cells appears to mediate its anti-HIV effect through interaction with both IL-10 and CRP, and its own protective effect on mucosal membranes (Arias et al., 2010).
Insights gained into the mechanism of action of acute-phase reactants and other innate molecules against HIV and how they are induced could be exploited for the future development of more efficient prophylactic vaccine strategies.

8. Conclusion

APR has major consequences during a local inflammation process with systemic consequences to maintain the whole organism homeostasis. The continuous discovery of new mediators/receptors of this response allow to more precisely tunes the knowledge about subtle necessary equilibrium to understand diseases set up to propose new possible therapeutic approaches. The double game of inflammatory processes to destroy the non-self and repair the self clearly is not ease to delimitate and this knowledge is a tremendous and pivotal challenge for a well adapted personalized medicine.
Moreover, data are mostly harvested from animal models that do not reflect physiopathological patterns that are generated in humans with their own kinetics. Nevertheless, today animal models are absolutely necessary, but observations need to be improved with more adapted reagents particularly for the *in vivo* real time observations of the physiopathological evolution and conditions.
Another imperious need is to assess functional concentrations of mediators/receptors such as IL-22 that are present in healthy individuals resisting to diseases such as infections, in a way to measure over the time their concentrations and understand their signification in terms of their homeostatic values in relation with complex networks

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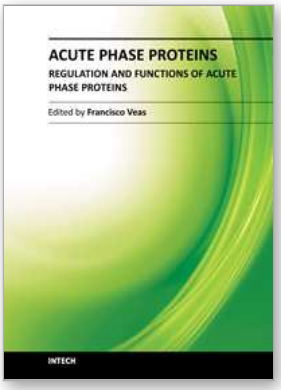

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The two volumes of Acute Phase Proteins book consist of chapters that give a large panel of fundamental and applied knowledge on one of the major elements of the inflammatory process during the acute phase response, i.e., the acute phase proteins expression and functions that regulate homeostasis. We have organized this book in two volumes - the first volume, mainly containing chapters on structure, biology and functions of APP, the second volume discussing different uses of APP as diagnostic tools in human and veterinary medicine.

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