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Regulatory Mechanisms Controlling Inflammation and Synthesis of Acute Phase Proteins

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1. Introduction

Inflammation is usually defined as a complex response of the animal organism to tissue injury or to invasion of foreign pathogens. Although inflammation often starts as a local reaction it can easily develop into a generalized systemic response involving the whole organism. Participation of inflammatory reactions in the pathogenesis of many diseases is today a generally accepted medical paradigm. These ideas have been thoroughly discussed in numerous excellent monographs and specialized recent publications (Nathan, 2002; Dinarello, 2008, 2010; Medzhitov, 2010) whereas our presentation is just a brief account focused on regulatory mechanisms involved in the initiation, development and termination of the "generalized inflammatory response" (**GIR**) and its relations to the induced synthesis of certain plasma and tissue proteins.

The results obtained by techniques of modern genomics indicate that these three phases of response to injury are tightly controlled and are characterized by distinct profiles of hundreds of activated genes. The fine tuning of gene expression during initiation, development and resolution of inflammation occurs at many levels starting from transcription and followed by changes in mRNA decay, receptors cross-talk, intracellular signaling cascades and posttranslational protein modifications. Disturbances in the regulatory network lead to either acute pathological states such as septic shock, or to various chronic autoimmune and auto-inflammatory diseases.

Discovery of C-reactive protein (**CRP**) in the blood of patients with febrile diseases some 80 years ago (Tillett & Francis, 1930) was seminal for the development of the idea of "acute phase reaction" (**APR**) and the concept of "acute phase proteins" (**APPs**) reflected as profound rearrangement of plasma protein profile accompanying systemic inflammatory reaction (Kushner, 1982). The so called "positive AP-proteins" increase their plasma concentration in a broad range – from barely 25 per cent above the control up to several hundred fold - at the expense of "negative APPs" which go down in comparison to control. Other metabolic changes during this response include fever, leukocytosis, negative nitrogen balance, altered levels of some ions and hormones, activation of clotting and complement pathways, as well as certain less defined phenomena (for references see (Gordon and Koj, 1985)). The principal features of APR resemble the unspecific innate immunological reaction

and some authors assume that in fact we are dealing with synonyms corresponding to the two sides of the same biological phenomenon (Koj, 2008). From historic perspective however, the APR corresponds to the metabolic response of liver, manifested predominantly as induced synthesis of acute phase proteins. For several years it was silently assumed that the term APP is limited to plasma proteins synthesized by and secreted from liver parenchymal cells. However, many resident proteins are also affected by inflammatory response and they are called "acute phase regulated intracellular proteins" i.e. APRIPs (Ruminy et al., 2001), or even more broadly – cytokine-responsive cellular proteins (Koj, 2008).

2. Initiation of generalized inflammatory response

Inflammation can be induced by two types of noxious stimuli: invasion of foreign pathogens of biological origin, or sterile tissue damage. In reality, however, the most common is mixed type of GIR. The pathogens include bacteria, fungi, yeasts, viruses or parasites as well as their products which after penetrating of the organism are present either in the extracellular space, or already in the cell compartments. In the first case they can be recognized by a special class of cell membrane receptors abounding on the surface of sentinel cells exposed to the environment. Receptors of this type were first discovered in *Drosophila* fruit fly and named Toll receptors, being important for embryonic development and protection against invading fungi. Their mammalian counterparts named Toll-like receptors **(TLRs)** have been extensively studied during last 15 years (Medzhitov et al., 1997). TLRs are able to discriminate between self and non-self by recognizing pathogen-associated molecular patterns **(PAMPs)** (Medzhitov, 2010). Typical examples of this class of PAMPs are lipopolysaccharides of the bacterial wall, or mannans from the yeasts cells (Takeuchi & Akira, 2010). Today more than ten mammalian TLRs are known and depending on their cellular localization and type of the ligand they are divided into two subgroups. TLRs from the first group are localized at the cell membrane (TLRs 1, 2, 4, 5, 6, 10), whereas others (TLRs 3, 7, 8, 9) are expressed intracellularly anchoring vesicles of the endoplasmic reticulum, endosomes and lysosomes (Kawai & Akira, 2010; Ospelt & Gay, 2010). Toll-like receptors are important in the initiation of molecular alarm during pathogen invasion of the host and also in response to other danger signals expressed in a variety of immune as well as non-immune cells. Effector or "sentinel" cells, such as neutrophils, dendritic cells and macrophages express almost all types of TLRs, in distinction to other specialized cells. The first group of TLRs recognizes mainly microbial membrane components (lipids, lipoproteins and proteins) whereas the other group responds to microbial nucleic acids. For example TLR1 acts mainly as a heterodimer together with TLR2 and recognizes lipopeptides originating from *Mycobacteria*. TLR2 responds also to material derived from bacteria, fungi, parasites and viruses (lipopeptides, peptidoglycan, lipoarabinomannan, zymosan or hemagglutinins), whereas the heterodimer TLR2/TLR6 binds lipopeptides. TLR4 was the first TLR identified in human cells and we know that it responds to bacterial lipopolysaccharides (LPS) from the membrane of Gram-negative bacteria (Akira et al., 2006). Another receptor from this group, TLR5, recognizes bacterial protein, flagellin, essential for movement of bacteria (Akira et al., 2006). The recently discovered human TLR10 was found to heterodimerize with TLR1 (Hasan et al., 2005) but so far its ligand was not determined. As already mentioned, TLRs from intracellular compartments may recognize nucleic acids: TLR3 binds double stranded RNA of viral origin, but also similar endogenous ligands from necrotic cells (Brentano et al., 2005). On the other hand, TLR7 and TLR8 respond to single-stranded

RNA from viruses and endogenous sources. Finally, TLR9 recognizes DNA-containing unmethylated CpG motifs. All the discussed TLRs differ not only in structure and ligand affinity but also in the intracellular signaling cascades. Their ability to form dimers certainly expands the array of recognized PAMPs. Signals generated by the formation of a PAMP-TLR complex activate at least one out of five specific adaptor cytoplasmic proteins (MyD88, MAL, TRIF, TRAF or SARM) (O'Neill & Bowie, 2007). These adaptors participate in transmission of a message from the plasma membrane through a multi-step cascade to a responsive transcription factor – NF-κB being the principal target (Fig.1).

Pathogen invasion and stimulation of Toll-like and NOD-like receptors
Macrophages, leukocytes, keratinocytes, epithelial and other sentinel cells

Pathogen-free tissue injury and/or environmental stress

Signaling cascade of TLRs and NLRs	→	Inflammasome assembly	←	DAMPs activated cellular sensors
Activation of NF-κB and other TFs		Activation of pro-caspase-1 and pro-IL-1β		Activation of NF-κB and other TFs

PRIMARY INFLAMMATORY RESPONSE
Synthesis and release of various cytokines
IL-1, TNF, IL-8, MCP-1, IL-6, IFNγ, VEGF

Stimulation of cytokine receptors on target cell

Signal transduction cascades
TRAF, IRAK, MAPK, JAK/STAT

Second wave of activation of transcription factors:
NF-κB, AP-1, C/EBP, STATs

SECONDARY INFLAMMATORY RESPONSE
Transcription of activated genes and synthesis of acute phase proteins
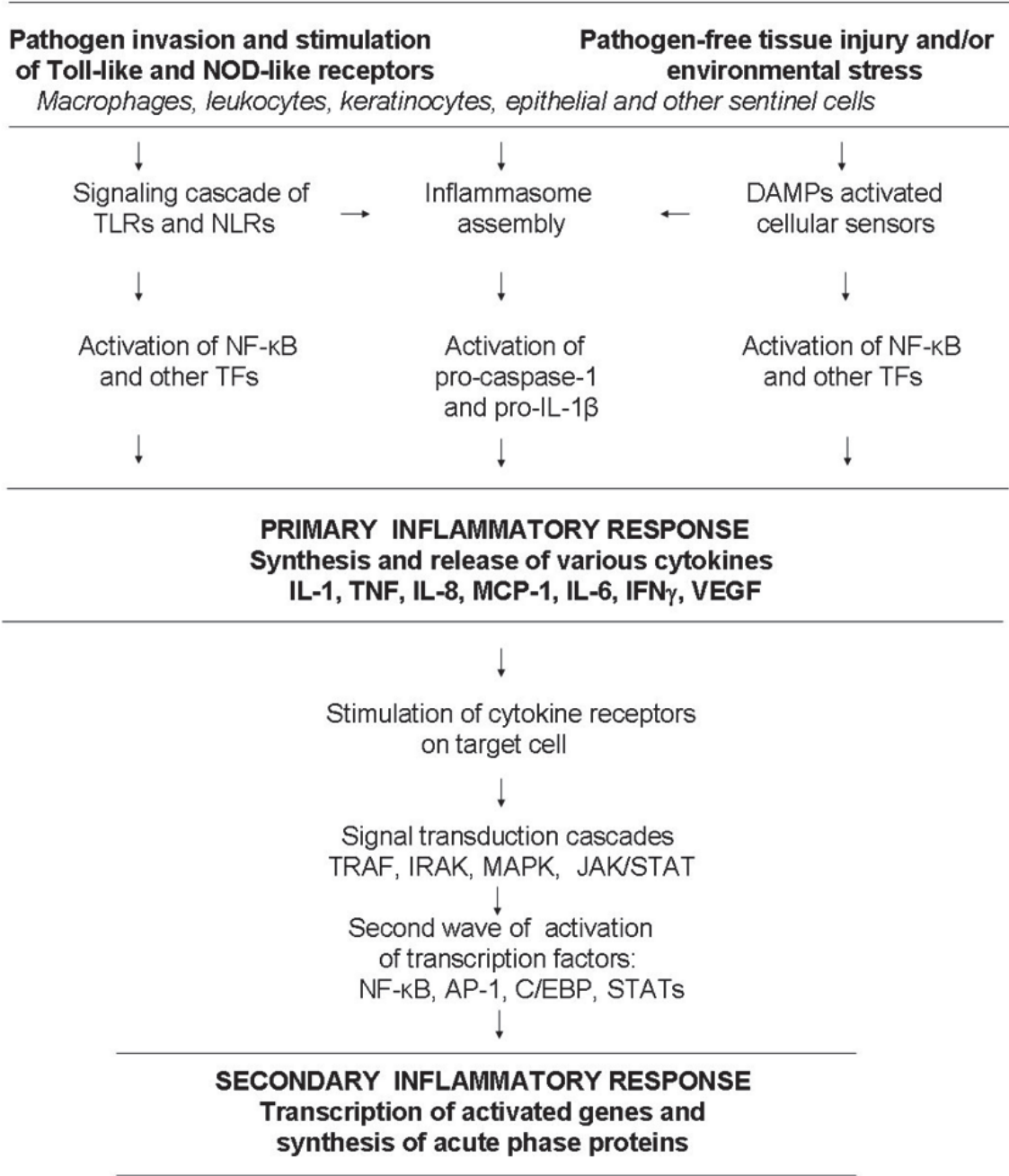
Fig. 1. Scheme of initiation and development of inflammatory response. For abbreviations used and for further detail see the text.

However, some pathogen-derived molecules, such as foreign DNA or RNA, may reach intracellular compartments of infected cells where they are recognized by and bound to NOD-like receptors (**NLRs**) (Akira et al., 2006; Ye & Ting, 2008). The NLRs belong to a large family of cytosolic pattern recognition receptors (34 members in mice, 23 in human) (Jin & Flawell, 2010) that are able to recognize various pathogen associated molecular patterns or danger-associated molecular patterns and thereby initiate the innate immune response against invading pathogens and cellular signals of damage or stress.

These NLRs, multi-domain receptor proteins, are characterized by leucine-reach repeats (LRRs) at the C-terminal region, a central nucleotide binding and oligomerization domain (referred to as NOD domain), toward N-terminal effector domain. From evolutionary point of view it is very interesting that animal NLRs show certain similarities to the products of plant disease-resistant genes (Martinon et al., 2009). Some NLRs act just as receptors while other constitute components of specialized cytosolic structures – **inflammasomes** (Schroder & Tschopp, 2010; Martinon et al., 2009). Certain NLRs interact with the ubiquitin ligase-associated protein SGT1 and HSP90, and this leads to the inhibition of inflammasome activity (Mayor et al. 2007).

In comparison to pathogen induced response the signaling elicited by pathogen-free tissue injury is even more complex and includes various **DAMPs** (damage-associated molecular patterns) such as crystals of uric acid or cholesterol (responsible for symptoms of gout or atherosclerosis) (Rock et al., 2010), fibers of asbestos and grains of silica (accumulated in lungs in asbestosis and silicosis) (Martinon et al., 2009; Rock et al., 2010), chemical irritants such as turpentine oil (Sheikh et al., 2007), deposits of denatured or modified proteins (such as inactivated alpha-1-proteinase inhibitor) (Koj & Guzdek, 1995), or fibrillar amyloid beta peptide found in the brain in Alzheimer disease (Halle et al., 2008). But commonly occurring pathogen-free tissue damage leading to inflammation can be also elicited by extreme temperatures, by hypo- or hyperosmolarity (Shapiro & Dinarello, 1997; Bode et al., 1999), by hypoxia-reoxygenation process (Wenger et al., 1995), UV radiation (Feldmeyer et al., (2007) and accumulation of reactive oxygen species (Bogdan et al., 2000). These signals may - by various means - stimulate cells either through specialized appropriate Toll-like receptors (Takeuchi & Akira, 2010) or certain scavenger receptors, or using other sensitive intracellular surveillance molecules, such as plasma membrane transporters (Schroder and Tchopp, 2010) or activation of MAP kinases (Bode et al., 1999; Chang & Karin, 2001). The use of alternative signaling routes occurs in case of hypoxia which is known to mobilize a specific transcription factor HIF-1 and proline hydroxylases (Zagorska & Dulak 2004; Oliver et al., 2009).

Usually the multi-step signaling cascade activated by pathogen-free tissue injury (or by stress of environmental origin) merges at some stage with the cascade initiated by foreign pathogens resulting in activation of transcription factors, among which the most important is NF-κB (Fig.1). This leads to a prompt transcription of sensitive genes resulting in accumulation of specific mRNAs coding mainly for IL-1β and other cytokines involved in the development of inflammation. It is understood now that translation of some of these mRNAs into active proteins may require an additional signal as it was earlier found in the case of IL-1β (Dinarello, 1996); if this signal is missing, initiation of the inflammatory response may be delayed or entirely aborted.

In order to briefly recapitulate current views on the initiation of inflammatory reaction one should emphasize the importance of signals indicating imminent danger to the cell/organism. Their detection is based on the ability of cells to recognize such signals by a small number of germline-encoded Pattern Recognition Receptors (PRRs). These PRRs are

able to discriminate between self and non-self of certain molecular structures that may appear either outside of the cell (e.g. bacterial LPS is bound to Toll-like receptors located on the cell membrane), or are found intracellularly (e.g. foreign DNA or RNA in the cytosol) where they are recognized by NOD-like receptors (NLRs). However, PRRs can be stimulated not only by binding Pathogen Associated Molecular Patterns (**PAMPs**) but also by host own stress and danger signals (**SAMPs and DAMPs**) derived from damaged cells. These signals are recognized by cytosolic, intracellular receptors, among which the most important are NLRs. Moreover, some NLRs are used for the construction of specialized subcellular structures – inflammasomes – serving as the activation platform for the key pro-inflammatory cytokine – IL-1β.

3. The role of inflammasomes

Undoubtedly, IL-1β is the key mediator in the host innate response to infection and the driving force in the development of inflammation. However, since IL-1β is synthesized as a leaderless pro-cytokine it must be processed for secretion and exhibition of biological activity (similar properties are shown also by IL-18 and IL-33) (Dinarello, 1996, 2008, 2010). The proteolytic activation of pro-IL-1β is accomplished by an enzyme initially named ICE (Interleukin-1-converting enzyme) but at present known as caspase-1 belonging to the family of cysteine-aspartyl proteases participating in apoptosis. Caspase-1 is synthesized as zymogen which undergoes autocatalytic processing. Only relatively recently it has been established that efficient activation of pro-caspase-1 and pro-IL-1β takes place in specialized cytoplasmic multiprotein platforms called **inflammasomes** (Dinarello, 2008; Martinon et al., 2009; Schroder & Tschopp, 2010).

As discussed by Martinon et al. (2009), the details of inflammasome structure are only partly revealed but several types of molecules can be distinguished. The best known NLRP3 inflammasome (alternative names – NALP3 or cryopyrin) includes NLRP3 protein which interacts with the **adaptor protein ASC** (apoptosis-associated speck-like protein with a caspase recruitment domain). The resulting complex binds and activates pro-caspase-1 to caspase-1 which in turn is ready to activate pro-IL-1β (Fig.2). It appears that activation of caspase-1 requires zinc and is dependent on pannexin-1, a protein localized upstream in this signaling cascade (Brough et al., 2009).

Assembly and activation of inflammasome can be induced by several factors discussed above, but recent review presented by Martinon et al., (2009) enlarges this list to include various signals of danger and stress (DAMPs or SAMPs). Extracellular ATP represents such a stress signal released locally and recognized by a specific purinergic receptor $P2X_7$ (Ferrari et al., 2006; Lister et al., 2007).

Charles Dinarello was probably first to report that in order to obtain active and mature IL-1β molecules two independent cellular signals are required for effective transcription and translation (Dinarello, 1996). When studying activation of NLRP3 inflammasome Bauernfeind et al., (2009) observed that this process also needs two signals: one provided by the NF-κB cascade is necessary but not sufficient, whereas the second signal is generated by extracellular ATP, or crystal-induced cell damage. Other inducers of inflammasome assembly include such widely different factors as reactive oxygen intermediates, products of lysosomal damage and leakage of potassium from the cell (Martinon et al., 2009; Rock et al., 2010). We know today that the inflammasome may act as a sensor of the oxidative stress by co-operation with thioredoxin (Jin & Flavell, 2010; Zhou et al., 2010). The broad spectrum of

modulators of inflammasome assembly and activation confirms the importance of these subcellular structures that are just being recognized as new targets in the anti-inflammatory therapies (Stehlik & Dorfleutner, 2007; Lamkanfi et al., 2009; Dinarello, 2010; Martinon et al., 2010; Rock et al., 2010).
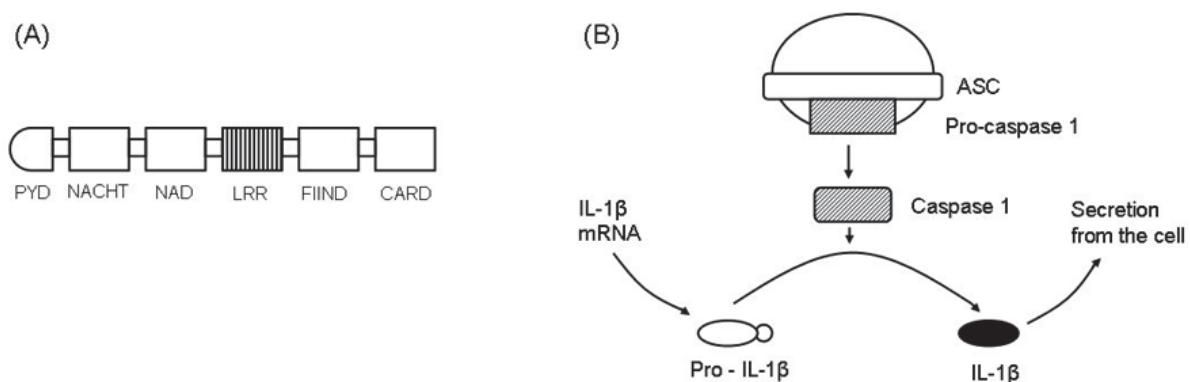

Fig. 2. Principal domains of NLRP1 protein (A) and schematic function of NLRP3 inflammasome (B).

The drawings are based on the data of Agostini et al., (2004); Dinarello, (2008) and Martinon et al. (2009). PYD, pyrin domain; NACHT, central nucleotide binding and oligomerization domain; NAD, NACHT-associated domain; LRR, leucine-rich repeats; FIIND, domain of poorly defined function; CARD, caspase recruitment domain; ASC, apoptosis speck-like protein adjacent to CARD at C-terminal where pro-caspase is initially located.

4. Inflammation control: components and rules

Local inflammation can be transformed within a few hours into a life-threatening generalized inflammatory response and thus the development of mechanisms controlling its course is of prime importance. The list of main players in the field of inflammation development and control is shown in Table 1, but their detailed analysis is beyond the scope of this brief review. The data obtained by techniques of functional genomics indicate that several hundreds of genes participate in the inflammatory response and their coordinated expression is tightly regulated (for references see Koj, 2008; Jura et al., 2008). These genes can be grouped into subsets as coding for various transcription factors, cytokines, chemokines, interferons, cellular growth factors and corresponding receptors, as well as those coding for adhesion molecules and enzymes involved in the production and removal of free radicals, or in modification of newly synthesized polypeptide chains by glycosylation or phosphorylation.

Most of these genes and their products share some striking features concerning the mechanism of biosynthesis and degradation of inflammatory mediators, and especially of cytokines:

*   Promoters of these genes often contain multiple binding sites for several transcription factors (TFs): the most important being NF-κB. Its activation can be achieved in several independent signaling cascades, one of them - induced by LPS – being shown in Fig. 3. However, NF-κB is more than just a transcription factor and should be rather regarded as an universal switch in the innate and acquired immune reactions (reviewed in Hoffmann & Baltimore, 2006). Other typical transcription factors used by inflammatory

mediators include AP-1, (activator protein-1, usually a hetero-dimer of c-Fos/c-Jun (Hattori et al., 1993)), STAT (signal transducer and activator of transcription known in six isoforms numbered STAT1 – STAT6 (Baumann, 2003; Heinrich et al., 2003; Sehgal, 2008), C/EBP (CAAT enhancer binding protein, occurring in four isoforms (Huang & Liao, 1994) and Elk-1 (Kasza et al., 2010) (for comprehensive list of earlier references see Ray et al., 1990; Koj, 1996, Ruminy et al., 2001). The interactions between the various TFs that compete for binding sites in the promoter regions of various genes are highly complex and regulation of IL-6 expression, described first by Sehgal et al., (1995) and later by van den Berghe et al., (2000), may provide some useful information.
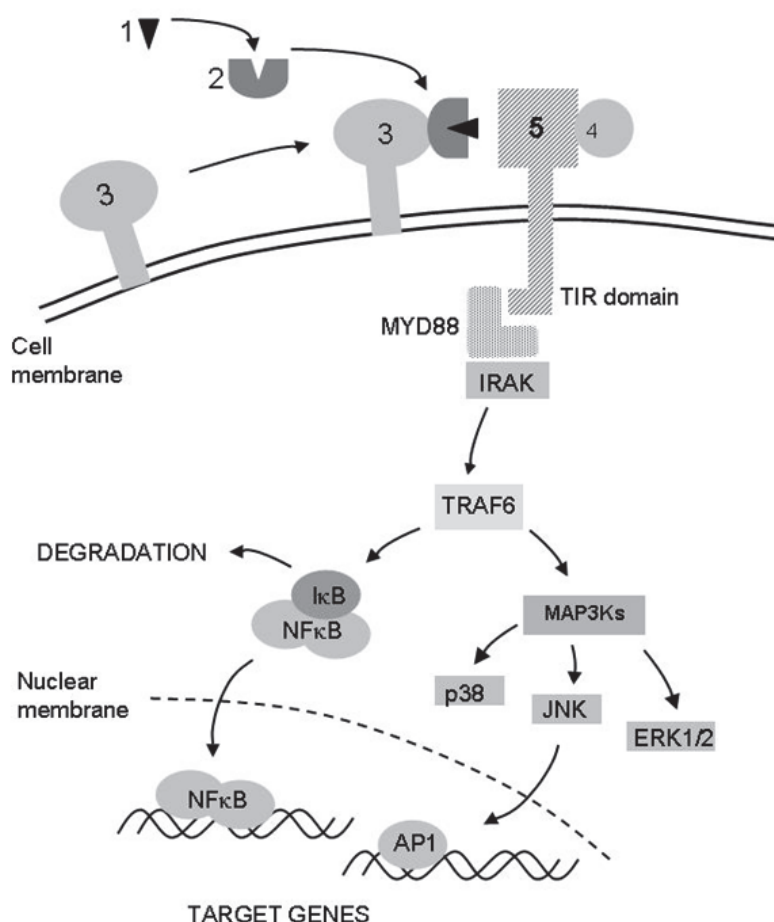

Fig. 3. Simplified scheme of a signaling pathway activated by bacterial endotoxin (LPS).

LPS (1) interacts with LPS-binding protein (2) and with help of plasma membrane receptor CD14 (3) is transferred to Toll-like receptor TLR4 (5) which requires MD2 accessory protein (4). Activation of TLR4 leads to the recruitment of an adaptor protein MyD88 with subsequent involvement of several adaptor or enzymatic proteins (some of them not shown on the scheme): Tollip, IRAK (IL-1R-Associated Kinase) and TRAF (TNF-Receptor Associated Factor). IRAK4 is phosphorylated and activates IRAK1, which in turn interacts with TNF receptor-associated factor 6 (TRAF6) complex causing its oligomerization and activation. Proteins from TRAF6 complex activate IKK and MAP kinases (ERK1/3, JNK, p38). IKK is a complex of two protein kinase subunits, IKKalfa and IKKbeta, and a regulatory subunit IKKgamma (NEMO). Activation of IKK complex leads to phosphorylation of NF-κB inhibitor (IkB) and its degradation, resulting finally in the release of NF-κB and its translocation to the nucleus. AP-1 (Activator protein-1) is another transcription factor activated by this cascade.

- The half-life of mRNAs coding for mediators of inflammation is considerably shorter than that of mRNAs of various housekeeping genes (Sharova et al., 2009). The short-lived mRNAs were found to possess (usually in the 3'untranslated regions) AU-rich elements (ARE) recognized by specific proteins that are able to destabilize mRNA and deliver it to the cellular sites of degradation: **exosomes and/or processing bodies** (P-bodies) (Chen et al., 2001; Garneau et al., 2007; Eulalio et al., 2007). The list of ARE-binding proteins involved in mRNA decay includes tristetraprolin (Stoecklin et al., 2004), AUF-1 and AUF-2, (Lu et al., 2006) TIA-1 and TIAR (Dean et al., 2004), KSRP (Gherzi et al., 2007) and HuR (Dean et al., 2004). This last protein (HuR) acts in a rather unusual way since it stabilizes mRNA and prolongs its life in the cell. On the other hand, macrophage chemotactic protein-induced protein-1 (MCPIP1), studied also in our laboratory (Mizgalska et al,. 2009; Skalniak et al., 2009), is able to degrade mRNAs coding for IL-1β, IL-6 and IL-12p40 (but not for TNFalpha), although it does not require the ARE signal (Matsushita et al., 2009; Mizgalska et al., 2009)
- Finally, the majority of proteins involved in the control of inflammatory response exhibit short half-lives being susceptible to degradation in a proteasome after initial ubiquitination (for references see Evans, 2005).

This variable length of life and a fast turnover of mediators of inflammation, achieved either at the stage of their mRNA or mature protein, permit for elastic control and fine regulation of inflammatory reactions. An additional mechanism used for the tuning of some inflammatory pathways depends on transient phosphorylation of susceptible proteins by kinases from the MAP family (Herlaar & Brown, 1999). According to Chang and Karin (2001) mammals express at least four distinctly regulated groups of mitogen activated protein kinases able to phosphorylate serine-threonine residues: Jun amino-terminal kinases (JNK), p38 proteins in four isoforms, and two groups of extracellular signal-regulated kinases (ERKs). The representatives of all groups participate in regulation of inflammatory mediators, usually in a multi-step cascade reactions. These cascades may stretch from cell membrane receptors to transcription factors in the cell nucleus; moreover, some of MAP kinases fulfill the role of cellular sensors directly responding to chemical and physical stresses (Chang & Karin, 2001). According to Winzen et al (1999) p38 MAP kinase contributes to cytokine- or stress-induced gene expression by stabilizing mRNAs through ARE-targeted mechanism. The central role of p38 MAPK in the early transcriptional responses to various types of stress has been confirmed in the recent studies discussed by Cuenda & Rousseau (2007) and Whitmarsh (2010). However, since disorganized cytokine signal transduction may have disastrous consequences so the action of protein kinases is monitored by protein phosphatases containing SH2 domain (Src homology 2 domain). Still this is not always sufficient and specific proteins (PIAS) inhibiting activated STATs have evolved (Wormald & Hilton, 2003).

Table 1 shows arbitrary assignment of many components: e.g. IL-6 family has not only proinflammatory but also some anti-inflammatory properties depending on the stage of inflammation (Scheller et al., 2011); the IL-1 family includes at least 11 separate proteins; VEGF is usually regarded as vascular endothelial growth factor but at the same time it shows strong pro-inflammatory activity. Leukotriene LTB4 stimulates migration of leukocytes but this effect is inhibited by lipoxin LXB4 (Conti et al., 1991).

5. Resolution of inflammation and termination of acute phase response

After the injury-elicited initiation of inflammatory reaction followed by fully developed inflammatory response the resolution phase is expected. In reality, however, this scheme is

not always observed and at least three different results are possible: (a) acute illness with a fatal outcome; (b) prolonged chronic disease; (c) prompt return to health after a period of reconvalescence.

a. When overproduction of proinflammatory mediatiors continues and negative effects of injury prevail, the generalized systemic inflammatory response may exceed the programmed limits of organism defense resulting in death. Such situations occur during the **acute septic shock syndrome** which is extremely resistant to medical treatment and death is caused not only by invading pathogens but often results from the excess of certain cytokines participating in the multiorgan failure (for references see Herzum & Renz, 2008).

b. When invading pathogens, or other injuring factors, continue their action on the organism but a transient equilibrium is achieved, the development of a **chronic inflammatory disease**, such as rheumatoid arthritis, may occur. Taking into account various mechanisms of molecular pathology, chronic inflammatory diseases are being currently divided into two separate groups: **autoimmune** (Zenewicz et al., 2010) and **auto-inflammatory** ones (Kastner et al., 2010). The first group includes rheumatoid arthritis, inflammatory bowel disease (Crohn disease), type 1 diabetes, psoriasis, lupus erythematosus and multiple sclerosis, and is regarded as dysfunction of T-cells. By contrast, the autoinflammatory diseases are caused by dysfunctional macrophages producing excesive amounts of IL-1beta. Typical examples of autoinflammatory diseases are: type 2 diabetes, cryopyrin-associated periodic syndromes (e.g. familial cold autoinflammatory syndrome, Muckle-Wells syndrome) and neonatal onset of multiinflammatory disease. These disorders respond well to the treatment aimed at limiting synthesis and release of IL-1beta (Dinarello, 2010).

c. Full recovery from the acute systemic inflammatory response goes through the **resolution phase** which represents more than just turning off production of proinflammatory mediators proteins and lipids. In fact, the synthesis of a new type of regulatory molecules is often initiated. First, the anti-inflammatory cytokines (listed in Table 1) appear and gain the field by inhibiting synthesis of proinflammatory cytokines. The most important is probably IL-10 family showing pleiotropic immunosuppressive and anti-inflammatory properties (Fickensher et al., 2002). However, as pointed out by Cavaillon (2001) the strict dichotomy of pro- and anti-inflammatory properties is artificial because the biologoical effects depend considerably on the biological context (Scheller et al.). We found that IL-4, IL-13 and IL-10 inhibit synthesis of TNFα and IL-6 in the whole blood stimulated *ex vivo* with LPS, but are ineffective, or even enhance production of IL-6 in cultured HUVEC endothelial cells (Guzdek et al., 2000). The most important anticytokine and antiinflammatory effects are probably exerted by suppressors of cytokine signaling (SOCS) and protein inhibitors of activated STATs (PIAS) (Ferguson & Johnston 2001; Wormald & Hilton, 2005). In Hawiger's laboratory a recombinant variant of cell-penetrating SOCS3 was obtained showing some protective effects in animal models of inflammation (Jo et al., 2005). Among lipid-derived molecules produced in the resolution phase antiinflammatory properties are shown by lipoxins and resolvins (Table 1 and Anderson, 2010). It should be reminded here that in all phases of inflammatory response complex changes in the profile of metabolic regulators occur on many levels - transcription, mRNA stability, translation and posttranslational modification of proteins (Evans, 2005).

The return to biological homeostasis may be facilitated and supported by pharmacological intervention. Traditionally used in therapy low molecular weight antiinflammatory drugs, such as glucocorticoids, salicylates, cyclosporin, pentoxifylline, tenidap, colchicine, statins, specific inhibitors of p38 MAP kinase, and many others, are now being supplemented with natural macromolecular cytokine inhibitors and antagonists (reviewed in Koj, 1998; Dinarello 2010). Particularly promising are various commercially available chimeric antibodies, some soluble cytokine receptors and constructs of designer cytokines non-existing in nature but powerful in action (Scheller & Rose-John, 2006; Dinarello, 2010; Scheller et al., 2011).

Cytokines:	-- Pro-inflammatory: IL-1, TNFα, IFN-γ, VEGF, IL-12, IL-17, IL-18, IL-23, IL-33 -- IL-6 family: IL-6, IL-11, LIF, OSM, CNTF, CT-1 - Anti-inflammatory: IL-4, IL-10, IL-13, IFNalpha, TGFbeta, IL-1Ra, MCPIP1 -- Chemokines: IL-8, MCP-1 -- Cellular growth factors: FGF, EGF, VEGF
Lipid derivatives:	-- glucocorticoids -- prostaglandins (PGE$_2$), -- leukotrienes (LTB4) -- lipoxins (LXB4) -- resolvins (RvE1 and E2)
Cell Adhesion Molecules - selectins and integrins:	-- VCAM-1, -- ICAM-1 -- E-selectin
Components of complement, clotting and fibrinolysis pathways:	-- more than a dozen proteins (including some clotting factors and plasminogen activators and inhibitors)
Certain intracellular enzymes and plasma acute phase proteins :	-- superoxide dismutases (MnSOD, ZnSOD) -- cyclooxygenases (COX-1 and COX-2) -- protein kinases from the MAP family (p38, ERKs) -- nitric oxide synthase (NOS) -- fibrinogen, CRP, SAA (and a dozen of other APPs)

Table 1. The main players in the field of inflammation development and control

However, apart from those just mentioned well defined autoinflammatory and autoimmune diseases, certain elements of inflammation can be found in various pathological processes, such as atherosclerosis (Libby, 2002) or neurodegenerative disorders (Glass et al., 2010). In this respect participation of liver in the inflammatory response is very important and only recently it has been fully evaluated as the source of various mediators, and especially acute phase proteins that fulfill various functions.

The pioneering and elegant experiments carried out on the perfused rat liver by Miller et al., (1951) demonstrated that all principal proteins present in the plasma of circulating blood

derive – with the notable exception of immunoglobulins – from the liver. Since the rat does not respond to injury by increased production of C-reactive protein, Miller's experiments were inconclusive and the origin of CRP remained a mystery until Hurlimann et al., (1966) demonstrated incorporation of radioactive amino acids into immunologically identified CRP after incubation of liver preparations from injured monkeys and rabbits. Today we know that the main acute phase proteins in the rat belong to alpha globulins (historic aspects of APP synthesis have been discussed in detail elsewhere (Kushner, 1982; Gordon & Koj, 1985; Koj, 2008).

6. Molecular mechanisms of induced synthesis of acute phase proteins

The progress in elucidating the mechanisms of liver acute phase response obtained a new impetus when APPs synthesis, studied both *in vivo* and in tissue culture, became a valuable model for molecular biology. After cultured liver cells became routinely used it was possible to conclude that the "Hepatocyte Stimulating Factor" responsible for synthesis of acute phase proteins is a cytokine distinct from interleukin-1 (Baumann et al., 1984) and named interleukin-6 (Gauldie et al., 1987). In subsequent years it was found that IL-6 is the most important member of a large cytokine family sharing common receptor subunit gp130 and showing a high degree of redundancy (Sehgal et al., 1995; Heinrich et al., 2003; Baumann, 2003). This family includes IL-6, IL-11, leukemia inhibitory factor (LIF), oncostatin M (OSM), cardiotrophin-1 (CT-1), cilliary neurotrophic factor (CNTF) and some other cytokines (Scheller et al., 2011). Recently Liang et al., (2009) reported that IL-22, although not belonging to IL-6 family, can induce almost all symptoms of acute phase response in the liver; however, the mechanism of its action is as yet not fully understood.

It should be emphasized here that as a rule several cytokines are involved in the regulation of liver-produced acute phase proteins, and on this ground at least two types of cytokines and corresponding APPs have been distinguished by Baumann and Gauldie (1994). Type 1 cytokines (IL-1 and TNF families) co-operate with type 2 cytokines (IL-6 family) in the induced expression of such proteins as CRP, serum amyloid A, C3 complement or alpha-1-acid glycoprotein, all belonging to type 2 APPs. On the other hand, synthesis of other proteins - human fibrinogen or rat alpha-2-macroglobulin, are stimulated only by cytokines of IL-6 family while the presence of IL-1 or TNF decreases the response. The balance between the signaling pathways induced by two types of cytokines is very delicate as indicated by the experiments of Uhlar & Whitehead (1999). They found that the magnitude of synergistic stimulation of SAA synthesis is influenced not only by cytokine concentrations but also by the order of addition of IL-1 and IL-6 to cultured human hepatoma cells. Table 2 provides examples of different classes of APPs after taking into account stimulation with two types of cytokines.

Positive acute phase proteins show increased levels after treatment with the appropriate cytokine whereas negative APPs are decreased. Class A – increased up to 200-fold; Class B - increased by 2-5 fold, Class C – increased by at least 25 per cent. Class D – decreased by at least 25 per cent. Please note species differences. Type 1 cytokines : IL-1 or TNFa; type 2 cytokines - IL-6 family. Abbreviations: CRP, C-reactive protein; FBG, fibrinogen; C3C, third component of the complement; ALB, albumin; SAA, serum amyloid A; HPT, haptoglobin; CEP, ceruloplasmin; TST, transthyretin (pre-albumin); A2M, alpha-2-macroglobulin; AGP, alpha-1-acid glycoprotein; HPX, haemopexin; TRF, transferrin.

Positive AP-proteins			Negative APPs
Class A	**Class B**	**Class C**	**Class D**
CRP /type 1 (primates, rabbit)	FBG / type 2 (many species)	C3C / type 1 (many species)	ALB / type 1&2 (many species)
SAA / type 1 (man, mouse)	HPT / type2 (man)	CEP / type 1 (many species)	TST / type 1 (many species)
A2M / type 2 (rat)	AGP / type 1 (many species)	HPX / type 2 (many species)	TRF / type 2 (many species)

Table 2. Classification of selected acute phase plasma proteins based on the magnitude of AP-response and type of stimulating cytokine (Koj, 1985a,c).

It should be remembered that many additional factors modulate the cytokine-induced change of APPs synthesis rate, the most important being glucocorticoids that act synergistically with IL-6, especially in the rat (Koj, 1985c; Ruminy et al., 2001).

Synthetic inhibitors of MAP kinases interfere with many signaling pathways (Herlaar & Brown, 1999; Lee et al., 2000). As shown by Westra et al., (2006) inhibition of p38 MAPK in cells of human hepatoma significantly reduced cytokine-induced synthesis of CRP and fibrinogen (but not of SAA). Among other low-molecular weight drugs statins – originally used for inhibition of cholesterol synthesis - were shown to possess broad anti-inflammatory properties (Sparrow et al., 2001) and effectively reduce certain symptoms of acute phase response (Munford, 2001).

A recent report by Patel et al., (2009) indicates that the aryl hydrocarbon receptor (AHR) can repress cytokine-induced synthesis of APPs in mouse liver. A somewhat similar downregulation of the AP-response was reported by Venteclef et al., (2006) for the liver receptor homolog 1 (LRH-1). Overexpression of LRH-1 resulted in the inhibition of IL-1- and IL-6-mediated FBG, SAA, CRP and HPT gene expression. All of the genes inhibited by LRH-1 in response to cytokine stimulation contain functional C/EBP DNA-binding sites within their promoter regions (Venteclef et al., 2006). Since LRH-1 was originally identified as a key player in cholesterol regulatory mechanisms the authors conclude that this liver orphan receptor could be a novel molecular link between cholesterol homeostasis and inflammation. Still another liver receptor, PPAR-α (peroxisome proliferators-activated receptor-alpha), was found to attenuate the IL-6-induced synthesis of APPs (Mansouri et al., 2008). Direct involvement of hepatic PPARα was demonstrated using a liver-restricted expression of PPARα in mice, while as a distal repercussion the decreased expression of adhesion molecules in aorta was observed.

Development of new techniques of the genomics era, such as subtractive hybridization, differential display or microarrays, provided a global approach in the studies of inducible gene expression and synthesis of APPs. Olivier et al., (1999) described a novel set of hepatic mRNAs preferentially expressed during acute inflammation elicited in the rat by turpentine injection. When sequencing 174 selected clones these authors identified 23 already known AP-proteins, 31 proteins known but so far not related to the AP-response, and discovered 36 novel proteins induced in the liver during turpentine-induced inflammation. More recently the Salier's group studied changes in the human liver transcriptome in patients

with systemic inflammation (Coulouarn et al., 2004). They found over 150 specific mRNAs expressed in the liver and correlating with the extent of inflammatory processes. This number was increased to over 600 genes in a model system of human hepatoma cells treated with the conditioned medium from endotoxin-stimulated macrophages (Coulouarn et al., 2005). The kinetic analysis of transcription rate and mRNA stability led the authors to a very important conclusion: inflammation-induced mRNAs appear in the cells not in a random fashion but as consecutive transcriptional waves corresponding to functionally related proteins produced in an orderly fashion.

In order to study the effects of low doses of IL-1 and/or IL-6 on human hepatoma cells HepG2 differential display was used in our laboratory (Wegrzyn et al., 2006). We found that out of 88 cDNA species modulated by IL-6 only 38 represented various known genes, 18 clones matched genomic clones in the NCBI data with hypothetical cDNA sequences, and the remaining 32 clones showed no homology with databases. When the cells were stimulated with the mixture of IL-1 and IL-6 only 43 cDNA fragments were amplified suggesting the prevailing negative regulation by IL-1. The identified transcripts modulated by IL-6 alone, or by both cytokines, were found to code for intracellular proteins engaged in general metabolism, protein synthesizing machinery and cellular signaling.

Since macrophages are important for the development of inflammation and the acute phase response, many attempts have been made to discover pathogen-induced changes in these cells using microarrays: in our case we identified IL-1 and IL-6 responsive genes in human monocyte-derived macrophages using Affymetrix microarrays (Jura et al., 2008). A major problem encountered in our experiments aroused from individual variability of basal transcriptome profile among blood donors. However, out of almost 5000 probe sets consistently detected in all array replicates we found more than 200 genes modulated by IL-1 and/or IL-6, among which 34 could be regarded as novel cytokine-responsive genes of various functions. A detailed analysis indicated that 125 transcripts were stimulated by IL-1 and 39 by IL-6, whereas the number of downregulated genes was similar for both cytokines (approximately 30 genes in each group). Among the identified IL-1 responsive genes we found one of particular interest, named ZC3H12A and coding for MCPIP1, which plays a pivotal role in the control of inflammation. Recent experiments indicate that MCPIP1 enhances decay of mRNAs coding for some inflammatory mediators (Mizgalska et al., 2009; Matsushita et al. 2009), but also interferes with NF-κB-dependent signaling pathway (Skalniak et al., 2009; Liang et al., 2009).

Last years brought abundant information on the role of microRNA in the regulation of gene expression – and the field of inflammation is no exception. As reported by Harris and co-workers (2008) miRNA-126 inhibits VCAM-1 expression in HUVEC culture and thus may be considered as a potential drug reducing leukocyte adherence to endothelial cells, and in consequence their migration to the site of injury.

7. Multiple biological functions of acute phase proteins

Acute phase proteins represent the products of a large group of genes conserved during evolution and regulated by numerous cytokines that show considerable redundancy. This indicates the importance of APPs in respect of survival value for the animal organism and explains the origin of accepted paradigm stating that "**the principal function of APPs is their ability to restore homeostasis disturbed by injury and inflammation** (Koj, 1985b)." Recent years brought further support of this idea as indicated by the data presented in Table 3, but only some of the results will be discussed here, starting from proteinase inhibitors.

Function	AP-proteins engaged
1. Inhibition of proteinases	Macroglobulins, serpins, kininogens:- over 20 proteins
2. Blood clotting and fibrinolysis	Fibrinogen, $\alpha_1$proteinase inhibitor, antithrombin III, $\alpha_2$antiplasmin, C1- inactivator, $\alpha_1$glycoprotein, serum amyloid P, C-reactive protein, kininogens
3. Anti-inflammatory properties	Proteinase inhibitors, fibrinopeptides, haptoglobin
4. Removal of pathogens and foreign materials	C3 complement, C-reactive protein, serum amyloid A and P proteins, fibrinogen
5. Modulation of immunological response	Proteinase inhibitors, C-reactive protein, α_2HS-glyco-protein, C3 complement, fibrinogen
6. Transport of various materials	Transferrin, ceruloplasmin, transthyretin, haptoglobin, hemopexin, $\alpha_1$glycoprotein, macroglobulins, albumin

Table 3. Selected examples of homeostatic functions of APPs

Human plasma contains at least ten distinct and well characterized proteins responsible for the inhibition of various serine-, cysteine-, aspartic- and metalloproteinases. The list of inhibitors includes: alpha-2-macrogloblin(A2M), alpha-1-proteinase inhibitor (API), alpha-1-antichymotrypsin (ACT), inter-alpha trypsin inhibitor (ITI), antithrombin III (AT3), C-1-inactivator (C1N), alpha-2-antiplasmin(APL), beta-1-anticollagenase (BAC) and high and low molecular weight kininogens (HMK and LMK, both able to inhibit cysteine proteinases). Among those ten inhibitors the most important are: API and ACT (both being strong acute phase reactants in man), and A2M (a spectacular APP in the rat).

The dynamic equilibrium between the blood or tissue proteinases and their natural inhibitors is drastically disturbed during acute inflammation (Koj et al., 1993). A massive release of proteolytic enzymes from injured tissues and infiltrating leukocytes or macrophages should be promptly neutralized by a range of antiproteases present in body fluids. Since the reaction between proteinases and inhibitors is in most cases irreversible, and the resulting complexes are removed, the enhanced proteolytic activity could seriously deplete the body reserves of these antiproteases. As demonstrated by many authors such situation occurs in certain cases of acute pancreatitis and in septic shock. However, the acute phase response usually facilitates replenishment of proteinase inhibitors due to their enhanced liver synthesis. In human hepatoma cells the expression of API and ACT is stimulated primarily by IL-6 whereas A2M synthesis in man (in distinction to the rat) is enhanced by IFNgamma (Kordula et al., 1992).

The **macroglobulin family of proteinase inhibitors** comprises a large group of proteins characterized by a broad specificity due to the presence of a characteristic bait region whereas irreversible binding of the enzyme requires a labile thiol ester. The entrapped proteinase may show still some activity toward small molecular weight substrates. Synthesis

of alpha-2-macroglobulin in the rat is greatly stimulated during inflammation whereas alpha-1 macroglobulin does not change significantly – and these two macroglobulins have different specificity in respect of proteinase inhibition (Tsuji et al., 1994).

The members of **serine proteinase inhibitors named serpins,** show considerable variations in their strict specificity   toward the target enzymes. API (initially named antitrypsin) inhibits also leukocyte elastases, whereas ACT blocks leukocytic cathepsin G. A charactertistic structural feature of all serpins is the existence of an exposed peptide loop which in the native form is in the strained position being replaced to a stable configuration by proteolytic attack. Recently it was found that two hormone-transporting proteins – thyroxin-binding globulin and cortisol-binding globulin, belong also to the serpin superfamily. Although they do not show detectable antiprotease activity, their molecules contain a characteristic polypeptide loop easily cleaved by proteinases (Pemberton et al., 1995). After cleavage of cortisol-binding protein by neutrophil elastase a tenfold decrease of affinity for cortisol was observed. In that way cortisol may be delivered preferentially to the inflammation site abounding in serine proteinases of leukocyte origin.

Rats appear to be unique in their ability to produce considerable amounts of **thiostatin - an inhibitor of cysteine proteinases** (known formerly as alpha-1-acute phase globulin, or rat major acute phase globulin). In fact thiostatin is a special type of kininogen releasing biologically active kinins upon treatment with trypsin-like enzymes (Lalmanach et al., 2010). Thiostatin is able to inhibit calpain, papain and cathepsin L.

As already mentioned, plasma proteinase inhibitors may fulfill some additional functions apart from the removal of specific enzymes. Thus it has been shown that macroglobulins bind highly toxic eosinophil cationic proteins, are involved in the transport of cellular growth factors and may reduce the effects of endotoxin-induced shock, but are also able to modulate immunological response: it was reported that API, ACT and A2M inhibit the activity of natural killer cells and reduce the antibody-dependent cell-mediated cytotoxicity (Ades et al., 1982).

Recent years brought abundant information on the role of some APPs in the modulation of immunological response, removal of pathogens or foreign materials and reduced inflammation. Pentraxins are multimeric proteins including "short pentraxins" (CRP and SAP produced in hepatocytes), and "long pentraxins" (PTX3 synthesized in macrophages, fibroblasts and in activated endothelium) (Szyper-Kravitz, 2006; Mantovani et al., 2008). All pentraxins fulfill the function of soluble pattern recognition receptors interacting with certain bacterial pathogens and with surface of apoptotic cells thus playing an important role in the removal of cell debris. Moreover, CRP and SAP bind and activate certain complement components important for the innate immunity. This may have negative effects in some diseases: it is known that during incipient heart infarct human CRP strongly activates complement cascade at the site of ischaemia thus enhancing tissue injury. Pepys and co-workers (2006) recommend to reduce the increased level of newly synthesized CRP by giving to a patient derivatives of phosphatidyl choline, known to be a good competitive ligand for CRP.

Besides pentraxins, mannose-binding lectin (MBL) and apolipoprotein A1 belong to protective molecules (Szyper-Kravitz, 2005). They are produced in hepatocytes but ApoA1 is a negative APP and MBL level is not affected by cytokines. Szyper-Kravitz et al., (2005) suggest that the discussed pentraxins, as well as MBL and ApoA1, are important for autoimmune diseases and thus are often used - along with CRP – as clinical markers of progression of inflammation.

Serum amyloid A (SAA) is a strongly induced and a well known AP-protein in man and mouse but recently Cheng et al., (2008) and He and co-workers (2009) made original observations. According to Cheng TLR2 is a functional receptor for SAA and its stimulation leads to enhanced activity of NF-κB that is accompanied by increased phosphorylation of MAPKs and accelerated degradation of IkBalpha. In this way SAA may affect the course of AP response and some inflammatory diseases. He and co-workers demonstrated that SAA is a potent endogenous inducer of granulocyte colony-stimulating factor (G-CSF) responsible for neutrophilia. This effect of SAA is dependent on Toll-like receptor TLR2.

As indicated by the results of Kramer et al., (2010) some APPs or their proteolytic fragments are involved in the earliest antiviral response in HIV-1 infection. The active components were identified as serum amyloid A and a peptide derived from alpha-1-proteinase inhibitor. Insights gained into the mechanism of action of acute phase reactants against HIV could be exploited for the development of prophylactic vaccine strategies.

The broadest conclusions on the homeostatic potential of APPs derive from the studies of Sander and Trautwein, (2010). They used an original global approach based on the fact that liver AP-response critically depends on gp130 subunit of the membrane-bound receptor of IL-6 family of cytokines, and subsequent interaction of gp130 with STAT3 transcription factor. By creating mice deficient in this receptor the authors blocked induced synthesis of APPs and this strongly increased the mortality of mice in a model of polymicrobial sepsis. Further experiments showed that hepatic gp130-STAT3 interaction was also essential for mobilization and tissue accumulation of myeloid-derived suppressor cells (MDSC), a cell population known from their anti-inflammatory properties in cancer. The authors identified two hepatocyte-produced proteins - serum amyloid A and Cxcl1/KC chemokine - as cooperatively promoting MDSC mobilization. They concluded that gp130 dependent communication between the liver and MDSCs through some APPs controls the inflammatory responses in the infected mice. The discussed results are related to the new function of SAA as an endogenous TLR2 ligand (Cheng et al., 2008).

8. Concluding remarks

Elucidation of molecular events concerning the initiation and development of inflammatory reaction has progressed considerably during the last 10 years. The membrane-bound and cytosolic receptors recognizing pathogen-associated - or stress-associated - molecular patterns deriving either from invading pathogens or from damaged cells, have been identified. These signals generated by stimulated receptors lead to assembly of inflammasomes - molecular platforms activating the main proinflammatory cytokine – interleukin-1. Then IL-1 and other cytokines utilize the multistep signaling cascades to activate the pivotal transcription factor NF-κB subsequently translocated to the nucleus. There, in cooperation with other TFs, NF-κB initiates transcription of hundreds of genes coding for various proteins participating in inflammation. This process is tightly regulated and properly tuned due to cooperation of many different transcription factors and subsequent stabilization or enhanced decay of specific mRNAs in exosomes. Recent studies led to identification of a new multifunctional regulatory protein MCPIP1, which can affect both mRNA stability and NF-κB signaling. Although the inflammatory response may occur in various forms, particularly important for the final outcome is the liver acute phase response regulated mainly by IL-6 family of cytokines. The liver-produced acute phase proteins exhibit multiple functions important for restoring homeostasis disturbed by injury

and inflammation. Particularly interesting are new data on APPs classified as proteinase inhibitors from three families (macroglobulins, serpins and thiostatins) and original findings on the role of protective molecules belonging to pentraxins and serum amyloid A protein. These discoveries create chances for new therapeutic strategies concerning the treatment of septic shock syndrome and chronic autoimmune or autoinflammatory diseases.

9. Acknowledgments

10. References

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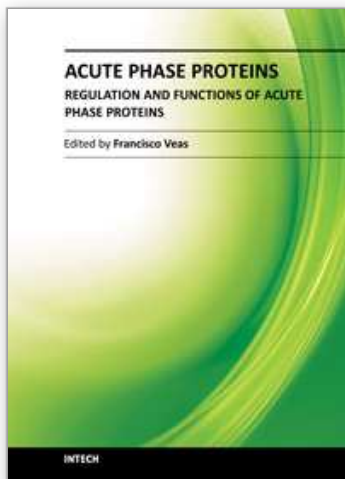
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Acute Phase Proteins - Regulation and Functions of Acute Phase Proteins

Edited by Prof. Francisco Veas

ISBN 978-953-307-252-4

Hard cover, 368 pages

Publisher InTech

Published online 03, October, 2011

Published in print edition October, 2011

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.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Jolanta Jura and Aleksander Koj (2011). Regulatory Mechanisms Controlling Inflammation and Synthesis of Acute Phase Proteins, Acute Phase Proteins - Regulation and Functions of Acute Phase Proteins, Prof. Francisco Veas (Ed.), ISBN: 978-953-307-252-4, InTech, Available from: http://www.intechopen.com/books/acute-phase-proteins-regulation-and-functions-of-acute-phase-proteins/regulatory-mechanisms-controlling-inflammation-and-synthesis-of-acute-phase-proteins

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