EUROPEAN JOURNAL OF INFLAMMATION Vol. 9, no. 2, 95-102 (2011)

EDITORIAL

INFLAMMATORY MARKERS: SERUM AMYLOID A, FIBRINOGEN AND C-REACTIVE PROTEIN – A REVISITED STUDY

V. SALINI[1] A. SAGGINI[2], G. MACCAURO[3], A. CARAFFA[4], Y.B. SHAIK-DASTHAGIRISAHEB[5] and P. CONTI[6]

[1]Orthopaedic Division University of Chieti-Pescara, Medical School, Chieti, Italy; [2]Department of Dermatology, University of Rome Tor Vergata, Rome, Italy; [3]Department of Orthopaedics, Catholic University of Rome, Rome, Italy; [4]Orthopaedics Division, University of Perugia, Perugia, Italy; [5]Department of Medicine, Boston University School of Medicine, Boston, MA, USA; [6]Immunology Division, University of Chieti-Pescara, Medical School, Chieti, Italy

Received March 23, 2011– Accepted June 14, 2011

The acute phase response is the part of the innate defence system of an animal against trauma, inflammation or infection. During this response, there is increased production and release of certain plasma proteins known as acute phase proteins, which include C-reactive protein (CRP), serum amyloid A (SAA) and fibrinogen (Fg). CRP consists of five identical subunits of 206 amino acids with a molecular weight of approximately 23 kDa. There is strong evidence from numerous studies that CRP is a predictor of inflammation. The acute-phase protein serum amyloid A (SAA) is a clinically useful marker of inflammation. SAA plays not only an important role in the development of AA amyloidosis (an important complication of rheumatoid arthritis) but also interacts with events closely involved in the metabolic syndrome as a high- and low-grade inflammatory modulator. Fibrinogen (Fg) is a high molecular weight plasma adhesion protein and is a biomarker of inflammation. It is synthesized and assembled in hepatocytes and fibroblasts and when secreted into the circulation, its plasma half-life ranges from 3 to 4 days. Several cytokines, are involved in the induction of acute phase protein synthesis, but the mutual importance of these cytokines seems to be cell-type specific and to vary in various experimental settings. Here we revisited the classic acute phase proteins SAA, C-Reactive protein and fibrinogen in their role in inflammation and their interrelationship with some cytokines.

Systemic and localized inflammation plays an important role in the development of acute and chronic inflammatory syndromes. The following inflammatory markers were studied: C-reactive, protein, fibrinogen, and serum amyloid A (SAA). Traumatic tissue injury from infection provokes a systemic inflammatory response termed acute-phase response, which is accompanied by hepatic synthesis of certain plasma proteins. Increased levels of serum amyloid A (SAA), C-reactive protein (CRP), and fibrinogen have been observed during the acute-phase response. The normal physiological homeostasis of the organism is perturbed in response to inflammatory stimuli, leading to alterations in a wide variety of biochemical processes. These changes are collectively referred to as the 'acute-

Key words: acute phase proteins, innate defence, amyloid A, fibrinogen, C-reactive protein, cytokines

Mailing address: Professor Vincenzo Salini,
Orthopaedics Division,
G. d'Annunzio University,
Via dei Vestini 35, 66013 Chieti, Italy
Tel: ++39 0871 358263
Fax: ++39 0871 560082
e-mail: v.salini@unich.it

0393-974X (2011)

phase response'; they represent the organism's first line of defence and precede the more specific changes of the immune response. C-reactive protein (CRP) and serum amyloid A (SAA) are the two major human acute-phase proteins; their plasma concentrations may increase by 1000-fold or more following an inflammatory stimulus.

Fibrinogen (Fg) is a biomarker of inflammation (1-5) which, when elevated, indicates the presence of inflammation and identifies individuals with a high risk for cardiovascular disorders. Fg is synthesized and assembled in hepatocytes and fibroblasts, and when secreted into the circulation, its plasma half-life ranges from 3 to 4 days. Fibrinogen (Fg) is a high molecular weight plasma adhesion protein and a biomarker of inflammation (6). Many inflammatory disorders are accompanied by an increased blood content of Fg (7-9). Increased levels of Fg result in changes in blood physical properties such as increases in plasma viscosity, erythrocyte aggregation, platelet thrombogenesis, alterations in vascular reactivity and compromises in endothelial layer integrity. These alterations exacerbate the complications in peripheral blood circulation during systemic inflammatory diseases (10-11). In addition to affecting blood viscosity by altering plasma viscosity and erythrocyte aggregation, growing experimental evidence suggests that Fg alters vascular reactivity and impairs endothelial cell layer integrity by binding to its endothelial cell membrane receptors and activating signalling mechanisms.

The increase of fibrinogen results in the following symptoms: a) an increase of blood viscosity, b) an increase in vascular reactivity, and c) a decrease in endothelial integrity. All these symptoms lead to vascular dysfunction. Infections, trauma and inflammatory processes induce a host response with increases in a large group of structurally and functionally diverse plasma proteins. Parenteral administration of foreign proteins also induces an increase in plasma fibrinogen.

Serum amyloid A (SAA)

The acute-phase protein serum amyloid A (SAA) is a clinically useful marker of inflammation and is strongly associated with increased risk of cardiovascular events (12). Chronically elevated SAA concentrations may contribute to physiological processes that lead to atherosclerosis, including endothelial dysfunction, an early and predictive event in the development of cardiovascular disease (13-15). Studies suggest that SAA can be a direct mediator in the development and progression of atherogenesis and atherothrombosis (16). SAA may affect key events underlying acute coronary syndromes, including cholesterol transport, contribute to endothelial dysfunction, promote thrombosis, and enhance leukocyte trafficking and activation (17-18). Novel therapeutic strategies to reduce SAA levels and/or oppose the actions of SAA may have beneficial effects on patients with inflammatory disease. SAA plays not only an important role in the development of AA amyloidosis (an important complication of rheumatoid arthritis), but also interacts with events closely involved in the metabolic syndrome as a high- and low-grade inflammatory modulator (19-20).

Serum amyloid A (SAA) protein is a major acute phase reactant in humans and many other species. Infections and traumatic inflammation are characterized by a rapid increase of SAA; its concentration in the plasma may augment many-fold (21-22). We have previously shown that the induction of synthesis of the two major human acute phase proteins, serum amyloid A (SAA) and C-reactive protein (CRP), are produced *in vitro* by hepatocytes stimulated by certain cytokines (23-24). Neither of these cytokines alone caused significant induction of either SAA or CRP. Serum amyloid A is an acute phase protein complexed to high density lipid protein (HDL) as an apoprotein (25-27). The molecular weight is 11.4-12.5 kDa in different species, and the protein has from 104 to 112 amino acids, with or without an insertion of eight amino acids at position 72. The protein is very well conserved throughout evolution, indicating an important biological function (28-30). The N-terminal part of the molecule is hydrophobic and probably responsible for the lipid binding properties. The most conserved part is from position 38 to 52, and this part is therefore believed to be responsible for the until now unknown biological function. The protein is coded on chromosome 11p in man. Acute phase SAA is first of all produced in hepatocytes after induction by cytokines, but extrahepatic expression of both acute phase and constitutive SAA

proteins has been demonstrated (31-35).

C-reactive protein (CRP)

C-reactive protein was first identified by Tillet and Francis more than 80 years ago. CRP consists of five identical subunits of 206 amino acids with a molecular weight of approximately 23 kDa. There is strong evidence from numerous studies that CRP is a predictor of inflammation (36-38).

Measurement of serum C-reactive protein (CRP) level is in widespread clinical use as a sensitive marker of inflammation. CRP has a role in the clearance of bacteria and of dying and altered cells, and might also have more complex immunomodulatory functions (39-41). Considerable evidence suggests CRP is an independent predictor of future cardiovascular events, but direct involvement in atherosclerosis remains controversial.

The plasma concentration of C-reactive protein (CRP), the first acute-phase protein to be identified, increases dramatically following tissue injury or inflammation. Although the physiological role of CRP is still not fully known, it has been suggested that concentrations might increase as part of the acute-phase response for facilitating non-specific immune functions, defence against bacterial pathogens, clearance of apoptotic and necrotic cells to prevent immunization against autoantigens and acceleration of the repair process (42-44). In agreement with the evidence that inflammation plays a pivotal role in the pathogenesis of atherosclerosis, CRP concentrations have been associated with cardiovascular disease, and measurement of CRP has therefore been proposed as a valuable aid to predict and stratify the risk of myocardial infarction and stroke. Native and monomeric CRP exert several prothrombotic activities, including activation of blood coagulation, impairment of the endogenous fibrinolytic capacity, and stimulation or enhancement of platelet adhesiveness and responsiveness (45-46). Inflammatory markers are ideal markers which enable early detection of patients with inflammatory syndrome, whereas inflammation markers are helpful in diagnosing and assessing the severity of inflammation.

Cytokines and acute-phase proteins

Several cytokines, first of all IL-1, IL-6 and TNF, are involved in the induction of SAA synthesis, but the mutual importance of these cytokines seems to be cell-type specific and to vary in various experimental settings (47). The role of corticosteroids in SAA induction is somewhat confusing. In most *in vitro* studies corticosteroids show an enhancing or synergistic effect with cytokines on SAA production in cultured cells. However, in clinical studies and *in vivo* studies on animals an inhibitory effect of corticosteroids is evident, probably due to the overall anti-inflammatory effect of the drug (48). To date, no drug has been found that selectively inhibits SAA production by hepatocytes. Effective anti-inflammatory or antibacterial treatment is the only tool for reducing SAA concentration in serum and reducing the risk of developing secondary amyloidosis (49). The function of SAA is still unclear. Interesting theories, based on current knowledge of the lipid binding properties of the protein and the relation to macrophages, in the transportation of cholesterol from damaged tissues has been advanced (50). The potential that SAA is a modifying protein in inflammation influencing the function of neutrophils and platelets is interesting and more directly related to the inflammatory process itself. One possible mediator of the acute-phase response is interleukin-1, a pro-inflammatory monokine released in response to traumatic tissue injury or infection. There is evidence that partially purified macrophage supernatants containing interleukin-1 activity stimulate hepatocyte secretion of SAA, CRP, and fibrinogen (51).

Interleukin-6 (IL-6) is a monocyte-derived mediator and has regulatory effects on acute phase protein genes which result in the induction of fibrinogen synthesis in primary hepatocytes, while the addition of interleukin-1 (IL-1) exerts a negative modulating influence on the IL-6-stimulated fibrinogen (52). It is clear that IL-1 inhibits IL-6-stimulated fibrinogen transcription and translation. We studied the effects of IL-1ra on the down-regulation of IL-6 stimulated fibrinogen by IL-1, using an Fg ELISA method (53).

Amyloidosis encompasses a spectrum of diseases in which there is disordered folding of certain proteins that lead to them being deposited as insoluble fibrils in the extracellular space (54). The result of this process is impaired tissue structure and function. Amyloidosis may be acquired or hereditary and local or systemic, and is defined according to the identity

of the fibril precursor protein (55). Amyloidosis is a clinical disorder caused by extracellular deposition of proteins that are normally soluble as insoluble, abnormal fibrils that impair organ function

More than 20 unrelated proteins can form amyloid fibrils *in vivo* (56). Local amyloid deposition occurs in the brain in Alzheimer's disease and in the pancreas in maturity-onset diabetes, but a direct role in the pathogenesis of these diseases remains unproven. Systemic amyloidosis, with amyloid deposits in the viscera, blood vessel walls and connective tissues, is usually fatal and is the cause of about one death per thousand in developed countries. Recent elucidation of fundamental aspects of the pathogenesis of amyloidosis, and developments in diagnosis and monitoring of this disorder have greatly improved outcome for patients (57).

Osteoarthritis is a worldwide heterogeneous group of conditions that leads to joint symptoms associated with defective integrity of articular cartilage (58), in addition to related changes in the underlying bone at the joint margins. The prevalence of the disease after the age of 65 is about 60% in men and 70% in women. The aetiology of osteoarthritis is multifactorial, with the end result being mechanical joint failure and varying degrees of loss of joint function. The pathophysiological events associated with osteoarthritis are beginning to be understood. Essential inflammatory cytokines, such as IL-1beta and TNF-alpha, are involved in initiating a vicious cycle of catabolic and degradative events in cartilage, mediated by metalloproteinases, which degrade cartilage extracellular matrix (59). The role of inflammation in the pathophysiology and progression of early osteoarthritis is supported further by the observation that C-reactive protein levels are raised in women with early knee osteoarthritis, and higher levels predict those whose disease will progress (60).

Increased levels of SAA, CRP, and fibrinogen have been observed during the acute-phase response (61). One possible mediator of the acute-phase response is interleukin-1, a pro-inflammatory monokine released in response to traumatic tissue injury or infection. There is evidence that partially purified macrophage supernatants containing interleukin-1 activity stimulate hepatocyte secretion of SAA, CRP, and fibrinogen. It is clear that recombinant interleukin-1, when injected intraperitoneally into mice, induced specific production of SAA mRNA and hence one phase of the acute-phase response. However, maximal induction of the acute-phase proteins C-reactive protein (CRP) and serum amyloid A (SAA) in the human hepatoma cell line Hep3B requires the combination of interleukin (IL)-6 and IL-1. In contrast, IL-1 inhibits fibrinogen induction by IL-6.

The synovium from osteoarthritis joints stains for IL-1beta and TNF-alpha. Nitric oxide, which exerts pro-inflammatory effects, is released during inflammation. Cartilage from patients with rheumatoid arthritis and osteoarthritis spontaneously produces nitric oxide *in vitro*. In experimental osteoarthritis, nitric oxide induces chondrocyte apoptosis, thus contributing to cartilage degradation. Hence, unregulated nitric oxide production in humans plays a part in the pathophysiology of the disease. These recent observations suggest that therapy can now be targeted at specific sites of pathophysiological pathways involved in the pathogenesis of osteoarthritis (60, 62-63). The novel strategies under consideration for the treatment of osteoarthritis can be divided into five main areas. These are COX-2 inhibitors, nitric oxide synthesis inhibitors and anti-oxidants, chondrocyte and bone growth promoters, metalloproteinase and cytokine inhibitors and gene therapy.

Interleukin-6 (IL-6) is the major cytokine so far characterized that is capable of regulating synthesis of almost all acute-phase proteins (64). IL-6 exhibits pleiotropic biological functions and is produced by a variety of cell types, including monocytes/macrophages, fibroblasts, endothelial cells and epithelial cells. IL-6 alone was capable of inducing synthesis of these two acute-phase proteins as well as fibrinogen and other cytokines, including interleukin-1 (IL-1), tumour necrosis factor alpha, interferon gamma, transforming growth factor /5, leukaemia inhibitory factor, interleukin-11 and oncostatin M, and also modulating synthesis of acute-phase proteins (65-66). These cytokines can act independently or, as is often the case, interact with each other and other extracellular signals, such as hormones, resulting in the production of specific patterns of acute-phase proteins.

However, beyond the utility of measuring markers of inflammation: SAA, reactive C protein and fibrinogen, to assess patients with subclinical inflammatory diseases who are at higher risk of

more severe events, further studies are needed to evaluate the therapeutic implications in this category of patients.

REFERENCES

1. Ross R. Atherosclerosis-an inflammatory disease. N Engl J Med 1999; 340(2):115-26.
2. Borrelli I, Loffredo S, Staiano RI, Frattini A, Bergamaschi A, Marone G, Triggiani M. Benzene metabolites inhibit the release of proinflammatory mediators and cytokines from human basophils. Int J Immunopathol Pharmacol 2010; 23:737-44
3. Izzicupo P, Di Valerio V, D'Amico MA, et al. NAD(P)H oxidase and pro-inflammatory response during maximal exercise: role of C242T polymorphism of the p22phox subunit. Int J Immunopathol Pharmacol 2010; 23:203-11.
4. Cianci R, Pagliari D, Pietroni V, Landolfi R, Pandolfi F. Tissue infiltrating lymphocytes: the role of cytokines in their growth and differentiation. J Biol Regul Homeost Agents 2010; 24:239-49.
5. Marotta F, Harada M, Dallah ED, Yadav H, Solimene U, Di Lembo S, Minelli E, Jain S, Chui DH. Protective effect of a poly-phytocompound on early stage nephropathy secondary to experimentally-induced diabetes. J Biol Regul Homeost Agents 2010; 24:41-49.
6. Wycoff HD. A microassay for plasma fibrinogen. J Lab Clin Med 1956; 47(4):645-8.
7. Cilia La Corte AL, Philippou H, Ariëns RA. Role of fibrin structure in thrombosis and vascular disease. Adv Protein Chem Struct Biol 2011; 83:75-127.
8. Cacciapaglia F, Spadaccio C, Gregorj C, et al. Apoptosis and autoimmunity induced by clodronate in systemic lupus erythematosus mononuclear circulating cells. Int J Immunopathol Pharmacol 2010; 23:535-42.
9. Capria A, De Nardo D, Baffetti FR, Barbini U, Violo A, Tondo T, Fontana L. Long-term anti-TNF-α treatments reverse the endothelial dysfunction in rheumatoid arthritis: the biological coherence between synovial and endothelial inflammation. Int J Immunopathol Pharmacol 2010; 23:255-62.
10. Riccioni G, D'Orazio N, Scotti L, et al. Circulating plasma antioxidants, inflammatory markers and asymptomatic carotid atherosclerosis in end-stage renal disease patients: a case control study. Int J Immunopathol Pharmacol 2010; 23:327-34.
11. Rosato E, Pisarri S, Salsano F. Current strategies for the treatment of autoimmune diseases. J Biol Regul Homeost Agents 2010; 24:251-59.
12. Hua S, Song C, Geczy CL, Freedman SB, Witting PK. A role for acute-phase serum amyloid A and high-density lipoprotein in oxidative stress, endothelial dysfunction and atherosclerosis. Redox Rep 2009; 14(5):187-96.
13. Richardson VJ. Divergent and synergistic regulation of matrix metalloprotease production by cytokines in combination with C-C chemokines. Int J Immunopathol Pharmacol 2010; 23:715-26.
14. Di Stefano A, Sozio P, Cerasa LS, Iannitelli A, Cataldi A, Zara S, Giorgioni G, Nasuti C. Ibuprofen and lipoic acid diamide as co-drug with neuroprotective activity: pharmacological properties and effects in β-amyloid (1-40) infused Alzheimer's disease rat model. Int J Immunopathol Pharmacol 2010; 23: 589-99.
15. Carlesimo M, Mari E, Arcese A, et al. Safety and efficacy of calcium folinate in psoriasis: an observational study. Int J Immunopathol Pharmacol 2010; 23:649-53.
16. Riccioni G, D'Orazio N, Speranza L, et al. Carotenoids and asymptomatic carotid atherosclerosis. J Biol Regul Homeost Agents 2010; 24:447-52
17. Marchese E, Vignati A, Albanese A, Nucci CG, Sabatino G, Tirpakova B, Lofrese G, Zelano G, Maira G. Comparative evaluation of genome-wide gene expression profiles in ruptured and unruptured human intracranial aneurysms. J Biol Regul Homeost Agents 2010; 24:185-95.
18. Castellani ML, Felaco P, Galzio RJ, et al. IL-31 a TH2 cytokine involved in immunity and inflammation. Int J Immunopathol Pharmacol 2010; 23:709-13.
19. Gasparini G, Saponaro G, Di Nardo F, Moro A, Boniello R, Cervelli D, Marianetti TM, Palazzoni G, Pelo S. Clinical experience with spiramycin in bisphosphonate-associated osteonecrosis of the jaw. Int J Immunopathol Pharmacol 2010; 23:619-26.
20. Conti AA. The parallel evolution of immunology and pharmacology. Int J Immunopathol Pharmacol 2010; 23:655-57.

21. Wilson PG, Thompson JC, Webb NR, de Beer FC, King VL, Tannock LR. Serum amyloid A, but not C-reactive protein, stimulates vascular proteoglycan synthesis in a pro-atherogenic manner. Am J Pathol. 2008; 173:1902-10.
22. Madonna R, Montebello E, Lazzerini G, Zurro M, De Caterina R. NA+/H+ exchanger 1- and aquaporin-1-dependent hyperosmolarity changes decrease nitric oxide production and induce VCAM-1 expression in endothelial cells exposed to high glucose. Int J Immunopathol Pharmacol 2010; 23:755-65.
23. Cherng JY, Liu CC, Shen CR, Lin HH, Shih MF. Beneficial effects of *Chlorella*-11 peptide on blocking LPS-induced macrophage activation and alleviating thermal injury-induced inflammation in rats. Int J Immunopathol Pharmacol 2010; 23:811-20.
24. Barausse G, Caramaschi P, Scambi C, et al. Clinical, serologic and instrumental data of ten patients affected by sclerodermatous chronic graft versus host disease: similarities and differences in respect to systemic sclerosis. Int J Immunopathol Pharmacol 2010; 23:373-77.
25. Wang X, Chai H, Wang Z, Lin PH, Yao Q, Chen C. Serum amyloid A induces endothelial dysfunction in porcine coronary arteries and human coronary artery endothelial cells. Am J Physiol Heart Circ Physiol 2008; 295:H2399-408.
26. Tavazzi E, Bargiggia V, Pichiecchio A, et al. HIV-related acute inflammatory leukoencephalopathy of undetermined origin: review of the literature. Int J Immunopathol Pharmacol 2010; 23:693-700.
27. Gigante A, Cappella M, Manzotti S, Cecconi S, Greco F, Di Primio R, Mattioli-Belmonte M. Osteoinduction properties of different growth factors on cells from non-union patients: *in vitro* study for clinical application. J Biol Regul Homeost Agents 2010; 24:51-62.
28. Giuca MR, Giuggioli E, Metelli MR, Pasini M, Iezzi G, D'Ercole S, Tripodi D. Effects of cigarette smoke on salivary superoxide dismutase and glutathione peroxidase activity. J Biol Regul Homeost Agents 2010; 24:359-66.
29. Navarro-González J, Mora-Fernández C, Gómez-Chinchón M, Muros M, Herrera H, García J. Serum and gene expression profile of tumor necrosis factor-α and interleukin-6 in hypertensive diabetic patients: effect of amlodipine administration. Int J Immunopathol Pharmacol 2010; 23:51-59.
30. Schiavoni G, Di Pietro M, Ronco C, de Cal M, Cazzavillan S, Rassu M, Nicoletti M, del Piano M, Sessa R. *Chlamydia pneumoniae* infection as a risk factor for accelerated atherosclerosis in hemodialysis patients. J Biol Regul Homeost Agents 2010; 24: 367-75.
31. Upragarin N, Landman WJ, Gaastra W, Gruys E. Extrahepatic production of acute phase serum amyloid A. Histol Histopathol. 2005; 20:1295-307.
32. Brazzelli V, Grasso V, Fornara L, Moggio E, Gamba G, Villani S, Borroni G. Homocysteine, vitamin B12 and folic acid levels in psoriatic patients and correlation with disease severity. Int J Immunopathol Pharmacol 2010; 23:911-16.
33. Tarozzi A, Merlicco A, Morroni F, Bolondi C, Di Iorio P, Ciccarelli R, Romano S, Giuliani P, Hrelia P. Guanosine protects human neuroblastoma cells from oxidative stress and toxicity induced by amyloid-β peptide oligomers. J Biol Regul Homeost Agents 2010; 24:297-306.
34. Szkodzinski, B Hudzik J, Romanowski W, Wilczek K, Danikiewicz A, Gasior M, Polonski L, Zubelewicz-Szkodzinska B. Serum concentration of insulin-like growth factor-I, but not tumor necrosis factor-alpha, measured twelve months after stenting of the infarct-related artery, is associated with in-stent restenosis. J Biol Regul Homeost Agents 2010; 24:149-56.
35. Ciprandi G, De Amici M, Tosca M, Marseglia G. Allergen-specific Ig classes in non-allergic individuals. J Biol Regul Homeost Agents 2010; 24: 335-40.
36. Singh T, Newman AB. Inflammatory markers in population studies of aging. Ageing Res Rev 2011; 10:319-29.
37. Zhang QL, Niu Q, Niu PY, Ji XL, Zhang C, Wang L. Novel interventions targeting on apoptosis and necrosis induced by aluminum chloride in neuroblastoma cells. J Biol Regul Homeost Agents 2010; 24:137-48.
38. Sebastiani GD, Bottini N, Greco E, Saccucci P, Canu G, Lucarelli P, Gloria-Bottini F, Fontana L. A study of adenosine-deaminase genetic polymorphism in

rheumatoid arthritis. Int J Immunopathol Pharmacol 2010; 23:791-95.

39. Kones R. Rosuvastatin, inflammation, C-reactive protein, JUPITER, and primary prevention of cardiovascular disease--a perspective. Drug Des Devel Ther. 2010;4:383-413.
40. Cantarini L, Rigante D, Lucherini OM, et al. Role of etanercept in the treatment of tumor necrosis factor receptor-associated periodic syndrome: personal experience and review of the literature. Int J Immunopathol Pharmacol 2010; 23:701-7.
41. De Berardis D, Conti CMV, Serroni N, et al. The effect of newer serotonin-noradrenalin antidepressants on cytokine production: a review of the current literature. Int J Immunopathol Pharmacol 2010; 23:417-22.
42. Zambetti G, Ciofalo A, Soldo P, et al. Autologous serum skin test reactivity and basophil histamine release test in patients with nasal polyposis: preliminary results. Int J Immunopathol Pharmacol 2010; 23:641-47.
43. Chmielewska J, Szczepankiewicz D, Skrzypski M, Kregielska D, Strowski MZ, Nowak KW. Ghrelin but not obestatin regulates insulin secretion from INS1 beta cell line via UCP2-dependent mechanism. J Biol Regul Homeost Agents 2010; 24:397-402.
44. Li Q, Kobayashi M, Inagaki H, et al. A day trip to a forest park increases human natural killer activity and the expression of anti-cancer proteins in male subjects. J Biol Regul Homeost Agents 2010; 24: 157-65.
45. Angelini A, Di Ilio C, Castellani ML, Conti P, Cuccurullo F. Modulation of multidrug resistant P-glycoprotein activity by flavonoids and honokiol in human doxorubicin-resistant sarcoma cells (MES-SA/Dx-5): implications for natural sedatives as chemosensitizing agents in cancer therapy. J Biol Regul Homeost Agents 2010; 24:197-205.
46. Stachowicz M, Mazurek U, Nowakowska-Zajdel E, Niedworok E, Fatyga E, Muc-Wierzgoń M. Leptin and its receptors in obese patients with colorectal cancer. J Biol Regul Homeost Agents 2010; 24:287-95.
47. Pham TNQ, Rahman P, Richardson VJ. Divergent effects of infliximab and anakinra therapies on macrophage phenotype from patients with refractory rheumatoid arthritis. Int J Immunopathol Pharmacol 2010; 23:491-501.
48. Vanderlocht J, van Elssen CHMJ, Senden-Gijsbers BLMG, Meek B, Cloosen S, Libon C, Bos GMJ, Germeraad WTV. Increased tumor-specific CD8+ T cell induction by dendritic cells matured with a clinical grade TLR-agonist in combination with IFN-γ. Int J Immunopathol Pharmacol 2010; 23:35-50.
49. Mori G, Centonze M, Brunetti G, et al. Osteogenic properties of human dental pulp stem cells. J Biol Regul Homeost Agents 2010; 24:167-75.
50. Colombo D, Flori L, Altomare G, Aste N, Sgarbi S. Clinical outcome evaluation following cyclosporine A treatment in moderate to severe psoriasis: a retrospective study. Int J Immunopathol Pharmacol 2010; 23:363-67.
51. Chiavaroli A, Brunetti L, Orlando G, Recinella L, Ferrante C, Leone S, Di Michele P, Di Nisio C, Vacca M. Resveratrol inhibits isoprostane production in young and aged rat brain. J Biol Regul Homeost Agents 2010; 24:441-46.
52. Ciprandi G, Cirillo I. Rupatadine improves nasal symptoms, airflow and inflammation in patients with persistent allergic rhinitis: a pilot study. J Biol Regul Homeost Agents 2010; 24:177-83.
53. Ciprandi G, De Amici M, Caimmi S, Marseglia A, Marchi A, Castellazzi AM, Marseglia G. Soluble serum HLA-G in children with allergic rhinitis and asthma. J Biol Regul Homeost Agents 2010; 24:221-24.
54. Migliore A, Bizzi E, Massafra U, Vacca F, Martin Martin LS, Ferlito C, Podestà E, Granata M, Laganà B. Can Cyclosporine-A associated to methotrexate maintain remission induced by anti-TNF agents in rheumatoid arthritis patients? (Cynar pilot study). Int J Immunopathol Pharmacol 2010; 23:783-90.
55. Castellani ML, Galzio RJ, Felaco P, et al. VEGF, substance P and stress, new aspects: a revisited study. J Biol Regul Homeost Agents 2010; 24:229-37.
56. Garzaro M, Raimondo L, Nadalin J, Pecorari G, Giordano C. Subjective assessment of palatability, digestibility and emotions in healthy volunteers after ingestion of an iced dessert: preliminary report. J Biol Regul Homeost Agents 2010; 24:391-95
57. Corsaro A, Anselmi C, Polano M, Aceto A, Florio T, De Nobili M. The interaction of humic substances

with the human prion protein fragment 90-231 affects its protease K resistance and cell internalization. J Biol Regul Homeost Agents 2010; 24:27-39.

58. Mazzoccoli G, Pazienza V, Piepoli A, Muscarella LA, Inglese M, De Cata A, Giuliani F, Tarquini R. Hypothalamus-hypophysis-thyroid axis function in healthy aging. J Biol Regul Homeost Agents 2010; 24:433-39
59. Yanagisawa R, Takano H, Inoue KI, Koike E, Sadakane K, Ichinose T. Size effects of polystyrene nanoparticles on atopic dermatitis-like skin lesions in NC/NGA mice. Int J Immunopathol Pharmacol 2010; 23:131-41.
60. Schmal H, Mehlhorn A, Stoffel F, Köstler W, Südkamp NP, Niemeyer P. *In vivo* quantification of intraarticular cytokines in knees during natural and surgically induced cartilage repair. Cytotherapy 2009; 11:1065-75.
61. Yanagitani N, Shimizu Y, Kazama T, Dobashi K, Ishizuka T, Mori M. Eosinophilic bronchiolitis indicating eosinophilic airway disease with overexpression of carcinoembryonic antigen in sinus and bronchiole: case report. J Biol Regul Homeost Agents 2010; 24:99-102.
62. Cascavilla N, Bisceglia M, D'Arena G. Successful treatment of Schnitzler's syndrome with anakinra after failure of rituximab trial. Int J Immunopathol Pharmacol 2010; 23:633-40.
63. Yasuda A, Inoue K-i, Sanbongi C, Yanagisawa R, Ichinose T, Yoshikawa T, Takano H. Dietary supplementation with fructooligosaccharides attenuates airway inflammation related to house dust mite allergen in mice. Int J Immunopathol Pharmacol 2010; 23:727-35.
64. Faraone-Mennella MR, Marini M, Ferone A, Cacace O, Liguoro A, Margonato V, Farina B, Veicsteinas A. Physical exercise activates the poly(ADP-ribosyl)ation system in rat testes. J Biol Regul Homeost Agents 2010; 24:325-34.
65. Sun W-Z, Chang M-C, Hsiao P-N, Chen C-A, Hsu Y-T, Hsieh C-Y, Cheng W-F. Morphine-sparing effect by COX-1 inhibitor sustains analgesic function without compromising antigen-specific immunity and anti-tumor effect of naked DNA vaccine. Int J Immunopathol Pharmacol 2010; 23:91-104.
66. Marotta F, Naito Y, Bishier MP, Jain S, Yadav H, Minelli E, Kumari A, Solimene U, Sollano J. Subclinical candiduria in patients with gastrointestinal malignancies: a preliminary study on the protective effect of a natural phytocompound. J Biol Regul Homeost Agents 2010; 24:317-24.