EDITORIAL

NUTRITION AND CANCER PREVENTION

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Cancer cells invade surrounding tissues and metastasize to distant sites. Diet high in fat is a strong link to, and perhaps causes, a high incidence of tumours. Trans-fatty acid might impair the function and it could be involved in the development of cancer. Cholesterol is also strongly suspected to be involved in the development of tumours, therefore it is important for everyone to eat well, especially for people with cancer to prevent the body tissues from breaking down and helping to rebuild the normal tissue that may have been affected by the treatments. Factors secreted by adipocytes and macrophages such as TNF-alpha and other inflammatory proteins are involved in inflammation in cancer. In addition, MCSF which up-regulates adipocyte tissue is also important for the stimulation of fat cell proliferation and is expressed by human adipocytes. Many cytokines, such as IL-1, IL-6, IL-8, IL-32, IL-33 and MCP-1, are biomarkers for cancer and chronic diseases along with transcription factors NFkB and AP-1; these last two factors are important bioactive substances on the molecular mechanism of the control of genes which in turn affect cellular metabolism. In this paper we revisit the interrelationship between cancer and metabolism.

Cancers arise from the uncontrolled growth and spread of abnormal cells. These cells invade surrounding tissues and metastasize to distant sites. Cancer cells grow more rapidly than normal; while

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normal cells are more concerned with function than growth. Many substances in food initiate and promote cancer such as nitrosamine, food additives that are found in processed meats, fungus toxin (aflotoxin), high fat intake, alcohol, etc. It is well known that a diet high in fat is strongly linked to, and perhaps causes, a high incidence of tumors (1-5). Fats such as trans-fatty acids might impair cell function and they could be involved in the development of cancer. In addition, dietary cholesterol is also strongly suspected to be involved in the development of tumors. Imbalanced and over-nutrition promotes obesity, diabetes, malignancy, osteoporosis, and infectious diseases. Therefore it is important for everybody to eat well, especially for people with cancer. A balanced diet can help maintain strength, can prevent body tissue from breaking down and can help rebuild the normal tissues that have been affected by the treatments. Cancer patients with good eating habits can have fewer infections and be able to be up and about more. Obesity has recently been linked to mortality from the majority of cancers. The clinical problem of excessive adipose tissue resides in its strong association with a number of chronic diseases: hyperlipidemia, high blood pressure, carbohydrate intolerance and diabetes, coronary atherosclerotic heart disease, gout, restrictive lung disease, gall bladder disease, degenerative arthritis, and cancer. Several studies indicate that in obesity there is an increase in adipocyte hypertrophy (increase in size) and often hyperplasia (increase in number). It is well known that adipose tissue is influenced by lymph node secretion which induce on it TNF type I receptor. Therefore, factors secreted by adipocytes and macrophages such as TNF alpha and other inflammatory proteins are involved in infection, inflammation and cancer (6-11). In addition, macrophage colony-stimulating factor (MCSF) which up-regulated in adipose tissue is also important since it is a stimulator of fat cell proliferation and is expressed by human adipocytes. Fibroblast growth factor (FGF) stimulates the replication of adipocytes and inhibits their differentiation, while leptin may participate in adipose tissue through the stimulation of angiogenesis. In addition, insulin-like growth factor-I (IGF-I) locally produced may act in the development of adipose tissue. Insulin and IGF-1 are important growth factors, acting through the tyrosine kinase growth factor cascade in enhancing tumor cell proliferation.

Fiber diet speeds the movement of undigested foods, bacteria, etc. through the intestines and reduces the incidence of cancer. The combination of vitamin diet with high intake of fiber and n-3 fatty acids (fish oil) is linked to cancer prevention, and have beneficial effects: prolong life span, inhibits diseases of aging, prevents obesity, increases DNA repair processes, and modulates immune functions (12-17). Research studies reported that *n*-3 fatty acids potentially act to reduce the incidence of new infections and it has been shown that the stress response following application of endotoxin, IL-1, or TNF is reduced when the animals are pretreated with *n*-3 fatty acids.

Consumption of these products including cereal and legumes can also protect against cardio vascular diseases. Isoflavones have also been shown to reduce cardiovascular disease risk factors. In recent studies, isoflavones have favorable effects on plasma lipid and lipoprotein concentrations, specifically by significantly reducing low-density and very-low-density cholesterol concentrations (18-23). It also inhibits ultraviolet light-induced cutaneous aging in mice and photodamage in humans (24-29).

Fruits and vegetables in general are popularly consumed not only in fresh and frozen forms but also as processed and derived products including canned fruits, yogurts, beverages, and jams. There is a growing trend in the consumption of fruits and their products, and a large and growing body of studies has convincingly established the anticancer potential of singly purified constituents found in fruits and vegetables (30-35). These products contain high levels of a diverse range of phytochemicals which include phenolics such as anthocyanins (pigments), quercetin, proanthocyanidins (flavanol polymers common to green tea, grape skin and seeds, blueberries, cranberries, dark chocolate, etc.), tannins (found in strawberries, black raspberries, red raspberries, blackberries, some nuts, etc.), and other flavonoid-related molecules. All these compounds have a potential anticancer action, prevention, and therapeutic involvement. Several studies have indicated potential roles for dietary antioxidants in the reduction of degenerative diseases such as vascular dementia, cardiovascular disease, and cancer.

Some of the known chemopreventive agents present in fruits and vegetables include vitamins

A, C, and E and folic acid; calcium and selenium; β-carotene, α-carotene, and lutein; and phenolic molecules such as anthocyanins, flavonols, flavanols, etc. have been reported that directly influence the metabolism and have biological effects *in vivo*. The major structural classes of phenolics are flavonoids (anthocyanins, flavonols and flavanols), condensed tannins (proanthocyanidins), hydrolyzable tannins (ellagitannins and gallotannins), phenolic acids etc. (36-41). These phenolics exhibit potent antioxidative properties that is widely accepted, but their biological properties extend beyond antioxidation. In fact, phenolics also exhibit anti-inflammatory properties, are able to induce carcinogen detoxification enzymes, and modulate subcellular signalling pathways of cancer cell proliferation, apoptosis, and tumor angiogenesis. Recent studies have shown that some fruit extracts and their singly purified phenolic constituents inhibit cell proliferation, modulate cell cycle arrest, and induce apoptosis in cancer cells with little or no cytotoxic effects in normal cells.

Vitamins, fibers and n-3 fatty acids are also associated with a reduced risk of several other chronic diseases. Omega-3 polyunsaturated fatty acids (from fish oil-eicosapentaenoic acid) posses the most potent immunomodulatory activities and act upon intracellular signaling pathways, transcription factor activity and gene expression. Omega-3 fatty acids have anti-inflammatory properties and, therefore, might be useful in the management of aging, inflammatory and chronic diseases and cancer. These diseases are characterized by an increased level of interleukin-1 family members, and TNF-alpha, which are classic proinflammatory cytokines.

The dietary supplementation with fish oils in patients with chronic inflammatory diseases and cancer reveal significant benefit, including decreased disease activity and a decreased use of anti-inflammatory drugs (42-47). Recently, dietary components with antioxidant activity have received particular attention because of their potential role in modulating oxidative stress associated with aging, chronic conditions and cancer. Several studies have indicated potential roles for dietary antioxidants in the reduction of degenerative diseases such as vascular dementia, cardiovascular disease, and cancer. Scientific investigation of the biochemistry of the structure and the mode of action of antioxidant vitamins have cleared up many of the puzzles regarding their medical relevancy to cancer. Antioxidants may in theory neutralize the reactive species that are produced by neutrophilic leukocytes during phagocytosis and as part of normal cellular respiration (48-53). Anti-oxidants may modulate signal transduction and gene expression in immune cells.

Many different fields of research-biochemistry, general medicine, immunology and cancer, have converged on this problem and each has gained from its participation in studying vitamins. Therefore, the risk of cancer may be reduced by dietary antioxidant vitamins which can interfere in this process in several different ways. One way is to prevent chemicals from being transformed into cancer-causing substances, or carcinogens. Another way is to keep the immune system operating and optimally activating so it can seek out and destroy cancer cells. The immune system of advanced stage cancer patients is frequently suppressed. Poor immune function has been correlated with poor clinical outcome. Immunotherapeutic strategies have been also previously attempted in an effort to enhance immune function and improve survival. However, while diet includes substances that encourage the growth of cancer, it also offers protection from the disease. A diet low in fat and alcohol, and high in fiber and vitamins, and minerals, inhibits the initiation and discourages the promotion of several tumors. Nutritional deficiencies, as well as dietary excesses, develop an influence on cancer promotion. The risk for cancer is related to the overall quality of the diet. However, there are no dietary guidelines that will guarantee protection from developing tumor.

Aging leads to declining health and mortality however, the condition proceeds are not well understood. It has been reported that in the process of aging multiple cellular and molecular events malfunction, ultimately leading to various chronic diseases. Immunosenescence is defined as the state of disregulated immune function that contributes to the increased susceptibility to infection, cancer and autoimmune diseases observed in old organisms, including humans. T cells from aged individuals are impaired in their response to mitogens and in their cytokine production and age-related T cell-mediated immunity dysfunction has been implicated in the etiology of many of the chronic degenerative diseases of the elderly, including arthritis, autoimmune

diseases, increased susceptibility to infectious diseases and cancer.

Both innate and adaptive immune responses decline with advancing age and in particular NK and NKT cell cytotoxicity decreases in aging, as well as interferon-gamma (IFN-gamma) production by both activated cell types. Certainly, without doubt, there is a relationship between inflammation, chronic diseases, aging and cancer. Chronic disease usually become gradually visible in middle-age after long exposure to an unhealthy lifestyle involving tobacco use, alcohol use, lack of regular physical activity, consumption of a high-fat diet or red meat and stress. Therefore, analysis of the molecular mechanisms of aging and its associated chronic diseases represents a fundamental key in improving longevity.

Most chronic diseases have been linked to diet, therefore, they are preventable by adopting lifestyle changes such as eating nutritious foods, avoiding tobacco and being physically active (48, 54-59). Exercise has been shown to enhance *in vitro* macrophage antitumor cytotoxicity (60-64) and, in accordance with the immune surveillance theory, it is to be expected that moderate exercise protects against malignancy whereas exhaustive exercise is linked to increased cancer risk. Relatively low intake of fruit and vegetables is a risk factor for many of the most important chronic diseases (65-70), whereas greater consumption of natural products - including, spices, nuts, whole-grain cereals, legumes, fruits and vegetables is associated with a lower risk of many diseases (71-76). Chronic inflammation is one of the foremost risk factors for different types of cancer. Additional risk factors of this pathology are weight gain, obesity, estrogen secretion and an imbalance in the production of adipokines, such as leptin and adiponectin. Several products such as transcription factor, nuclear factor-kappaB (NFκB), inflammatory eicosanoids, reactive oxygen species and cytokines are thought to be involved in chronic inflammation-induced cancer. These important factors have an influence on inflammatory reactions in malignant tissue damage when their levels are abnormal. The biomarkers, in chronic diseases and cancer are: NF-κB and STAT3, inflammatory cytokines and chemokines, TNF-α, IL-1, IL-6, IL-8, IL-32, IL-33 and monocyte chemotactic protein, COX-2, and matrix metalloproteinases, C-reactive protein, adhesion molecules, VEGF, and other factors are common in most chronic diseases and cancer.(77-81).

Transcription factors such as NF-κB and AP-1 are the most important bioactive substances on the molecular mechanisms of the control of genes which in turn affect cellular metabolism. Members of the NF-κB family of transcription factors are evolutionarily conserved, central coordinators inflammatory responses and have a prominent role in innate and adoptive immunity.

NF-κB regulates a variety of molecules involved in host defense against pathogens and is constitutively active in most cancers, while in unstimulated cells, NF-κB remains inactive. NF-κB is activated by cigarette smoke, bacteria, viruses, stress, and other factors. Signal transducer and activator of transcription 3 (STAT3) regulates many critical functions in human normal and malignant tissues, such as differentiation, proliferation, survival, angiogenesis and immune function. Constitutive activation of STAT3 is implicated in a wide range of human cancers. Recently, STAT3 has been studied as a cancer therapeutic target. STAT3 is also one of the central regulators of inflammation, which helps in tumor growth and metastasis.

Recent data have demonstrated that AP1 transcription factor induction is essential for cancer promotion. AP-1 controls inflammation and its activity is induced by growth factors, cytokines, and oncoproteins. AP-1 is involved in proliferation, survival, differentiation, and transformation cells and can be activated by tumor promoter involving PKC phosphorylation.

It has been reported that, in cancer patients, IL-1β and IL-6 are associated with clinical features of the cachectic condition, such as weakness, loss of appetite, weight loss and sarcopenia (82-87). Several studies have shown an association between dietary factors and the incidence of cancer. Recently the calcium polyp prevention study demonstrated that calcium supplementation can reduce the incidence of the colon cancer, but the effect depends on vitamin D levels. The mechanisms of direct action of vitamin D on colonic epithelium include regulation of growth factor and cytokine synthesis and signalling, as well as modulation of the cell cycle, apoptosis, and differentiation. However, to clarify the effects of fruit and vegetable extracts in cancer prevention,

treatment and therapy, more studies are strongly recommended in this area of research.

REFERENCES

1. Halliwell B. Antioxidants in human health and disease. Annu Rev Nutr 1996; 16:33-50.
2. Negrev N, Tashev R, Radev R, Anogeianaki A, Ivanova M. Hormones of hypothalamic-pituitary-thyroid axis are significant regulators of synthesis and secretion of vitamin K-dependent plasma coagulation factors. J Biol Regul Homeost Agents 2011; 25:21-26.
3. Belizário JE. Pathogens and dead cells cooperate with cytokines in activating the innate and adaptive response. Eur J Inflamm 2011; 9:1-11.
4. Karam WG, Rady A, Abdallah Hajj Hussein I, et al. Cytology and clinical spectrum of sexually transmitted infections in Lebanese women as revealed by Pap smear: a cross-sectional study from 2002-2006. J Biol Regul Homeost Agents 2011; 25:453-9.
5. Kourelis TV, Moustakakis MN, Silk R, Pharm D, Boruchov A, Bilgrami SF. Decitabine for acute myeloid leukemia in a patient undergoing hemodialysis. Eur J Inflamm 2011; 9:289-92.
6. Hausman DB, DiGirolamo M, Bartness TJ, Hausman GJ, Martin RJ. The biology of white adipocyte proliferation. Obesity Reviews 2001: 2; 239-54.
7. Guarino F, Cantarella G, Caruso MA, Russo C, Mancuso S, Arcidiacono G, Cacciola RR, Bernardini R, Polosa R. Endothelial activation and injury by cigarette smoke exposure. J Biol Regul Homeost Agents 2011; 25:259-68.
8. Luppi F, Covi M, Velluti G, Spagnolo P, Fabbri LM, Richeldi L. Co-trimoxazole effect on human alveolar macrophages of AIDS patients. J Biol Regul Homeost Agents 2011; 25:461-4.
9. Melillo L, Valente D, D'Arena G, et al. Combination treatment of flag with non-pegylated liposomal doxorubicin (MYOCET(TM)) in elderly patients with acute myeloid leukemia: a single center experience. Int J Immunopathol Pharmacol 2011; 24:703-9.
10. Savastano S, Balato N, Gaudiello F, Di Somma C, Brancato V, Colao A, Ayala F, Tarantino G. Insulin-like growth factor-1, psoriasis, and inflammation: a ménage à trois? Eur J Inflamm 2011; 9:277-83.
11. Zanna P, Maida I, Turpin Sevilla MC, et al. Molecular characterization of novel melanoma cell lines. J Biol Regul Homeost Agents 2011; 25:239-47.
12. Fernandes G. Progress in nutritional immunology. Immunol Res 2008; 40(3):244-61.13. Sedriep S, Zhong K, Nakanishi K, et al. Advantage of carbonate- versus citrate-based alkalinization on bone metabolism in moderately exercising aged male rats fed an acidogenic diet. J Biol Regul Homeost Agents 2011; 25:341-9.
14. Zoccali C, Chichierchia G, Prencipe U, Nuzzo C, Anelli V, Ferraresi V. A greenstick osteoporotic tibial fracture while on chemotherapy in a 12-year-old girl with osteosarcoma of the knee: does a preventive role exist for agents that reduce iatrogenic bone loss and skeletal-related events? J Biol Regul Homeost Agents 2011; 25:131-5.
15. Riccioni G, Scotti L, Di Ilio E, Bucciarelli V, Ballone E, De Girolamo M, D'Orazio N, Martini F, Aceto A, Bucciarelli T. Lycopene and preclinical carotid atherosclerosis. J Biol Regul Homeost Agents 2011; 25:435-41.
16. Boyaci H, Pala A, Argun Bariş S, Başyigit I, Yildiz F, Ilgazli A. The effects of inhaled steroid and theophylline on systemic inflammation in COPD. Eur J Inflamm 2011; 9:241-8.
17. Sancilio S, Di Giacomo V, Quaglietta AM, et al. TRAIL promotes a pro-survival signal in erythropoietin-deprived human erythroblasts through the activation of an NF-κB/IκBα pathway. J Biol Regul Homeost Agents 2011; 25:375-86.
18. Anthony MS, Clarkson TB, Hughes Jr CL, Morgan TM, Burke GL. Soybean isoflavones improve cardiovascular risk factors without affecting the reproductive system of peripubertal rhesus monkeys. J Nutr 1996; 126:43-50.
19. Rosato E, Molinaro I, Pisarri S, Salsano F. Subcutaneous immunoglobulin therapy in a patient with myopathic dropped head syndrome and common variable immunodeficiency. J Biol Regul Homeost Agents 2011; 25:667-70.
20. Sedriep S, Xia X, Marotta F, et al. Beneficial nutraceutical modulation of cerebral erythropoietin expression and oxidative stress: an experimental study. J Biol Regul Homeost Agents 2011; 25:187-94.

21. Silambarasan G, Ramanathan T, Nabeel MA, Kalaichelvan VK, Kathiresan K, Balasubramanian T. Anti-inflammatory activity of the marine cyanobacterium *trichodesmium erythraeum* against carrageenan-induced paw oedema in wistar albino rats. Eur J Inflamm 2011; 9:53-56.
22. Trellakis S, Farjah H, Bruderek K, Dumitru CA, Hoffmann TK, Lang S, Brandau S. Peripheral blood neutrophil granulocytes from patients with head and neck squamous cell carcinoma functionally differ from their counterparts in healthy donors. Int J Immunopathol Pharmacol 2011; 24:683-93.
23. Kantar A, Carloni M, Kulkarni N, Fedeli D, Falcioni G. Retention of flunisolide in rat lungs after single inhalation. Eur J Inflamm 2012; 10:127-31.
24. Wei H, Saladi R, Lu Y, et al. Isoflavone genistein: photoprotection and clinical implications in dermatology J Nutr 2003; 133:3811S-19S
25. Buonsenso D, Pirronti T, Genovese O, Gargiullo L, Ranno O, Valentini P. Side effects of the immune system: lessons from tuberculosis-related immune reconstitution inflammatory syndrome. Eur J Inflamm 2012; 10:1-10.
26. D'Alimonte I, Nargi E, Mastrangelo F, et al. Vascular endothelial growth factor enhances *in vitro* proliferation and osteogenic differentiation of human dental pulp stem cells. J Biol Regul Homeost Agents 2011; 25:57-69.
27. Cassano N, Mastrandrea V, Principi M, Loconsole F, De Tullio N, Di Leo A, Vena GA. Anti-tumor necrosis factor treatment in occult hepatitis B virus infection: a retrospective analysis of 62 patients with psoriatic disease. J Biol Regul Homeost Agents 2011; 25:285-9.
28. Zhu J-S, Xu Z-P, Song M-Q, Zhang Q. Effect of oxymatrine combined with low dose 5-FU on lymphatic vessel and microvascular endothelial cell growth of gastric cancer in a severe combined immunodeficient mouse orthotopic implantation model. Eur J Inflamm 2011; 9:45-51.
29. Colombo D, Ammirati E. Cyclosporine in transplantation - a history of converging timelines. J Biol Regul Homeost Agents 2011; 25:493-504.
30. Block G, Patterson B, Subar A. Fruit, vegetables, and cancer prevention: a review of the epidemiological evidence. Nutr Cancer 1992; 18:1-29
31. Miliaras S, Anogeianaki A, Kefala V, Miliaras D, Kokaraki G, Koutsonikolas D, Liangouris J, Anogianakis G. The role of P53 and Bcl-2 proteins in 7, 12- dimethylbenz-(A)-anthracene-induced tumor growth. J Biol Regul Homeost Agents 2011; 25:359-64.
32. Veda P. Why are neutrophils polymorphonuclear? Eur J Inflamm 2011; 9:85-93
33. Patella V, Incorvaia C, Ricciardi L, Florio G, Saija A, Frati F, Gangemi S. The adhesion molecule ICAM-1 is overexpressed in patients with hymenoptera venom allergy and decreases after ultrarush venom immunotherapy. J Biol Regul Homeost Agents 2011; 25:465-8.
34. Nemeth C, Humpeler S, Kallay E, et al. Decreased expression of the melatonin receptor 1 in human colorectal adenocarcinomas. J Biol Regul Homeost Agents 2011; 25:531-42.
35. Krysiak R, Okopien B. Recurrent drug-induced insulin autoimmune syndrome in a patient with premature ovarian failure. Eur J Inflamm 2012; 10:121-5.
36. Malaveille C, Hautefeuille A, Pignatelli B, Talaska G, Vineis P, Bartsch H. Dietary phenolics as anti-mutagens and inhibitors of tobacco-related DNA adduction in the urothelium of smokers. Carcinogenesis 1996; 17(10):2193-200.
37. Ruiz-Pérez MV, Sánchez-Jiménez F, Quesada AR, Medina MA. A re-evaluation of the mitogenic effect of serotonin on vascular endothelial cells. J Biol Regul Homeost Agents 2011; 25:13-20.
38. Antonelli A, Fallahi P, Ferrari SM, Di Domenicantonio A, Moreno M, Lanni A, Goglia F. 3,5-diiodo-Lthyronine increases resting metabolic rate and reduces body weight without undesirable side effects. J Biol Regul Homeost Agents 2011; 25:655-60.
39. Maghbooli Z, Hossein-Nezhad A, Shirzad M, Behzadi H. The role of osteoprotegrin/ nuclear factor kb ligand in coronary collateral development Eur J Inflamm 2011; 9:57-64.
40. Cernysiov V, Mauricas M, Girkontaite I. Leucocyte infiltration in lymphoid organs and peritoneal cavity upon immunization: dependence on circadian rhythmicity and melatonin 24-h profile. Eur J

Inflamm 2011; 9:219-29.
41. Pompa G, Bignozzi I, Cristalli MP, Quaranta A, Di Carlo S, Annibali S. Bisphosphonate and osteonecrosis of the jaw: the oral surgeon's perspective. Eur J Inflamm 2012; 10:11-23.
42. Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. J Am Coll Nutr 2002; 21(6):495-505.
43. Mazzoccoli G. The timing clockwork of life. J Biol Regul Homeost Agents 2011; 25:137-43.
44. Pandolfi F, Cianci R, Casciano F, Pagliari D, De Pasquale T, Landolfi R, Di Sante G, Kurnick JT, Ria F. Skewed T-cell receptor repertoire: more than a marker of malignancy, a tool to dissect the immunopathology of inflammatory diseases. J Biol Regul Homeost Agents 2011; 25:153-61.
45. Binici DN, Güneş N, Kayataş K, Pişkinpaşa N. The effects of interferon-α2b on intestinal flora in peritoneal fibrosis. Eur J Inflamm 2011; 9:135-39.
46. Angelini A, Centurione L, Sancilio SA, Castellani ML, Conti P, Di Ilio C, Porreca E, Cuccurullo F, Di Pietro R. The effect of the plasticizer diethylhexyl phthalate on transport activity and expression of P-glycoprotein in parental and doxo-resistant human sarcoma cell lines. J Biol Regul Homeost Agents 2011; 25:203-211
47. Romano G, Barbagli G, Lazzeri M. The use of topical hyaluronic acid and silver sulfadiazine (Altergen®) in patients undergoing two-stage anterior urethroplasty with oral mucosal graft. Eur J Inflamm 2011; 9:175-183.
48. Pederson BK, Hoffman-Goetz L. Exercise and the immune system: regulation, integration, and adaptation. Physiol Rev 2000; 80(3):1055-81 .
49. Malerba M, Ragnoli B, Salameh M, Sennino G, Sorlini ML, Radaeli A, Clini E. Sub-clinical left ventricular diastolic dysfunction in early stage of chronic obstructive pulmonary disease. J Biol Regul Homeost Agents 2011; 25:443-51.
50. Rigante D, Zampetti A, Bersani G, et al. Serum interleukin-18 in children with Henoch-Schönlein purpura: a promising marker of disease activity. Eur J Inflamm 2011; 9:157-68.
51. Failli A, Consolini R, Legitimo A, Orsini G, Romanini A, Spisni R, Castagna M, Miccoli P. Evaluation of *in vitro* cytotoxicity of oxaliplatin and 5-fluorouracil in human colon cancer cell lines: combination versus sequential exposure. J Biol Regul Homeost Agents 2011; 25:575-88.
52. Di Carlo S, Perrotti V, Giganti M G, Piattelli A, Quaranta M, Modesti A, Bei R. Patients with periimplantitis, unlike those with a healthy peri-implant microenvironment, display antibodies to more than one heat shock protein (HSP 27, HSP 65 and HSP 90) linear epitope. Eur J Inflamm 2011; 9:257-267.
53. Masuelli L, Pompa G, Fabrizi M, et al. Histological evaluation of peri-implant soft tissues in immediately loaded implants featuring different implant-abutment connections: a preliminary study. Eur J Inflamm 2012; 10:91-98.
54. Ahlborg B, Ahlborg G. Exercise leukocytosis with and without beta-adrenergic blockade. Acta Med Scand 1970; 187:241-246.
55. Migliore A, Massafra U, Bizzi E, Giovannangeli F, Tormenta S. Intra-articular ultrasound-guided injection of Sinovial® forte 1.6% in patients affected by symptomatic hip osteoarthritis: effectiveness and safety in a large cohort of patients. Eur J Inflamm 2012; 10:71-79.
56. Aslani S, Hossein-Nezhad A, Mirzaei K, Maghbooli Z, Asgarabad SN, Karimi F. Tandem repeats of the CATT element of macrophage migration inhibitory factor gene may predict gestational diabetes mellitus severity. Eur J Inflamm 2011; 9:193-97.
57. Tarantino G, Colao A, Capone D, et al. Circulating levels of cytochrome c, gamma-glutamyl transferase, triglycerides and unconjugated bilirubin in overweight/obese patients with non-alcoholic fatty liver disease. J Biol Regul Homeost Agents 2011; 25:47-56.
58. Orciani M, Morabito C, Emanuelli M, Guarnieri S, Sartini D, Giannubilo SR, Di Primio R, Tranquilli AL, Mariggiò MA. Neurogenic potential of mesenchymal-like stem cells from human amniotic fluid: the influence of extracellular growth factors. J Biol Regul Homeost Agents 2011; 25:115-30.
59. Iezzi M, Quaglino E, Cappello P, Toto V, Sabatini F, Curcio C, Garotta G, Musiani P, Cavallo F. HCG hastens both the development of mammary carcinoma and the metastatization of HCG/LH and ERBB-2 receptor-positive cells in mice. Int J

Immunopathol Pharmacol 2011; 24:621-30.
60. Cannon JG. Exercise and resistance to infection. J Appl Physiol 1993; 74:973–981.
61. Mazurek U, Owczarek A, Nowakowska-Zajdel E, Wierzgoń J, Grochowska-Niedworok E, Kokot T, Muc-Wierzgoń M. Statistical analysis of differential gene expression in colorectal cancer using CLEAR-test. J Biol Regul Homeost Agents 2011; 25:279-83.
62. Belloli L, Carlo-Stella N, Ughi N, Marasini B. Cancer in Italian patients with systemic sclerosis. Eur J Inflamm 2011; 9:151-6.
63. Verratti V, Brunetti L, Tenaglia R, et al. Physiological analysis of 8-Iso-PGF2 alpha: a homeostatic agent in superficial bladder cancer. J Biol Regul Homeost Agents 2011; 25:71-76.
64. Petruzzi M, Campus G, Paparusso F, Lucchese A, Lauritano D, De Benedittis M, Serpico R. Analysis of plasma fibronectin levels in patients affected by oral lichen planus. Eur J Inflamm 2012; 10:45-50.
65. Block G, Patterson B, Subar A. Fruit, vegetables, and cancer prevention: a review of the epidemiological evidence. Nutr Cancer 1992; 18:1-29
66. Lo Russo L, Papale M, Perrone D, et al. Salivary proteomic signatures of oral squamous cell carcinoma. Eur J Inflamm 2012; 10:61-70.
67. Braido F, Schenone G, Pallestrini E, Reggiardo G, Cangemi G, Canonica GW, Melioli G. The relationship between mucosal immunoresponse and clinical outcome in patients with recurrent upper respiratory tract infections treated with a mechanical bacterial lysate. J Biol Regul Homeost Agents 2011; 25:477-85.
68. Zhang J, Zhu J-S, Zhou Z, Chen W-X, Chen N-W. Therapeutic effects of ethyl pyruvate on tumor growth and metastasis in a severe combined immunodeficiency mouse orthotopic implantation model. Eur J Inflamm 2012; 10:25-32.
69. Giordano N, Papakostas P, Pecetti G, Nuti R. Cytokine modulation by endothelin-1 and possible therapeutic implications in systemic sclerosis. J Biol Regul Homeost Agents 2011; 25:487-92.
70. Yang M-L, Lee J-C, Hsu C-H, Kao C-H. Intratonsillar abscess: diagnosis and treatment of a rare disease. Eur J Inflamm 2012; 10:117-19
71. Ames BN, Wakimoto P. Are vitamin and mineral deficiencies a major cancer risk? Nat Rev Cancer, 2002; 2:694-704
72. Impellizzeri D, Mazzon E, Di Paola R, et al. PBS-1086, a Rel inhibitor of NF-kB, ameliorates collagen-induced arthritis in mice. Eur J Inflamm 2012; 10:51-59.
73. Marotta F, Chui DH, Jain S, et al. Effect of a fermented nutraceutical on thioredoxin level and TNF-α signalling in cirrhotic patients. J Biol Regul Homeost Agents 2011; 25:37-45.
74. Valentini V, Terenzi V, Cassoni A, Bosco S, Brauner E, Shahinas J, Pompa G. Giant cell lesion or Langerhans' cell histiocytosis of the mandible? A case report. Eur J Inflamm 2012; 10:159-64.
75. Giganti MG, Minella D, Testa B, et al. A pilot study on the transcriptional response of androgen- and insulin-related genes in peripheral blood mononuclear cells induced by testosterone administration in hypogonadal men. J Biol Regul Homeost Agents 2011; 25:291-4.
76. Gambarini G, Al Sudani D, Di Carlo S, Pompa G, Pacifici A, Pacifici L, Testarelli L. Incidence and intensivity of postoperative pain and periapical inflammation after endodontic treatment with two different instrumentation techniques. Eur J Inflamm 2012; 10:99-103.
77. Prasad S, Sung B, Aggarwal BB Age-associated chronic diseases require age-old medicine: role of chronic inflammation. Prev Med 2012; 54(S):S29-37.
78. Mazzoccoli G, Sothern RB, De Cata A, Giuliani F, Fontana A, Copetti M, Pellegrini F, Tarquini R. A timetable of 24-hour patterns for human lymphocyte subpopulations. J Biol Regul Homeost Agents 2011; 25:387-95.
79. Antonelli A, Ferri C, Ferrari SM, et al. Hepatitis C is associated with high levels of circulating N-terminal pro-brain natriuretic peptide and interleukin-6. Eur J Inflamm 2012; 10:133-138.
80. Germano V, Picchianti Diamanti A, Ferlito C, Podestà E, Salemi S, Migliore A, D'Amelio R, Laganà B. Cyclosporine A in the long-term management of systemic lupus erythematosus. J Biol Regul Homeost Agents 2011; 25:397-403.
81. Testarelli L, Nocca G, Lupi A, Pacifici L, Pompa G, Vozza I, Gambarini G. Biocompatibility of root canal filling materials: differences between vitality and functionality tests. Eur J Inflamm 2012; 10:105-10

82. Scheede-Bergdahl C, Watt HL, Trutschnigg B, Kilgour RD, Haggarty A, Lucar E, Vigano A. Is IL-6 the best pro-inflammatory biomarker of clinical outcomes of cancer cachexia? Clin Nutr 2012; 31(1):85-8.
83. Battelli MG, Ravaioli M, Musiani S, Scicchitano V, Grazi GL, Bolognesi A. Increased serum level of xanthine oxidoreductase in liver transplanted patients. J Biol Regul Homeost Agents 2011; 25:77-84.
84. Trubiani O, Ballerini P, Murmura G, Pizzicannella J, Giuliani P, Buccella S, Caputi S. Toll-like receptor 4 expression, interleukin-6, -8 and CCL-20 release, and NF-KB translocation in human periodontal ligament mesenchymal stem cells stimulated with LPS-*P. Gingivalis*. Eur J Inflamm 2012; 10:81-89.
85. Pizzicannella J, Rabozzi R, Trubiani O, Di Giammarco G. Histidine-tryptophan-ketoglutarate solution helps to preserve endothelial integrity of saphenous vein: an immunohistochemical and ultrastructural analysis. J Biol Regul Homeost Agents 2011; 25:93-99.
86. Dell'Edera D, Guanciali Franchi P, Lioi MB, Epifania AA, Tinelli A, Monti Condesnitt V, Brizzi A, Malvasi A. Biochemical and molecular characterization of von Willebrand disease type 2N in a pregnant patient who gave birth under analgesia with remifentanil. J Biol Regul Homeost Agents 2011; 25:469-75.
87. Pacifici L, Meleo D, Pompa G, Pacifici A, Gambarini G, Testarelli L. Oral focal mucinosis of the tongue: a rare clinical case. Eur J Inflamm 2012; 10:111-15.