أ.د. ناصر غالي يوسف/كليه الطب

1. **Vitamin D attenuates myocardial injury following ischemia/reperfusion via induces ERK1/2.**

Abstract

Myocardial injury caused by ischemia followed by reperfusion mediates a complex series of inflammatory response that reduces the benefit of medical interventions, such as percutaneous coronary intervention, thrombolytic therapy, and coronary bypass surgery. Therefore, suppression of ischemia/reperfusion (I/R) -mediated myocardial injury is highly priority in clinical practice. The objective of this study was to investigate whether vitamin has some protective effect on heart after myocardial I/R, and the mechanistic pathway of this effect. Methods: Adult (4 - 6 months) male Albino-Webster mice were randomly divided into 2 groups: (1) sham-control group, (2) ischemia and reperfusion (I/R) operated group, (3) vehicle-treated group, and (4) vitamin D-treated group receiving vitamin D 20 mg/kg once daily shortly before I/R. 72h later, hemodynamics and Evan blue staining were applied to evaluate cardiac function and area at risk (AAR). ELISA technique applied to investigate myocardial and plasma expression of cytokines (IL-1β, IL-6, and TNF-α), chemokine (MCP-1), and cTn-I. In addition, the activity of pERK1/2 was analyzed by Western blot. Further, the ischemia changes and myocytes injured were examined by Hematoxylin and Eosin (H&E) stain. The results demonstrated that treatment of vitamin D markedly improved left ventricular function (LVF) in mice, and reduced plasma level of cTn-I as marker of cardiac injury. Moreover, the effects of vitamin D was associated with attenuations in both chemokine and cytokines expression following I/R, that accompanied by down-regulation of activation of ERK1/2 pathway. Conclusions: Together, the present study results show treatment with vitamin D was able to improve LV function after I/R, which was associated with reductions of inflammatory response and activity of pERK1/2 as mechanistic of its action.

2. **Notch1 ligand signaling pathway activated in cervical cancer: poor prognosis with high-level JAG1/Notch1. Arch Gynecol Obstet. 2015 Oct;292(4):899-904.**

Abstract

Notch signalings are regulated multiple cellular processes during cancer progression. We aimed to investigate the significance and prognostic value of expression of Notch1 and JAG1 in cervical cancer to determine whether they could serve as prognostic predictors. Methods/materials:The expression of Notch1/JAGD1 was investigated by real-time PCR, western blot assay and its association with overall survival of patients was analyzed by statistical analysis. Results: Notch1 and JAGD1 expression level were significantly elevated in cervical cancer in comparison to normal specimens and other types of Notch receptors and ligands. It is also proved that Notch1 and JAGD1 expression were to be associated with cervical cancer invasion, lymph node metastasis, and FIGO system. In addition, survival analysis proved that elevated Notch1 and JAGD1 expression were associated with poor overall survival of patients (P = 0.01, P = 0.02 log-rank test), respectively. Conclusions: The present data proved the over-expression of Notch1/JAGD1 and its association with tumor progression in human cervical cancer, which might be a potential valuable biomarker for cervical cancer and further studies need.

3. **Immunohistochemical determination of estrogen and progesterone receptors in breast cancer: pathological correlation and prognostic indicators. *American Journal of BioMedicine* 2014; 2(12):1229-1239.**

Abstract

Carcinoma of the breast is the most common malignancy of women globally and the incidence has more risen in recent years. The current study was conducted with the objective of assessing estrogen receptor (ER) and progesterone receptor (PR) reactivity patterns of mammary cancers and to evaluate their association with clinicopathological features. A total of 61 cases of breast carcinoma were examined retrospectively using immunostains for estrogen receptor (ER) and progesterone receptor (PR). Staining pattern and intensity were correlated with histological subtypes and nuclear grades of tumors. The left breast was more commonly involved (57%) and tumor size ranged from 0.5-13.0cm. The predominant morphology was infiltrating ductal carcinoma (85.3%). The majority of the cases presented as grade II (55.3%) lesions with tumor necrosis (70%) and lymph node involvement (71.3%). Positive nuclear staining for ER and PR was observed in 70.5% and 57.5 % of invasive carcinomas, respectively. In ER+ cases, fifty-five cases (90%) gave diffuse immunohistochemical reaction for ER; in the remaining 10%, a focal ER reaction was seen. In PR+ cases, 49 cases (80%) gave diffuse immunohistochemical reaction for PR and in remaining 20% of PR+ tumors, the reaction was heterogeneous. In ductal infiltrative carcinomas the percentage of cases showed ER+ nuclear labeling is higher than those in cases of infiltrative lobular carcinomas. Assessment of ER and PR as prognostic markers for the clinical management of breast cancer patients is strongly advocated to provide best therapeutic options.

4. **Mechanistic role of microRNA in breast cancer cell activity.** ***Pathophysiology of cell injury*** **2014; 2:.22-34.**

   Let-7 and its family members are highly conserved across species in sequence and function. They form an important class of regulators that participate in diverse biological functions including development, cell proliferation, differentiation, and apoptosis and, misregulation of let-7 leads to a less differentiated cellular state and the development of cell-based cancer. A growing body of evidence suggests that restoration of let-7 expression may be a useful therapeutic option in cancers, where its expression has been lost. Using breast cancer as a model, we have determined that breast cancer cells express high levels of the microRNA let-7, suggesting that let-7 is a marker for cancers.

5. **Fibronectin promotes migration and invasion of ovarian cancer cells through up-regulation of FAK–PI3K/Akt pathway.** ***Cell biology international*** **2013; 38 (1), 85-91.**

   Abstract

   Ovarian cancer is the leading cause of death from gynecological malignancy, and the fourth most common cause of cancer death among American women. This study investigates the mechanism of fibronectin (FN) in stimulating ovarian cancer cell migration and invasion through up-regulation of focal adhesion kinase (FAK) pathway. Human ovarian cancer cells (OVCAR-3, A2780/CP70) were cultured and treated with fibronectin (10 μg/mL). Trans-well plates were used to conduct the migration assay, real-time RT-PCR for FAK mRNA expression, and FAK siRNA for blocking FAK expression. Western blots were used for P-FAK, P-PI3K, and P-Akt analysis. Fibronectin-treated OVCAR-3, A2780/CP70 cells have increased ability to migrate and invade. It significantly promoted this behavior through the phosphorylation of FAK. The cell displayed significantly increased signaling regulation of the FAK pathway (p-PI3K/P-Akt). Furthermore, siRNA FAK-treated cells had reduced the levels of p-PI3K/P-Akt after induced by fibronectin. Our results indicate that FAK inhibition can suppress ovarian cancer cells migration and invasion through inhibiting downstream signaling (PI3K/AKT), which might be a therapeutic target or biomarker for ovarian cancer.

6. **Ghrelin reduces myocardial injury following global ischemia and reperfusion via suppression of myocardial inflammatory response.** ***American journal of BioMedicine*** **2013; 1(2):38-48.**

   Abstract

   Ghrelin is a small endogenous peptide principally produced and secreted by the gastric mucosa, with a major role in appetite and metabolism regulation. We hypothesized that anti-inflammatory therapy, as

produced by exogenous administration of ghrelin, would decrease the myocardial inflammatory response to global hypothermia I/R, thereby affording myocardial protection. Heterotopic cervical heart transplantation that allows to subject donor hearts to global hypothermic ischemia and blood reperfusion, which very closely stimulates I/R conditions associated with cardiac surgical operations. Ghrelin administration prior to blood reperfusion significantly decreased serum concentrations of cTn-I versus animals subjected I/R alone, with a significantly attenuated VCAM-1 expression in I/R animals pre-treated with ghrelin. The tissue concentrations of pro-inflammatory cytokines (IL-6, IL-1β, and MCP-1) were ameliorated by the administration of ghrelin prior to reperfusion versus the concentrations observed in animals subjected to I/R alone. Significantly fewer monocytes in the tissue sections of I/R+ghrelin animals versus those subjected to I/R alone. Exogenous ghrelin administration prior to reperfusion of an ischemic heart resulted in a significant reduction in myocardial injury as measured by cTn-I. The reduced myocardial injury was accompanied by an attenuated tissue expression of several pro-inflammatory mediators, including VCAM-1, IL-6, IL-1β, and MCP-1.

7. **Enhanced monocyte chemoattractant protein-1 production in aging mice exaggerates cardiac depression during endotoxemia.** ***Crit Care*** **2014; 18:527.**

Abstract

Endotoxemia and the systemic inflammatory response syndrome have a significant impact on post-surgery outcome, particularly in the elderly. The cytokine response to endotoxin is altered by aging. We tested the hypothesis that vulnerability to endotoxemic cardiac depression increases with aging due to age-related augmentation of myocardial inflammatory responses. METHODS: Adult (4 to 6 months) and old (20 to 22 months) C57/BL6 mice were treated with endotoxin (0.5 mg/kg, iv). Left ventricle (LV) function was assessed using a microcatheter system. Chemokines and cytokines in plasma and myocardium were analyzed by enzyme-linked immunosorbent assay (ELISA). Mononuclear cells in the myocardium were examined using immunofluorescence staining. RESULTS: Old mice displayed worse LV function (cardiac output: 3.0 ± 0.2 mL/min versus 4.4 ± 0.3 mL/min in adult mice) following endotoxin treatment. The exaggerated cardiac depression in old mice was associated with higher levels of monocyte chemoattractant protein-1 (MCP-1) and keratinocyte chemoattractant (KC) in plasma and myocardium, greater myocardial accumulation of mononuclear cells, and greater levels of tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β) and interleukin 6 (IL-6) in plasma and myocardium. Neutralization of MCP-1 resulted in greater reductions in myocardial mononuclear cell accumulation and cytokine production, and greater improvement in LV function in old mice while neutralization of KC had a minimal effect on LV function. CONCLUSION: Old mice have enhanced inflammatory responses to endotoxemia that lead to exaggerated cardiac functional depression. MCP-1 promotes myocardial mononuclear cell accumulation and cardiodepressant cytokines production, and plays an important role in the endotoxemic cardiomyopathy in old mice. The findings suggest that special attention is needed to protect the heart in the elderly with endotoxemia.

8. **A TLR4-MCP-1-macrophage IL-18 cascade plays a major role in myocardial injury and cardiac dysfunction after permanent ischemia.** ***Journal of Surgical Research*** **2011; 165 (2): 265-266.**

Abstract

Myocardial ischemia induces an inflammatory response involving an up-regulated chemokine expression and macrophage (Mf) accumulation. Toll-like receptor 4 (TLR4) has been linked to post-ischemic myocardial injury, and it mediates myocardial expression of MCP-1, a key chemokine for Mfaccumulation, after ischemia. However, the role of Mf in post-ischemic myocardial injury and heart failure is not well understood. We hypothesize that TLR4 mediates myocardial injury through up-regulation of chemokine expression and macrophage accumulation.

9. **Aging augments myocardial inflammatory response to ischemia and reperfusion: an obligatory role of TLR4. *Shock* 2012; 37: Issue - p 31–119.**

Abstract

Increasing number of cardiac surgery with obligatory global myocardial ischemia and reperfusion (I/R) is performed in patients 65 years or older. Aging is a well-known risk factor of exaggerated post-I/R myocardial injury. Thus, understanding of the mechanism of I/R injury in aging heart is important for cardiac protection in older patients undergoing cardiac surgery. Although the myocardial inflammatory response contributes to the mechanism of I/R injury, the effect of aging on myocardial inflammatory response to I/R remains to be characterized. This study tested the hypothesis that aging augments the myocardial inflammatory response to I/R through TLR4.Methods and Results: We examined the myocardial inflammatory response to global I/R using a mouse heart transplant model. We found that myocardial production of MCP-1 following I/R was increased in hearts of old mice (18–22 months old) compared to those of adult mice (4–6 months old). Elevated myocardial levels of MCP-1 in aging hearts were associated with exaggerated mononuclear cell infiltration and troponin-I release. MCP-1 KO reduced myocardial mononuclear cell infiltration and troponin-I release caused by global I/R. While myocardial TLR4 levels were not significantly increased in aging hearts, TLR4 deficiency attenuated myocardial MCP-1 production in aging hearts following I/R, resulting in reduced age-related differences in myocardial mononuclear cell infiltration and troponin-I release.Conclusions: These results demonstrate that aging augments the myocardial inflammatory response to I/R in mice and that myocardial TLR4 is obligatory in the mechanism underlying the augmented inflammatory response to I/R in aging hearts.

10. **Expression of Human Interleukine-37 Protects Mouse Heart Against Ischemic Injury Through Suppression of Monocyte Chemoattractant Protein-1-Mediated Mononuclear Cell Accumulation. *Circulation,* 2011; 124: A8603**.

11. **Novel Toll-like receptor-4 deficiency attenuates trastuzumab (Herceptin) induced cardiac injury in mice. *BMC Cardiovasc Disord* 2011; 11: 62.**

Abstract

Cardiac inflammation and generation of oxidative stress are known to contribute to trastuzumab (herceptin) induced cardiac toxicity. Toll-like receptors (TLRs) are a part of the innate immune system and are involved in cardiac stress reactions. Since TLR4 might play a relevant role in cardiac inflammatory signaling, we investigated whether or not TLR4 is involved in trastuzumab induced cardiotoxicity. Methods: Seven days after a single injection of herceptin (2 mg/kg; i.p.), left ventricular pressure volume loops were measured in HeN compotent (TLR4+/+) and HeJ mutant (TLR4-/-) treated with trastuzumab and control mice. Immunofluorescent staining for monocyte infiltration and analyses of plasma by (ELISAs) for different chemokines including: MCP-1and tumor necrosis factor-α (TNF-α), Western immunoblotting assay for ICAM-1, and used troponin I for cardiac injury marker. Results: Trastuzumab injection resulted in an impairment of left ventricular function in TLR-4 competent (HeN), in contrast TLR4-/- trastuzumab mice showed improved left ventricular function EF%, CO; $p < 0.05$, attenuation of mononuclear cell infiltration in TLR4 -/-; $p < 0.05$ vs.TLR-4 competent (HeN), reduced level of cytokines TNF-α, MCP-1 and ICAM-1 expression in TLR4-/-, marked reduction of myocardial troponin-I levels in TLR4-deficient mice. Data are presented as means ± SE; $n = 8$ in each group $p < 0.05$ vs.TLR-4 competent (HeN). Conclusions: Treatment with trastuzumab induces an inflammatory response that contributes to myocardial tissue TLR4 mediates chemokine expression (TNF-α, MCP-1and ICAM-1), so in experimental animals TLR4 deficiency improves left ventricular function and attenuates pathophysiological key mechanisms in trastuzumab induced cardiomyopathy.

12. **Ghrelin Reduces Myocardial Injury Following Global Hypothermic Ischemia/Reperfusion Via Suppression of The Myocardial Inflammatory Response.** ***Journal of Surgical Research*** **2011; 165 (2): 0022-4804.**

Abstract

During most cardiac surgical operations, the heart must endure the obligatory injuries of hypothermic ischemia followed by blood reperfusion. Mechanisms of inflammation are recognized to contribute to injuries of ischemia/reperfusion (I/R). However, effective anti-inflammatory treatment for myocardial protection is currently lacking. Ghrelin is an endogenous peptide, principally produced by the gastric mucosa. It has recently been demonstrated to have potent anti-inflammatory actions.

13. **Prognostic impact of expression Notch-1 in invasive bladder transitional cell carcinoma.** ***J Clin Oncol*** **2012; 30:(suppl 5; abstr 299)**

Abstract:

Background: Notch signal pathway plays a fundamental role in mediator of tumorigenesis, either as a tumor promoter or suppressor, depending on cellular context and expression levels; we investigated the prognosis of invasive bladder transitional cell carcinoma patients with over-expression of Notch-1. Methods: Tumor tissue samples from 78 resected patients with invasive bladder transitional cell carcinoma were obtained, and immunohistochemistry was used to evaluate the expression of the molecular markers Notch-1 and Jagged-1. To further confirm the immunohistochemical results tissue samples were subjected to RT-PCR and Western blot analysis, staining evaluation results were analyzed statistically in relation to various clinicopathological characters. Kaplan–Meier and Cox proportional hazards regression methods were used to assess associations of Notch-1 expression with invasive bladder transitional cell carcinoma survival. Results: Survival time in patients with high expression of Notch-1 and Jagged-1 was significantly shorter than that in patients with low expression p=0.009 and more recurrence p=0.01, in multivariate analysis, Notch1 expression was proved to be an independent predictor of prognosis; (hazard ratio Notch-1 was 1.93 (95% CI, 1.02-3.03; P =0.014), expression was not related to patient sex or age. Conclusions: Notch-1 expression is associated with tumor progression, indicating that Notch-1 may be involved in the carcinogenesis and progression of invasive bladder transitional cell carcinoma. These findings also suggest that Notch-1 may be a potential diagnostic marker and therapeutic target in patients.

14. **The role of IL-23 in regulating metastatic prostate cancer through STAT-3/ROR-gamma signaling.** ***Journal of clinical oncology*** **2013;32:4.**

Abstract:

Background: Interleukin-23 (IL-23) plays an important role in expanding the Th17 cell population and induce signal transducer and activator of transcription 3 (STAT-3) to up-regulates the expression of Retinoic Acid Receptor-Related Orphan Receptor Gamma-T (ROR-gamma). STAT-3 regulates the expression of a variety of genes in response to cellular stimuli, and thus plays a key role in cell growth and apoptosis. Furthermore, recent studies identified a critical role for ROR-gamma in lineage specification of uncommitted CD4+ T helper cells into Th17 cells. The goal of this study is to evaluate prospectively the prognostic importance of circulating IL-23 in patients with metastatic prostate cancer through downstream signaling. Methods: The study involved 140 men diagnosed with stages I to IV prostate cancer and 120 healthy controls. IL-23 serum concentration measure by a quantitative enzyme immunoassay technique associated with clinical-pathological variables. Blocking IL-23 with anti-p19 Ab in mice inoculation with two types of metastatic prostate cancer cell lines (LNCaP and DU-145) to study the pathway of IL-23 in vivo by using western blot and real-time RT-PCR. Results: We found a statistically significant higher systemic IL-23 level in the metastatic group in comparison with non-metastatic group (19.32±5.35 pg/ml vs. 7.25±3.42 pg/ml, $p<0.05$). Patients with shorter overall survival presented higher IL-23 levels, suggesting a negative prognostic correlation. Furthermore, systemic delivery of blocking Abs directed against IL-23 completely inhibited STAT3/ROR-gamma levels in

mice. Conclusions: These results demonstrate that STAT3/ROR-gamma, is a downstream mediator for IL-23–induced prostate metastasis in murine mice. IL-23 may represent an attractive therapeutic target or a biomarker in metastatic prostate cancer by blocking downstream effects. However, further studies are needed in larger samples to better investigate the implications of IL-23 in prostate cancer.

15. **Differences in the survival rate between premenopausal and postmenopausal women with lung cancer: US SEER database.** ***American journal of BioMedicine*** **2014; 2(3):315–322.**

Abstract

In the United State, lung cancer remains the leading cause of cancer death in both men and women. Several reports have suggested a role for estrogens in the development and/or progression of lung cancer, especially in women. Data from the national SEER registry between the years of 1990-2011 was analyzed, women between the ages 31-50 years old were chosen as representative of the premenopausal group (n=1595) and 51-70 year-old women represented the postmenopausal group (n=7075) as defined by the American College of Obstetricians and Gynecologists. For comparison, men were divided into two categories: younger men (n=2233) aged 31- 50 years and older men (n=10908) aged 51-70 years. Survival rates were analyzed by Kaplan-Meier method and compared by Z-test through SEER*Stat software version 7.0.9. The adenocarcinoma had a significant difference between premenopausal and postmenopausal groups (62% vs. 51%) respectively. Furthermore, the survival rate in premenopausal inferior to postmenopausal women in both SCC and BAC $P<0.05$. Premenopausal women more commonly underwent curative surgery, 42%, and 19% of postmenopausal women treated palliative. Additionally, for every stage of disease, 55% of postmenopausal women have radiotherapy. The results suggest varying estrogen effects between the histology sub-types of NSCLC and support clinical strategies need to block the ER pathway for the treatment of NSCLC.

16. **Over expression of Notch-1 induced tamoxifen resistance through down regulation of ESR1 in positive estrogen receptor breast cancer.** ***J Clin Oncol*** **2012; 30: (suppl; abstr e11046).**

Abstract:

Background: Tamoxifen is one of the most widely used drugs in the treatment of estrogen-receptor positive breast cancer, and acquired resistance to tamoxifen during treatment are largely unknown and recent research showed that lower levels of ESR1 associated with tamoxifen resistance in ER-positive breast tumors, from other hand highly expression of Notch-1 and/or Jagged-1 has negative prognostic significance in breast cancer, in this study we show the cross-talk between Notch and the lower levels of ESR1 estrogen receptor positive breast cancer. Methods: A retrospective study with clinico-pathological analysis of 195 patients had ER-positive breast cancer used tamoxifen as an adjuvant systemic therapy, gene expression profiling of paraffin-embedded tumors for ESR1, Real-time PCR and Western blot analysis were performed to detect Notch-1/Jagged-1. Results: From 195 patients 32% had tamoxifen resistance which related with lower levels of ESR1 expression ($P=0.019$) and there was, a highly significant association of over expression Notch1 protein with the lower levels of ESR1 ($P=0.006$). Conclusions: The results from this study demonstrate for the first time that Notch-1 regulate levels of ESR1 in ER-positive breast cancer, and partly responsible for tamoxifen resistance, the Notch signaling pathway may be a potential therapeutic target beside current breast cancer therapy and need further investigation to know the mechanism of this pathway.

17. **Novel therapeutic role of siglec-E in down-regulation TLR4-mediated inflammatory response after global myocardial ischemia and reperfusion.** ***Cardiovascular research*** **2014; 103:s90. doi: 10.1093/cvr/cvu091.169**

Abstract

Myocardial ischemia and reperfusion (I/R)-induced tissue injury involve a robust inflammatory response. Our previous study found that TLR4-mediated MCP-1 production and monocytes accumulation contributes to the mechanism of myocardial injury following global myocardial I/R. Sialic acid binding Ig-like lectin receptors (Siglecs) have been implicated in the control of monocyte responses. We test the hypothesis that Siglec-E down-regulated TLR4-mediated inflammatory response following global myocardial I/R. Synergeneic heterotopic abdominal heart transplant was perfomed in mice strain (WT, TLR4-/-, Siglec-E-/-) for global myocardial I/R by using microsurgical techniques for vascular anastomoses. The donor's thoracic aorta was anastomosed end-to-side to the recipient's infrarenal abdominal aorta, and the donor's pulmonary artery was anastomosed to the recipient's inferior vena cava. Donor hearts were subjected to 4 h global ischemia followed by 4 h reperfusion. Our result shows that Siglec-E-/- donor heart significantly exaggerated monocyte/neutrophil recruitment myocardial injury and increased the inflammatory response (cytokines and chemochines). Interestingly the TLR4-activation signaling was significantly prevented by Siglec-E. We concluded that the use of Siglec-E might serve as a therapeutic clinical option in the treatment of cardiac injury induced by global myocardial I/R.

18. Vitamin E and Telmisartan attenuates doxorubicin induced cardiac injury in rat through down regulation of inflammatory response. *BMC Cardiovascular Disorders* 2012, 12:63.

Abstract

The importance of doxorubicin (Dox), as a potent antitumor antibiotic, is limited by the development of life-threatening cardiomyopathy. It has been shown that free radicals are involved in acute doxorubicin-induced toxicity. The aim of this study was to determine the protective effect of vitamin E and telmisartan in acute doxorubicin induced cardiotoxicity. Methods: Thirty two male Sprague - Dawly rats were involved in this study and were randomly separated into 4 groups, eight rats in each group, one group received normal saline I.P as control and second group received doxorubicin 20 mg/kg I.P, the other two groups also received doxorubicin 20 mg/kg I.P as single dose after seven cumulative doses (for seven days) of vitamin E (100 mg/kg) and telmisartan (1 mg/kg) respectively. Immunofluorescent staining for monocytes infiltration and analyses of plasma by (ELISAs) for MCP-1and troponin I. Western immunoblotting assay for ICAM-1, while left ventricular function was analyzed by microcatheter, also estimated the level of oxidative stress parameters (MDA and Catalase) and cardiac enzymes activities (CK-MB and LDH) before starting drugs treatment and after treatment period by 48 hours. Results: The immunofluorescent staining showed that administration of vitamin E and telmisartan are attenuated of mononuclear cell infiltration; ($p < 0.05$ vs. Dox group), also reduced the level of chemokines MCP-1 and ICAM-1 expression compared with Dox group only, and there is marked reduction of myocardial troponin-I levels with improved LV function in vitamin E and telmisartan treated group. Doxorubicin treatment increased MDA, LDH, CK-MB levels significantly ($P < 0.01$), and were counteracted by administration of vitamin E and telmisartan, but did not significantly affect serum catalase activity. Conclusions:Antioxidant effect (Vitamin E and telmisartan) have been shown to decrease doxorubicininduced cardiotoxicity.

21. **Expression of IL-32 modulates NF-κB and p38 MAP kinase pathways in human esophageal cancer. *Cytokine.* 2013;61(1):223-7.**

Abstract

Esophageal cancer is the seventh leading cause of cancer death in males in USA, and there is a strong link has been demonstrated between inflammation and esophageal cancer, interleukin (IL)-32 is a recently described pro-inflammatory cytokine characterized by the induction of nuclear factor NF-κB activation, the p38MAPK also plays an important role in key cellular processes related to inflammation and cancer. We investigated whether the IL-32 expression may be involved in esophageal carcinogenesis through modulates the activity of NF-κB and p-p38 MAPK. METHOD: Malignant esophageal tissue and blood

samples were obtained from 65 operated untreated patients, normal samples was obtained from 35 patients operated for other reasons as control. IL-32 expression visualized by immunohistochemistry, Real time RT-PCR for IL-32 mRNA expression, NF-κB phosphorylation and phosphorylated p38mapk were analyzed by immunoblotting, ELISA for further detection IL-32 and cytokines (TNF-α, IL-1β, IL-6 and IL-8) concentration in the patient's sera. RESULTS: IL-32 expression was increased in immunohistochemical staining for malignant esophageal tissue and it's correlated with the relative expression level of IL-32 mRNA P=0.007, the P-NF-κB level elevated in tumor tissue compared with control and no difference in the total NF-κB level P=0.003 while the IL-32 up-regulated the P-pNF-κB in the esophageal tumor P=0.005. There is increase in p-p38MAPK activation underlying IL-32 expression in tumor P=0.004, but no change in total p38 MAPK in malignant esophagus. The plasma level of IL-32 expression was increased in malignant esophageal patients P=0.01, with increased in the levels of the cytokines TNF-α, IL-6, and IL-1βP<0.05. CONCLUSIONS: Understanding the pathway of IL-32 expression to stimulate the secretion cytokines via the activation of NF-κB and up-regulation of p-p38MAPK may or may not prove to be a therapeutic target, or a biomarker, and future studies will finally answer this hypothesis generated.

22. **Role of NF-κβ and oxidative pathways in atherosclerosis: Cross-talk between dyslipidemia and Candesartan.** ***Cardiovasc Ther.*** **2013 Apr 9. doi: 10.1111/1755-5922.12033.**

Purpose

The objective of this study is to assess the effect of the candesartan on the progression of atherosclerosis through the downregulation of NF-κβ and interference with oxidative pathway. Methods: Twenty-four rabbits were assigned to three groups: control group fed normal diet; induced untreated group fed 1% cholesterol diet; and treated candesartan group also fed 1% cholesterol diet. Plasma lipid profiles were measured, and ELISA for plasma cytokines and chemokine was performed. Analyses of NF-κβ and VCAM-1 were performed using Western blotting with RT-PCR for NF-κB activity at mRNA. Doppler ultrasound was used to evaluate aortic intima-media thickness, and atheroma was detected by H&E staining. Immunofluorescent staining was performed to confirm accumulation of monocytes and PMNs. Results: Candesartan markedly reduced the levels of the plasma lipid profile including total cholesterol [TC], triglycerides [TG], and LDL-C, while significantly elevating levels in the plasma HDL-C, in addition to reducing cytokine (TNF-α, IL-6, IL-1β) and chemokine levels (MCP-1). Also, it decreased the aortic malondialdehyde (MDA) concentration and elevated the aortic glutathione (GSH) level compared with untreated animals ($P < 0.05$). The triplex Doppler ultrasound study confirmed that the candesartan attenuated intima-media thickness at 6 months of study. All candesartan-treated rabbits showed significantly attenuated atherosclerosis lesions with reduced accumulation of monocytes and had significantly reduced VCAM-1 expression and NF-κβ activity. Conclusion: Candesartan retards the progression of atherosclerosis via interference with NF-κβ and oxidative pathways.

23. **Letrozole versus anastrozole in postmenopausal women with chemotherapy-refractory negative HER-2 metastatic breast cancer: a randomised, multicentre, open-label, non-inferiority phase 3 study. American journal of BioMedicine.**

Abstract

Breast cancer is the most common form of cancer affecting elderly women in worldwide, although the usually reported incidence of breast cancer is close to 50% in women 65 years or older, reaching 47% after 70 years in the updated Surveillance, Epidemiology, and End Results (SEER) database. Third-generation aromatase inhibitors are being considered as an alternative to tamoxifen as first-line therapy for advanced breast cancer. These newer therapies are more expensive, and will gain greater acceptance if they can demonstrate cost-effectiveness. We assessed the efficacy and toxicity of letrozole versus anastrozole in these patients. For this randomized, open-label, phase 3 head-to-head study, we enrolled patients (from centers in North America, Europe, Africa, Australia and Asia) aged 65 years or older with chemotherapy-refractory metastatic breast cancer, ECOG performance status of 2 or less. Using a computer-generated randomization sequence, we assigned patients to receive letrozole or anastrozole. The

primary endpoint was overall survival assessed for non-inferiority (retention of ≥50% of the letrozole treatment effect; historical hazard ratio [HR] for letrozole vs best anastrozole 0·55). The data from this study show that letrozole is at least as effective as anastrozole as first-line therapy of metestatic breast cancer in postmenopausal women. A total of 56.7% of patients in the letrozole group and 41.3% of patients in the anastrozole group gained clinical benefit from treatment.

24. **Crucial role of TLT2 ligation to exaggerated interleukine-8/macrophage inhibitory protein-2 following myocardial ischemia in rat.** ***Cardiovascular research*** **2014; 103: S123-S123.**

25. **Critical role IL-37 to ameliorate endotoxemic cardiac depression in aging mice: a critical role of suppression cardiodepressant cytokines.** ***Cardiovascular research*** **2014; 103: S92-S92.**

26. **Herbal extract targets in Leishmania tropica.** ***Journal of Parasitic Diseases;*** **2014**

Abstract

The present study aims to investigate the effect of some herbal extract such as phenolic compounds on the viability of Leishmania tropica promastigotes in vitro. Four tested chemical agents (caffeic acid (CA), ferulic acid (FA), syringic acid (SA) and 4-hydroxybenzoic acid (4-HBA)) were used in this study. The viability of Leishmania tropica promastigotes was investigated under five different concentrations (10, 15, 20, 25 and 30 mg/ml) of each agent after (72 h). CA was the most active agent on the promastigotes viability after 72 h exposure to 30 mg/ml concentration so that the parasiticidal effect reach (53 × 104) promastigote/ml. FA is the second agent in parasiticidal effect that parasiticidal effect reach to (50 × 104 promastigote/ml) at a concentration (30 mg/ml), 4-HBA is the third agent in parasiticidal effect that reach to (48 × 104 promastigote/ml) at a concentration (30 mg/ml), SA is the weakest agent in parasiticidal activity that reach to (44 × 104 promastigote/ml) at a concentration (30 mg/ml). It can be concluded that (CA, FA, SA and 4-HBA) possess acidal effect on the Leishmania tropica promastigotes in vitro.