Investigational
Medicinal Chemistry & Pharmacology

Review Article Open Access

Interleukin-8 in Tissue Injury and Inflammation

Nathan Isaac Dibal*[1], Sani Hyedima Garba[1], Tamunotonye Watson Jacks[1]

Abstract

Background: Inflammation is a vascular or tissue response that occurs as a result of infection, tissue injury or irritation. The review is aimed at describing the functions of Interleukin-8 (IL-8) and its role in tissue injury and inflammation.

Methods: Articles were searched from the internet using the following search words; Inteluekin-8, IL-8 structure and functions, role of IL-8 in tissue injury, inflammation and inflammatory response, IL-8 in hepatic, nervous, cardiac and kidney injuries.

Results: The result showed that Cytokines are multifunctional proteins that play an important role in cell-to-cell communication, they regulate a number of physiological and pathological processes, such as inflammation, development, differentiation, and cell death. IL-8 is a cytokine that plays an important role in autoimmune disorder and inflammatory diseases, it is regulated by several factors such as steroid hormones, inflammatory signals and environmental stress. IL-8 levels have been reported to significantly increase in serum, plasma, cerebrospinal fluid, gastric juice and urine of patients with brain, cardiac, renal, gastric and hepatic injuries.

Conclusion:IL-8 effect is localized to the damage cells or tissues and are specific to injury type. Therefore, it is believed to have a role in the pathogenesis of certain type of disease conditions and traumatic injuries.

Keywords: Cytokines; chemokines; inflammatory diseases; damage cells.

Background

Inflammation is a vascular or tissue response that occurs as a result of infection, tissue injury or irritation. Inflammatory response is mediated by endogenous substances leading to the accumulation of fluid and leukocytes within tissues [1, 2]. Signs of inflammation include redness and warmth, swelling, pain and tenderness. The endogenous substances that mediate inflammation are increasingly expressed with the progress of inflammation from acute to chronic; they consist of inflammatory proteins such as cytokines, adhesion molecules and receptors [3]. When there is tissue injury, local macrophages react by producing cytokines that stimulates the blood vessels and attract large number of leukocytes to migrate from blood vessels into tissues. These leukocytes phagocytose foreign cells and secrete substances that kill pathogens and damage cells [4]. Cytokines are small proteins released by immune

*Correspondence: nathandibal@unimaid.edu.ng *(Nathan Isaac Dibal)*
Department of Human Anatomy, College of Medical Sciences, University of Maiduguri PMB 1069 Maiduguri, Borno State, Nigeria.

Citation on this article: Dibal NI, Garba SH, Jacks TW. Investigational Medicinal Chemistry and Pharmacology (2018) 1(1):1.

cells and brain parenchymal cells that influence the interaction and communication between cells. They are released via autocrine, paracrine or endocrine actions. Historically, cytokines have been defined as lymphokines when secreted by lymphocytes, monokines when secreted by monocytes, chemokines (having chemotactic/attractant properties) and interleukins (cytokines made by one leukocyte that act on other leukocytes) [5]. Pathological changes can be determined in tissues of laboratory animals because they can be sacrificed and the desired tissues processed for either light or electron microscopy. Pathological changes in tissues of living animals or humans can only be determined through biopsy. Because of the inability to get some tissues without surgery (liver, kidney and pancrease), serum or plasma levels of either biochemical markers, oxidative stress markers or tissue necrosis factors (TNF) are used to estimate pathological changes within tissues. While some markers like albumin and creatinine are tissue specific, others like TNF and Interleukin-8 (IL-8) are elevated in serum or plasma in all types of tissue injury.

Damage-associated molecular patterns (DAMPs) and Pathogen-associated molecular patterns (PAMPs) trigger the inflammatory response tissue damage and infection respectively. Infection can often lead to tissue damage and vice versa, thus the activation of DAMPs and PAMPs usually co-occur. These in turn activate pattern recognition receptors (PRRs) such as TLRs, which induce the transcription of proinflammatory cytokines by factors such as NF-kB and MAPKs, which can then promote the further transcription of cytokines. IL-1β is produced in response to PAMPs via NOD-like receptors (NLRs), which ultimately activate caspase-1, resulting in the cleavage of Pro IL-1β to mature IL-1β [6] (Figure 1).

Interleukin-8 (IL-8) is a pro-inflammatory CXC chemokine (chemotactic cytokines) that play important role in autoimmune disorder and inflammatory diseases like rheumatoid arthritis, abdominal aortic aneurysms, angiogenesis, gastritis and inflammatory bowel disease [7]. IL-8 was discovered in 1987 as a neutrophil-activation cytokine but is now considered as neutrophil activation factor, monocyte derived chemotactic factor, mitogen-stimulated human leukocyte protein, and/or T cell chemotactic factor. The crystalline structure of human IL-8 (Figure 2) corresponds to a dimeric molecule which is composed of a six-stranded β-sheet and two parallel α-helices [8]. IL-8, TNF-α and other cytokines are released by phagocytes, monocytes, fibroblasts, endothelial cells, keratinocytes and other cells and tissues that are exposed to infectious agents, toxins, radiation and trauma. They are considered as the most important tissue-derived chemo-attractants for neutrophils. Chemokine proteins are divided into CXC and CC based on the position of the first two cysteines; either separated by one amino acid or in an adjacent position. CXC chemokines usually exhibit chemotactic activities against neutrophils and lymphocytes and are clustered on human chromosome 4 while CC chemokines generally exert chemotactic activities on monocytes [9, 10]. Pro-inflammatory cytokines exert pleiotropic effect by acting in contrast to the function of target cells [11]. Cytokines are multifunctional proteins that play an important role in cell-to-cell communication, they regulate a number of physiological and pathological processes, such as inflammation, development, differentiation, and cell death. IL-8 is regulated by several factors such as steroid hormones, inflammatory signals and environmental stress [12]. IL-8 act with interleukin-1 (IL-1) by attracting leukocytes to the site of injury, irritation or infection and activating neutrophils to exert phagocytic effect on bacteria and infected or damage cells [13, 14]. IL-8 is chemotactic for fibroblasts and stimulates deposition of fibronectin, and collagen I during wound healing [15]. IL-8 receptors are found on monocytes, T-lymphocytes, eosinophil, fibroblast and basophils as a result these cells also secrete IL-8 but their response to IL-8 is weaker than neutrophils. Therefore, the main role of IL-8 is recruitment of neutrophils to site of tissue injury or infection [16]. Several studies revealed an association between leukocyess and interleukin-8 (IL-8) and the increase in IL-8 concentration in inflammatory cells [17,18]. Therefore, this review is aimed at describing the functions of IL-8 and its role in tissue injury and inflammation.

Methods

Articles were searched from the directory of open access journals, Google scholar, PubMed, science direct and Scopus databases using the following keywords; Inteluekin-8 (IL-8), IL-8 structure, IL-8 functions, role of IL-8 in tissue injury and inflammation, tissue injury, inflammatory response, IL-8 in hepatic injury, IL-8 in nervous system injury, IL-8 in cardiac injury, IL-8 in kidney injury etc. The criteria used for selecting articles are as follows:

i. Articles that describe the structure and function of IL-8.
ii. Articles that state the role of IL-8 in tissue injury and inflammation.
iii. Articles that described tissue injury and inflammatory response.
iv. Articles that established the role of IL-8 in different kind of tissue injuries.

Articles that met the selection criteria were selected for the review

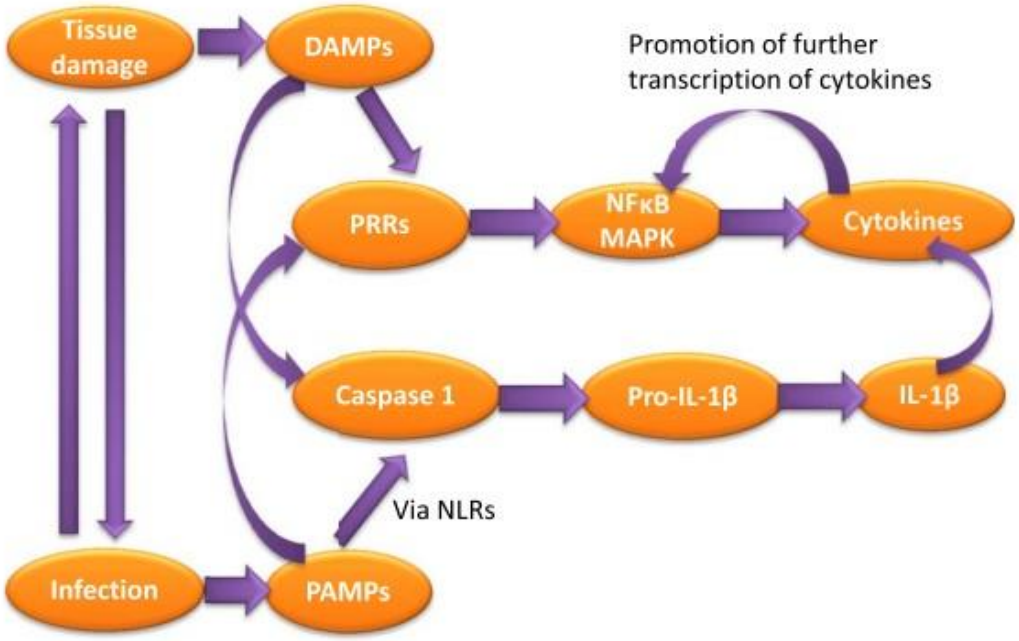

Figure 1. Mechanisms of Inflammation [6].

Results and discussion

Forty six articles that met the selection criteria were used to describe the structure and function of IL-8 and its role in tissue injury and inflammatory response associated with different disease conditions.

Role of IL-8 in Tissue Injury and Inflammatory Disease. IL-8 plays an important role in tissue injury and the inflammatory response of many tissues and organs such as brain, spinal cord, liver, kidneys, stomach, heart and spleen; IL-8 levels tend to increase in either plasma, serum, gastric juices, tissue fluids and cerebrospinal fluids following injuries/inflammation of the tissues involve.

IL-8 and central nervous system injury. The studies [19, 20] reported a significant increase in serum and cerebrospinal fluid (CSF) levels of IL-8 in patients with head injury compared with that of healthy control, the CSF IL-8 level was higher than serum level in 50% of the patients with head injury. The patients with blood brain barrier (BBB) malfunction showed higher CSF IL-8 levels than those with normal BBB function, the relationship between high CSF IL-8 and BBB malfunction suggest the role of IL-8 in altering the physiology of BBB.

Earlier study by Kostulas et al. [21] reported higher levels of IL-8 mRNA expressing mononuclear cells in patients with acute ischemic stroke as compared with healthy controls, they also reported a significant increase in plasma IL-8 levels in patients with acute ischemic stroke as compared to that of healthy controls. IL-8 production was said to increase significantly in LPS-stimulated human fetal microglial cells 24 hours after stimulation. IL-1β and TNF-α also increase the production of IL-8 by fetal microglial cells, the production of IL-8 by fetal microglial cells in response to LPS, IL-1β and TNF-α stimuli was inhibited by IL-4, IL-10 and TGF-β1. These suggest that human fetal microglial cells produce IL-8 in response to LPS, IL-1β and TNF-α stimuli while anti-inflammatory cytokines such as IL-4, IL-10 and TGF-β1 inhibits the synthesis of IL-8 [22].

The serum level of IL-8, TGF-β1 and nitric oxide (NO) were significantly elevated in patients with traumatic brain injury and spontaneous intra-cerebral hemorrhage compare to control patients, these shows that IL-8, TGF-β1 and NO are important mediators of inflammation and brain Damage [23]. Central venous plasma levels of IL-8 of patients with severe traumatic brain injury survivors were significantly lower than non-survivors indicating that IL-8 could be a predictive sign of mortality in severe traumatic brain injury patients [24]. Serum concentration of IL-8 were reported to be significantly higher in fibromyalgia patients as compared to healthy controls [25]. Furthermore, stress and immune activation can stimulate glia cells to release pro-inflammatory cytokines and chemokines like IL-8. Therefore, fibromyalgia patients had three times higher concentration of IL-8 in cerebrospinal fluid as compared to serum.

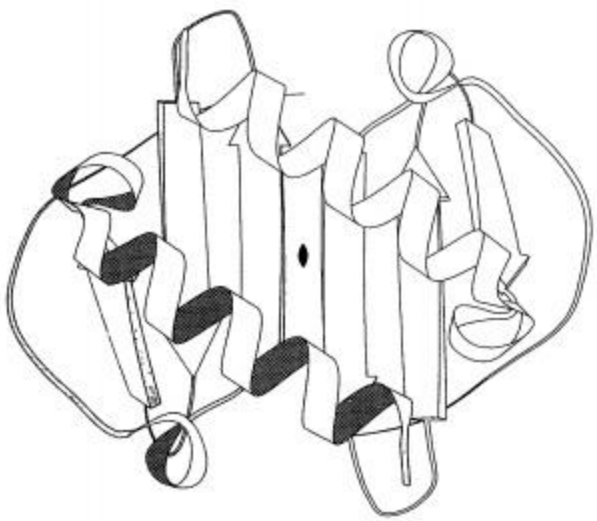

Figure 2. Human IL-8 Structure [8].

Research by Yousefzadeh-Chabok et al. [26] reported a significant increase in the serum levels of IL-8 and IL-6 in traumatic brain injury patients with unfavourable outcomes (death, vegetative life and severe disability) as compared to patients with favourable outcomes (moderate disability and good recovery), they concluded that increased in serum IL-8 and IL-6 are predictive markers of unfavourable outcomes in patients with severe traumatic brain injury. Khan et al. [27] reported a significant increase in IL-8 levels of dorsal root ganglion and sciatic nerve in rats 3-8 days after four different sciatic nerve injury; the injuries consist of partial sciatic ligation, neuritis, complete sciatic transection and chronic constriction injury. Their findings showed that serum IL-8 levels did not change in all models of nerve injury suggesting that IL-8 effect is localized to the damage cells or tissues and are specific to injury type.

IL-8 and Cardiovascular injury. Early study by Meki et al. [28] reported a significantly higher serum IL-8 concentration in scorpion envenomed children compare to controls. In their research, severely envenomed victims with toxic myocarditis and moderately envenomed victims with carditis had significantly higher levels of IL-8 than victims with mild cases of envenomation. They also show positive correlation between serum levels of cardiac troponin I (cTnI) and IL-8 in victims with toxic myocarditis suggesting that both cTnI and IL-8 may be involved in the pathogenesis of myocardial injury of scorpion envenomed victims.

A research conducted by Middleton et al. [29] established a relationship between increase IL-8 expressions with increase in T-lymphocytes and increase in the size of abdominal aortic aneurysm (AAA). The study also reported an increase in IL-8 level with progress of mural inflammation suggesting the involvement of IL-8 in the pathogenesis of AAA and its chemotactic role in T-lymphocytes aggregation within aneurysm wall leading to further inflammation and the release of more cytokine within the aneurysm wall.

A positive correlation between inflammatory cytokines (IL-8 and IL-1β) with cardiac injury and adverse cardiac events (ACEs) in critically injured patients was reported by De'Ath et al. [30]. They noticed a significant increase in IL-8 and IL-1β level in ACE patients 72 hours after critical injury and a 2.8 times increase in IL-8 level at 24 hour in patients with ACE compared to patients without.

High levels of IL-8 was noticed in ST-elevation myocardial infarction patients complicated with heart failure [31]. The high IL-8 levels were correlated with less improvement in the function of left ventricle six weeks after primary PCI-treatment suggesting the role of IL-8 in the reperfusion related injury of post-ischemic myocardium. Serum IL8 levels were significantly higher in female patients with risk of myocardial infarction compared to controls. Twofold increase in serum IL-8 concentration was associated with lower risk of myocardial infarction in females while the increase in serum IL-8 in males was associated with a slightly higher risk of myocardial infarction [32].

IL-8 and Gastric injury. Exposure of *Helicobacter pylori, Pseudomonas aeruginosa, Campyloribacter jejuni* and *Escherichia coli* to human gastric cancer cell lines enhance the production of IL-8 by the gastric cancer cell lines [33]. There is a significant positive correlation between high serum IL-8 levels with gastric mucosal injury and gastric cancer [34]. Despite the increase in IL-8 expression in gastric mucosa that is exposed to *H. pylori*, increase in IL-8

expression is a sign of poor prognosis of gastric cancer [35]. Gastric juice from patients on proton pump inhibitors (PPIs) cause a significant increase in IL-8 production by primary bronchial epithelial cells (PBEC) compared to gastric juice of patients off PPI. Cystic fibrotic PBEC exposed to gastric juices from patients on PPI and off PPI produced a significantly higher IL-8 than normal PBEC exposed to gastric juice from patients on PPI and off PPI [36].

IL-8 and Liver injury. There was a significant increase in serum IL-8 levels in patients with chronic liver disease (CLD) compared to controls [37]. Patients with liver cirrhosis had significantly higher IL-8 levels than patients with CLD but without cirrhosis. Patients with both alcoholic and cholestatic liver diseases had the highest IL-8 levels while patients with hepatitis B and hepatitis C had lowest levels of serum IL-8.

The role of functional blockage of IL-8 receptors in murine alcoholic steatohepatitis was described by Wieser et al. [38]. They showed that experimental induction of alcoholic liver disease is driven by CXCR1/2-dependent activation of neutrophils, CXCR1/2-specific pepducins significantly reduce liver inflammation and mortality associated with alcoholic liver disease in mice. Because hepatic neutrophil infiltration and triglyceride accumulation was significantly reduce by CXCR1/2 blockage in alcoholic liver disease, CXCR1/2 blockage cured previously established cases of alcoholic liver disease and prevented further mortality that may occur as a result of the disease. They concluded that increase in human alcoholic hepatitis may increase pathogenic neutrophil activation while its blockage via pepducins improves recovery.

IL-8 and Renal injury. Higher levels of urine IL-8 was noticed in patients with glomerular leukocyte infiltration as compared to those of patients without infiltration, suggesting the role of IL-8 in the pathogenesis of glomerular diseases. Plasma IL-8 levels were also reported to significantly increase in patients with IgA nephropathy, acute glomerulonephritis, lupus nephritis, purpura nephritis, membranoproliferative glomerulonephritis and cryoglobulinemia [39].

The plasma concentration of IL-8 in autosomal dominant polycystic kidney disease (ADPKD) patients with normal glomerular filtration rate was significantly increased, this suggest the role of cytokines like IL-8 in the parthenogenesis of ADPKD [40]. Serum levels of IL-8 were significantly increased in patients with acute kidney injury that underwent cardiopulmonary bypass [41, 42]. This indicates the role of serum IL-8 levels in the early diagnosis of acute kidney injury. Urine and serum IL-8 levels were increased in patients with acute kidney injury within 24 hours after liver transplant [43].

Earlier study by Shanmuganathan et al. [44] to identify the association between polymorphism of IL-8 gene and patients with diabetic chronic kidney disease (CKD) and patients on continuous ambulatory peritoneal dialysis (CAPD) showed the presence of polymorphism in +781 cytosine/thymine (C/T) of IL-8 gene in diabetic CKD and CAPD patients suggesting its role as an inflammatory marker in CKD and CAPD. Hydrogen peroxide (H2O2) a reactive oxygen species (ROS) stimulated Gα12 and renal injury leading to increase in IL-8 expression *in-vivo* and *in-vitro* [45]. An increase in urine IL-8 level was observed in marathon runners immediately after marathon suggesting the occurrence of structural renal tubule damage after marathon [46].

Conclusions

IL-8 concentrations are found to be elevated in many disease conditions and traumatic injuries. Increase in IL-8 concentrations in serum, plasma, cerebrospinal fluid, gastric juice and urine are specific to certain type of tissue injury. Therefore, IL-8 alone cannot be used in the diagnosis of disease conditions. Because of its role in the inflammatory response of many cells, IL-8 may have a role in the pathogenesis of many diseases and can be used to predict the severity of certain disease conditions and survival rate of patients.

Authors' Contribution

NI Dibal proposed the topic, SH Garba and TW Jacks approve the topic and provide editing and technical support, the manuscript was written and approved by all authors.

Conflict of interest

The authors have no conflict of interest to declare

Article history:
Received: 18 April 2018
Received in revised form: 07 May 2018
Accepted: 08 May 2018
Available online: 08 May 2018

References

1. Fierro IM, Serhan CN. 2001. Mechanisms in anti-inflammation and resolution: the role of lipoxins and aspirin-triggered lipoxins. *Brazilian J Med. Biol. Res*. 34:555-566.
2. Van Dyke TE, Kornman KS. 2008. Inflammation and Factors That May Regulate Inflammatory Response. *J Periodontol.* 79:1503-1507.
3. Barnes PJ. 2011. Similarities and differences in inflammatory mechanisms of asthma and COPD. *Breathe* 7:229-238.
4. Bian Z, Guo YL, Ha B, Zen K, Liu Y. 2012. Regulation of the Inflammatory Response: Enhancing Neutrophil Infiltration under Chronic Inflammatory Conditions. *J Immunol.* 188:844-853.
5. Dugue R, Nath M, Dugue A, Barone FC. 2017. Roles of Pro- and Anti-inflammatory Cytokines in Traumatic Brain Injury and Acute Ischemic Stroke. *Intech* 212-260.

6. Walker AK, Kavelaars A, Heijnen CJ, Dantzer R. 2014. Neuroinflammation and Comorbidity of Pain and Depression. *Pharmacol. Rev.* 66:80–101.
7. Koch AE, Polverini PJ, Kunkel SL, Harlow LA, DiPietro LA, Elner VM, Elner SG, Strieter RM.1992. Interleukin-8 as a macrophage-derived mediator of angiogenesis. *Science* 258:1798-1801.
8. Baldwin ET, Weber IT, ST. Charles R, Xuan J, Apella E, Ydmada M, Matsushima K, Edwards BFP, Clorc GM, Gronenborn, AM, Wlodawcr A. 1991. Crystal Structure of Interleukin-8: Symbiosis of NMR and Crystallography. *Proc. Natl. Acad. Sci. USA* 88:502-506.
9. Oppenheim JJ, Zachariae CO, Mukaida N, Matsushima K. 1991. Properties of the novel pro inflammatory supergene "intercrine" cytokine family. *Annu. Rev. Immunol*. 9:617-648.
10. Harada A, Sekido N, Akahoshi T, Wada T, Mukaida N, Matsushima K. 1994. Essential involvement of interleukin-8 (IL-8) in acute inflammation. *J Leukocyte Biol.* 56:559-564.
11. Lotti F, Maggi M. 2013. Interleukin 8 and the male genital tract. *J Reprod. Immunol.* 100:54– 65.
12. Waugh DJ, Wilson C. 2008. The interleukin-8 pathway in cancer. *Clin. Cancer Res.* 14:6735–6741.
13. Fraczek M, Kurpisz M. 2007. Inflammatory mediators exert toxic effects of oxidative stress on human spermatozoa. *J Androl.* 28: 325–333.
14. Kobayashi Y. 2008. The role of chemokines in neutrophil biology. *Front Biosci.* 13: 2400–2407.
15. Qazi BS, Tang K, Qazi A. 2011. Recent Advances in Underlying Pathologies Provide Insight into Interleukin-8 Expression-Mediated Inflammation and Angiogenesis. *Intern J Inflam.* 2011:1-13.
16. Baggiolini M, Dewald B, Moser B. 1994. Interleukin-8 and related chemotactic cytokines-CXC and CC chemokines. *Adv. Immunol.* 55:97–179.
17. Wu H, Yang S, Wu X, Zhao J, Zhao J, Ning Q, Xu Y, Xie J. 2014. Interleukin-33/ST2 signaling promotes production of interleukin-6 and interleukin-8 in systemic inflammation in cigarette smoke-induced chronic obstructive pulmonary disease mice. *Biochem. Biophy. Res. Comm.* 450:110–116.
18. Aghazarian A, Stancik I, Huf W, Pfluger H. 2015. Evaluation of Leukocyte Threshold Values in Semen to Detect Inflammation Involving Seminal Interleukin-6 and Interleukin-8. *Urol.* 86:52-56.
19. Kossmann T, Stahel PF, Lenzlinger PM, Redl H, Dubs RW, Trentz O, Schlag G, Morganti-Kossmann MC. 1997. Interleukin-8 Released into the Cerebrospinal Fluid After Brain Injury Is Associated with Blood-Brain Barrier Dysfunction and Nerve Growth Factor Production. *J Cerebral Blood Flow Metabol.* 17:280-289.
20. Morganti-Kossman, MC, Lenzlinger PM, Hans V, Stahel P, Csuka E, Ammann E, Stocker R, Trentz O, Kossmann T. 1997 Production of cytokines following brain injury: beneficial and deleterious for the damaged tissue. *Mole Psych.* 2:133–136.
21. Kostulas N, Kivisa¨kk P, Huang Y, Matusevicius D, Kostulas V, Link H. 1998. Ischemic Stroke Is Associated With a Systemic Increase of Blood Mononuclear Cells Expressing Interleukin-8 mRNA. *Stroke* 29:462-466.
22. Ehrlich LC, Hu S, Sheng WS, Sutton RL, Rockswold GL, Peterson PK, Chao CC. 1998. Cytokine Regulation of Human Microglial Cell IL-8 Production. *J Immunol.* 160:1944-1948.
23. Hadidi E, Mojtahedzadeh M, Paknejad MH, Nikfar S, Zamani MJ, Sahraian MJ, Eftekhar B, Khajani MR, Najafi A, Ghaffarzadeh M, Eftekhari R, Soleimani V, Esmaily H, Rouini MR,Abdollahi M. 2006. Alterations of blood IL-8, TGF-β1 and nitric oxide levels in relation to blood cells in patients with acute brain injury. *Therapy* 3:399–405.
24. Gopcevic A, Mazul-Sunko B, Marout J, Sekulic A, Antoljak N, Siranovic M, Ivanec Z, Margaritoni M, Bekavac-Beslin M, Zarkovic N. 2007. Plasma Interleukin-8 as a Potential Predictor of Mortality in Adult patients with Severe Traumatic Brain Injury. *Tohoku J Exp. Med.* 211:378-393.
25. Kadetoff D, Lampa J, Westman M, Andersson M, Kosek E. 2012. Evidence of central inflammation infibromyalgia-Increased cerebrospinal fluid interleukin-8 levels. *J Neuroimmunol.* 242:33–38.
26. Yousefzadeh-Chabok S, Moghaddam AD, KazemnejadLeili E, Saneei Z, Hosseinpour M, Kouchakinejad-Eramsadati L, Razzaghi A, Mohtasham-Amiri Z. 2015. The Relationship between Serum Levels of Interleukins 6, 8, 10 and Clinical Outcome in Patients with Severe Traumatic Brain Injury. *Arch Trauma Res.* 4:e18357.
27. Khan J, Hassunb H, Zusman T, Korczeniewska O, Eliav E. 2017. Interleukin-8 levels in rat models of nerve damage and neuropathic pain. *Neurosci. Letters* 657:106–112.
28. Meki AAM, El Deen ZMM, El Deen HMM. 2002. Myocardial Injury in Scorpion Envenomed Children: Significance of Assessment of Serum Troponin I and Interleukin-8. *Neuroendocrinol. Letter* 23:133-140.
29. Middleton RK, Bown MJ, Lloyd GM, Jones JL, London NJ, Sayers RD. 2009. Characterisation of Interleukin-8 and Monocyte Chemoattractant Protein-1 Expression within the Abdominal Aortic Aneurysm and their Association with Mural Inflammation. *Eur. J Vasc. Endovasc. Surg.* 37:46-55.
30. De'Ath HD, Manson J, Davenport R, Glasgow S, Renfrew I, Davies LC, Uppal R, Brohi K. 2013. Trauma-Induced Secondary Cardiac Injury Is Associated With Hyperacute Elevations In Inflammatory Cytokines. *Shock* 39:415-420.
31. Husebye T, Eritsland J, Arnesen H, Bjørnerheim R, Mangschau A, Seljoflot I, Andersen GO. 2014. Association of Interleukin 8 and Myocardial Recovery in Patients with ST-Elevation Myocardial Infarction Complicated by Acute Heart Failure. *PLOS ONE* 9: e112359.
32. Velásquez IM, Frumento P, Johansson K, Berglund A, Faire U, Leander K, Gigante B. 2014. Association of interleukin 8 with myocardial infarction: Results from the Stockholm Heart Epidemiology Program. *Int. J Cardiol.* 172:173–178.
33. Sharma SA, Tummuru MKR, Miller GG, Blaser AJ. 1995. Interleukin-8 Response of Gastric Epithelial Cell Lines to Helicobacter pylori Stimulation *in-vitro*. *Infect Immunity* 63:1681–1687.
34. Yamada S, Kato S, Matsuhisa T, Makonkawkeyoon L, Yoshida M, Chakrabandhu T, Lertprasertsuk N, Suttharat P, Chakrabandhu B, Nishiumi S, Chongraksut W, Azuma T. 2013. Predominant mucosal IL-8 mRNA expression in non-cagA Thais is risk for gastric cancer. *World J Gastroenterol.* 19:2941-2949.
35. Lee KE, Khoi PN, Xia Y, Park JS, Joo YE, Kim KK, Choi SY, Jung YD. 2013. Helicobacter pyloriand interleukin-8 in gastric cancer. *World J Gastroenterol.*19:8192-8202.
36. Pauwels A, Verleden S, Farre R, Vanaudenaerde BM, Raemdonck DK, Verleden G, Sifrim D, Dupont LJ. 2013. The effect of gastric juice on interleukin-8 production by cysticfibrosis primary bronchial epithelial cells. *J Cystic Fibros.* 12:700–705.
37. Zimmermann HW, Seidler S, Gassler N, Nattermann J, Luedde T, Trautwein C, Tackle F. 2011. Interleukin-8 Is Activated in Patients with Chronic Liver Diseases and Associated with Hepatic Macrophage Accumulation in Human Liver Fibrosis. *PLOS ONE* 6:e21381.
38. Wieser V, Adolph TE, Enrich B, Kuliopulos A, Kaser A, Tilg H, Kaneider NC. 2017. Reversal of murine alcoholic steatohepatitis by pepducin-based functional blockade of interleukin-8 receptors. *Gut* 66:930–938.
39. Wada T, Yokoyama H, Tomosugi N, Hisa Y, Ohta S, Naito T, Kobayashi K, Mukaida N, Matsushima K. 1994. Detection of urinary interleukin-8 in glomerular diseases. Kidney Int. 46:455-460.
40. Merta M, Tesar V, Zima T, Jirsa M, Rysava R, Zabka J. 1997. Cytokine Profile in Autosomal Dominant Polycystic Kidney Disease. *Biochem. Mole Biol. Int.* 41:619-624.
41. Liangos O, Kolyada A, Tighiouart H, Perianayagam MC, Wald R, Jaber BL. 2009. Interleukin-8 and Acute Kidney Injury following Cardiopulmonary Bypass: A Prospective Cohort Study. *Nephron Clin. Pract.* 113:148–154.

42. Liu KD, Altmann C, Smits G, Krawczeski CD, Edelstein CL, Devarajan P, Faubels S. 2009. Serum Interleukin-6 and interleukin-8 are early biomarkers of acute kidney injury and predict prolonged mechanical ventilation in children undergoing cardiac surgery: a case-control study. *Critical Care* 13:
43. Sirota JC, Walcher A, Faubel S, Jani A, McFann K, Devarajan P, Davis CL, Edelstein CL. 2013. Urine IL-18, NGAL, IL-8 and serum IL-8 are biomarkers of acute kidney injury following liver transplantation. *BMC Nephrol.* 14:17.
44. Shanmuganathan R, Ramanathan K, Padmanabhan G, Vijayaraghavan B. 2017. Evaluation of Interleukin 8 gene polymorphism for predicting inflammation in Indian chronic kidney disease and peritoneal dialysis patients. *Alexandria J Med.* 53:215–220.
45. Kim AK, Richard B, Boucher I, Yu W, Kong T, Denker BM. 2019. Gα12 Regulates Interleukin-8 Expression after Epithelial Cell Injury. Open J Pathol. 6:154-161.
46. Mansour SG, Verma G, Pata RW, Martin TG, Perazella MA, Parikh CR. (2017) Kidney Injury and Repair Biomarkers in Marathon Runners. *Am. J Kidney Dis.*70:252-261.