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Chapter 1 : Cytokines, vol 4: Interleukin-8(NAP-1) and Related Chemotactic Cytokines - CORE

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This is an open access article distributed under the Creative Commons Attribution License , which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Abstract Interleukin-6 is currently attracting significant interest as a potential therapeutic target in systemic sclerosis SSc. In this paper, the biology of interleukin-6 is reviewed, and the evidence for interleukin-6 dysregulation in SSc is explored. The role of inteleukin-6 classical and trans signalling pathways in SSc relevant phenomena such as chronic inflammation, autoimmunity, endothelial cell dysfunction, and fibrogenesis is discussed. The existing evidence that interventions designed to block interleukin-6 signalling are of therapeutic relevance in SSc is evaluated. Introduction Systemic sclerosis SSc is a connective tissue disease characterised by fibrosis, vasculopathy, and immunological abnormalities. Over recent years, it has become clear that inflammation plays a crucial role in mediating the pathophysiological process underlying SSc, especially early in the disease. Endothelial cell activation and dysfunction are central to the disease pathogenesis, may be driven by a proinflammatory environment, and may result in the generation of a profibrotic phenotype. Interleukin-6 IL-6 is a pleiotropic cytokine. In addition to its role in the acute phase response, IL-6 has diverse roles in driving chronic inflammation, autoimmunity, endothelial cell dysfunction, and fibrogenesis. Therefore, it is currently attracting a great deal of interest in the rheumatology community as a potential therapeutic agent in SSc, a disease which at present lacks treatments directed at the underlying pathogenesis. Recent evidence has suggested that IL-6 may play important roles in endothelial cell dysfunction and fibrogenesis in this disease, and clinical trials are currently being designed to further explore whether Tocilizumab, a monoclonal antibody directed against the IL-6 receptor, may be of therapeutic benefit to patients with SSc. Interleukin-6 Biology Interleukin-6 biology is complex. Few cells express the interleukin-6 receptor IL-6R, gp This receptor is expressed on hepatocytes, monocytes, B cells, and neutrophils in humans. It is also found on a subset of T cells, but there is evidence that T cells respond to IL-6 predominantly through a process known as trans signalling [1]. Endothelial cells and fibroblasts do not express the IL-6R and are also thought to respond to IL-6 through trans signalling [2]. Soluble IL-6R sIL-6R is produced by two separate mechanisms, firstly by proteolytic cleavage from the surface of neutrophils and secondly by secretion from neutrophils and monocytes of an alternatively spliced version [3 â€” 6]. Although the regulation of the proteolytic cleavage of sIL-6R has not been fully elucidated, it is known to be stimulated by C-reactive protein CRP. Cleavage from the surface of neutrophils, but not monocytes, is also stimulated by chemoattractants interleukin-8 IL8 , C5a, leukotriene B4 LTB4 , and platelet activating factor PAF [7]. We and others have shown that there is an increased concentration of the neutrophil chemoattractant IL-8 in SSc serum [8 , 9], which may stimulate the release of sIL-6R from neutrophils. In addition, there are reports in the literature that LTB4 levels are elevated in the bronchoalveolar lavage fluid of patients with SSc lung disease [10], that may also contribute to the generation of sIL-6R. Endothelial cell activation via trans signalling results in an increase in the expression of adhesion molecules intercellular adhesion molecule-1 ICAM-1 , vascular cell adhesion molecule-1 VCAM-1 , the release of chemokines IL-8 and monocyte chemotactic protein-1 MCP-1 , and the release of IL-6 [2 â€” 12] Figure 1. IL-6 receptors are expressed on leukocytes including neutrophils, but they are not expressed on tissue-resident cells, for example, endothelial cells. Interleukin-6 in Systemic Sclerosis IL-6 is a cytokine with several potentially important roles in the pathogenesis of SSc. It is elevated in the serum of patients with systemic sclerosis, especially those with diffuse skin involvement and early in the disease course [13 , 14]. Immunocytochemistry studies have also demonstrated that IL-6 may be elevated in lesional tissue later in the disease, when other proinflammatory cytokines have dissipated. Several other observations further support a role for this interleukin in SSc. Fibroblasts isolated and cultured from the lesional skin of patients with SSc constitutively produce higher levels of IL-6 than nonlesional or healthy donor fibroblasts [15]. This demonstrates the importance of

considering local concentrations of cytokines in disease. Serum concentrations may not necessarily reflect local levels of a relevant cytokine at the lesional site. Hence, the use of in vitro models to explore local interactions between fibroblasts, endothelial cells, and immune cells, in the presence of locally elevated levels of cytokines, is of particular importance. Stimulated and unstimulated fibroblasts from lesional skin have also been shown to produce increased levels of IL-8 which may be implicated in local release of sIL-6R from neutrophils [16]. Previous research has shown that peripheral blood mononuclear cells from SSc patients, when cultured in vitro, produce higher levels of IL-6 and sIL-6R in the culture supernatants than control peripheral blood mononuclear cells, though levels of sgp were equivalent [17]. In addition, it is important to note that hemodynamic flow may suppress ILinduced signalling in endothelial cells [20]. As such flow is dysregulated in SSc, this may play an important role in modulating the effects of IL-6 on endothelial cells in this disease. Interleukin-6 Effects on B Cells IL-6 also has a profound effect on B cells, promoting plasma cell differentiation and antibody production. This may explain the polyclonal B-cell expansion and hypergammaglobulinaemia which is frequently seen in SSc [11]. B-cell depletion using rituximab monoclonal antibody directed against CD20 in 9 patients with progressive SSc skin disease, refractory to cyclophosphamide therapy, resulted in a clinical improvement in skin score after 3 months, which persisted up to 36 months. This was paralleled by a decrease in serum IL-6 concentration [21]. Interleukin-6 and Effects on Inflammation IL-6 has been implicated in the generation and propagation of chronic inflammation. Initially in acute inflammation, proinflammatory cytokines promote neutrophil accumulation and the release of IL This promotes differential regulation of chemokine production by endothelial cells, promoting MCP-1 production and decreasing IL-8 production, therefore favouring monocyte accumulation. In addition, IL-6 may have a role in promoting neutrophil apoptosis and therefore the resolution of acute nonspecific inflammation [23 , 24]. Others however have reported an antiapoptotic effect of IL-6 on neutrophils [25], while Biffl et al. We have been unable to reproduce any ILspecific effect on neutrophil apoptosis in our laboratory at concentrations of IL-6 ranging from 0. Conversely, IL-6 reportedly rescues T cells from apoptosis, which promotes a chronic inflammatory cell infiltrate [27 â€” 30]. IL-6 trans signalling also promotes the release of IL-6 from fibroblasts and endothelial cells in a positive autocrine feedback system. Therefore, it can be envisaged that IL-6 may have a role in propagating chronic inflammation, such as that seen in SSc. This is in keeping with immunocytochemical experiments which demonstrate that IL-8 and IL-6 are overexpressed in the lesional skin of patients with SSc, though in different patterns: IL-6 has also been implicated in autoimmunity. Furthermore, autoimmune phenomena increase with age, in concert with an age-related increase in sIL-6R shedding [37]. Using antibodies which specifically blocked classical IL-6 signalling and trans signalling pathways, they discovered that the classical IL-6 pathway was both necessary and sufficient for the development of pathogenic Th17 T cells which are implicated in autoimmunity and for the generation of antitype II collagen IgG responses which are associated with disease manifestations in the CIA model. They also demonstrated in the AIA model that IL-6 trans signalling was responsible for driving local inflammatory responses [38]. SSc is a disease associated with autoimmune phenomena. Many different autoantibodies are found in SSc see Table 1 , and the autoantibody profile in many cases correlates with clinical manifestations. There is, however, no convincing evidence for a direct role for autoantibodies in pathogenesis though some investigators have reported that antiendothelial cell antibodies, found in a proportion of patients, are associated with endothelial cell activation [39 , 40]. Systemic sclerosis-associated autoantibodies, potentially pathogenic antibodies which have been described in a proportion of patients with systemic sclerosis. Reviewed in [41]. Interleukin-6 and Effects on Fibrogenesis Fibroblasts from patients with SSc are phenotypically unique. When isolated and cultured in vitro they continue to produce an excess of collagen [42 , 43]. IL-6 is a profibrogenic cytokine. It has been shown to either increase or decrease fibroblast proliferation, increase fibroblast collagen, glycosaminoglycan, and tissue inhibitor of metalloproteinases-1 TIMP-1 synthesis, and increase MCP-1 and IL-6 production [43 â€” 48]. IL-6 regulates the expression of vascular endothelial growth factor VEGF , an important mediator of angiogenesis and fibrosis which is elevated in patients with SSc [49]. One case series has indicated that the use of tocilizumab, which blocks IL-6 trans signalling, in 2 patients with diffuse cutaneous SSc dcSSc , one with renal involvement and the other with lung fibrosis, resulted in a decrease in

skin thickening as measured by Rodnan skin score and Vesmeter which measures viscoelasticity or hardness of the skin. In addition, skin biopsies taken before and after tocilizumab treatment indicated a reduction in collagen [50]. There is also evidence for increased endothelial cell apoptosis though corroborative in vivo evidence for this is lacking [51]. The University of California at Davis line chicken, an animal model for SSc, shows evidence of early endothelial cell apoptosis, preceding the inflammatory cell infiltrate and the development of fibrosis [39 â€" 52]. Serum markers of endothelial cell activation, for example, von Willebrand factor vWF , sICAM-1, and sE-selectin are elevated in the serum of patients with SSc and appear to correlate with disease activity [53 â€" 55]. Previous studies have shown a role for IL-6 in endothelial cell activation. We have recently shown that SSc serum, in the presence of neutrophils, is capable of increasing endothelial cell activation and apoptosis in an ILdependent manner [56]. It is postulated that in this circumstance the neutrophils are acting as donors of IL-6R. In our studies, spiking pooled control serum with IL-6 resulted in increased endothelial cell apoptosis and E-selectin expression in the presence of neutrophils, mimicking the effects of SSc serum. Complement inactivation did not abrogate the effects of SSc serum, neither did the addition of catalase to mop up reactive oxygen species. The serine protease inhibitor AEBSF partially blocked the effects of SSc serum on endothelial cell apoptosis but did not significantly affect the activation of endothelial cells by SSc serum [56]. Strategies to remove or block the effects of IL6 in SSc serum including immunodepletion of IL6 and the addition of an anti-IL6 blocking antibody reversed the effects of SSc serum on endothelial cell activation and apoptosis [56]. Most significantly, however, sgp which specifically blocks IL6 trans signalling abrogated the effects of SSc serum [56]. Conclusion IL-6 blockade and specifically the blockade of IL-6 trans-signalling may have merit in the treatment of SSc, a disease that so far lacks treatment options directly targeting the pathogenic mechanism. IL-6 trans signalling is specifically implicated in driving local inflammation and inducing endothelial and fibroblast responses, and therefore targeting this IL-6 signalling pathway may be most profitable in SSc. However, SSc also has important and possibly pathogenic autoimmune phenomena, and targeting the classical IL-6 signalling pathway may be necessary in order to influence this important aspect of the disease. The currently available drug Tocilizumab targets both the classical and the trans signalling pathways. Other agents are in development which specifically block trans signalling, and they may be useful in mouse models of SSc to delineate which signalling pathway is most important for this disease. In addition, it is also found in immunohistochemistry samples in both early and late disease and in both dcSSc and lcSSc. Fibroblasts and monocytes isolated from SSc patients autonomously produce IL-6 in vitro. Early, small-scale nonrandomised controlled trials point to an important role for IL6 in SSc. B-cell depletion results in a decrease in serum IL-6 levels, reflected in a simultaneous reduction in skin score. More importantly, blocking IL-6 trans signalling with Tocilizumab has resulted in an improvement in skin score in 2 patients with diffuse disease. These data firmly establish IL-6 as an attractive candidate therapeutic target, especially in terms of preventing fibrosis. However, in addition, new and exciting data imply that IL-6 has a role in the endothelial and inflammatory manifestations of this disease, which may make it a potential target in a much broader range of SSc patients with active vascular or inflammatory e. Studies are being designed to address these important questions; the results are eagerly awaited. View at Google Scholar S. View at Google Scholar R.

Chapter 2 : Degradation of interleukin 8 by the serine protease MucD of Pseudomonas aeruginosa

Interleukin-8 (IL-8) is a peptide with chemotactic and activating effects on neutrophils. It is recognized today as the prototype of a new class of chemotactic cytokines which are gaining increasing attention as tissue-derived inflammatory mediators.

Function[edit] IL-8, also known as neutrophil chemotactic factor, has two primary functions. It induces chemotaxis in target cells, primarily neutrophils but also other granulocytes, causing them to migrate toward the site of infection. IL-8 also stimulates phagocytosis once they have arrived. IL-8 is also known to be a potent promoter of angiogenesis. IL-8 can be secreted by any cells with toll-like receptors that are involved in the innate immune response. Usually, it is the macrophages that see an antigen first, and thus are the first cells to release IL-8 to recruit other cells. The homodimer is more potent, but methylation of Leu25 can block the activity of homodimers. IL-8 is believed to play a role in the pathogenesis of bronchiolitis , a common respiratory tract disease caused by viral infection. The genes encoding this and the other ten members of the CXC chemokine family form a cluster in a region mapped to chromosome 4q. A number of variables are essential for the successful chemotaxis of neutrophils, including the increased expression of high affinity adhesion molecules to secure the neutrophil to the endothelium near the affected site and is therefore not washed away into the circulatory system , and that the neutrophil can digest its way through the basement membrane and the extracellular matrix ECM to reach affected site. CXCL8 plays a key role in inducing the cell signalling necessary to bring about these changes. Once this occurs weak interactions are made between the selectins expressed on the neutrophil and endothelial cells expression of which is also increased through the action of CXCL8 and other cytokines. On the neutrophil these are: L selectins, and on the endothelial cell: P and E selectins. This causes the "rolling" phase of chemotaxis. Once the neutrophil is rolling along the endothelium, it will come into contact with a CXCL8 molecule expressed on the surface which stimulates the cell signalling pathway, mediated through a G-coupled-protein-receptor. The expression and affinity of LFA-1 is significantly increased to maximise binding. This causes the neutrophil to slow down more until it is stationary. Another key function of the cell signalling stimulated by CXCL8, is the initiation of the oxidative burst. This process allows the build up of proteolytic enzymes and reactive oxygen species ROS which are necessary to break down the ECM and basement membrane. These are released in secretory granules, along with more integrins. The release of ROS and damaging enzymes is regulated to minimise host damage, but continues to reach site of infection at which it will carry out its effector functions. The chemoattractant activity of IL-8 in similar concentrations to vertebrates was proven in Tetrahymena pyriformis, which suggests a phylogenetically well-conserved structure and function for this chemokine. Interleukin-8 secretion is increased by oxidant stress, which thereby cause the recruitment of inflammatory cells and induces a further increase in oxidant stress mediators, making it a key parameter in localized inflammation. Through its action as a signalling molecule IL-8 is capable of recruiting and guiding neutrophils to the lung epithelium. Overstimulation and dysfunction of these recruited neutrophils within the airways results in release of a number of pro-inflammatory molecules and proteases resulting in further damage of lung tissue. Regulation of expression[edit] The expression of IL-8 is negatively regulated by a number of mechanisms.

Chapter 3 : Interleukin - Wikipedia

Interleukin 8 Nap 1 And Related Chemotactic Cytokines Cytokines Vol 4 EPub Format Smart Description Of Interleukin 8 Nap 1 And Related Chemotactic Cytokines Cytokines.

Advanced Search Abstract Mucosal immune system activation may represent a critical determinant of adverse consequences associated with bacterial vaginosis BV , such as sexual human immunodeficiency virus transmission, upper genital tract infections, postsurgical infections, and adverse pregnancy outcomes. Concentrations of sialidase, prolidase, and anti-Gardnerella vaginalis hemolysin Gvh immunoglobulin A IgA were higher in vaginal fluids of 75 fertile women with BV, compared with concentrations in vaginal fluids of 85 healthy control subjects. Interleukin IL -8 levels were positively associated with anti-Gvh IgA response and inversely correlated with high levels of prolidase and sialidase in women with BV. IL-8 concentration was strongly associated with leukocyte count in both healthy and BV-positive women. The absence of leukocytes in most women with BV likely is due to lack of IL-8 induction. Parallel impairment of innate and adaptive mucosal immune factors, likely through microbial hydrolytic effects, may allow for the ascent of microorganisms to the upper genital tract and may facilitate viral infections. Bacterial vaginosis BV is the main vaginal syndrome afflicting fertile and pregnant women [1â€”5]. BV is a polymicrobial disorder characterized by an overgrowth of several anaerobic or facultative bacteria mainly Gardnerella vaginalis, Prevotella species, Bacteroides species, Mobiluncus species, gram-positive cocci, and Mycoplasma species and by a reduction or absence of lactobacillus colonization [1]. Although BV is associated with several adverse outcomes, such as upper genital tract infections, pelvic inflammatory disease, endometritis, postsurgical infections, increased susceptibility to human immunodeficiency virus HIV infection, preterm delivery PTD , and low birth weight LBW , many basic questions regarding the pathogenesis of BV remain unanswered [1â€”3 , 6â€”11]. Some researchers found increased levels of proinflammatory cytokines, such as interleukin IL -1 and IL-8, in vaginal fluid of women with BV [12â€”15]. Such findings are not in line with the clinical observation of scarcity of inflammation. The reasons for the absence of inflammatory signs in most women with BV remain unexplained. Recently, a mucosal IgA response against the G. Such adaptive antigen-specific immune response is inversely correlated with the presence in the vaginal fluid of sialidase, a microbial enzyme that is associated with BV [18â€”22]. These results suggest that a subset of women with BV may be exposed to more-aggressive microbial colonization, characterized by high microbial enzymatic activity and diminished anti-Gvh IgA levels. To date, no study has examined the relationship of microbial enzyme activity [22 , 23], an antigen-specific IgA response, and proinflammatory chemokine levels in vaginal fluid of BV-positive women. Chemokines are a family of low-molecularweight proinflammatory cytokines that stimulate recruitment of leukocytes. IL-8 is a CXC chemokine specific for neutrophil recruitment that is released by host cells after exposure to various microbial pathogens and is considered to have a major impact in the activation of immune effector cells against the invading microorganisms [24]. In this study, we examined the relationship of anti-Gvh IgA response and prolidase and sialidase levels with factors of the local innate immune response, specifically, IL-8 level and leukocyte count. Patients and Methods Study population. Nonpregnant women 19â€”50 years old were recruited during routine gynecologic examinations for Pap smears in 2 clinics located in Udine and Trieste in northern Italy, from December through May No study participant had a severemedical condition, including malignancies, and none was positive for yeast vaginitis, Trichomonas vaginalis, Neisseria gonorrhoeae, or Chlamydia trachomatis. Further exclusion criteria were partial or total hysterectomy and physiological menopause. All enrolled women denied having had sexual intercourse or using douches or vaginal suppositories in the last 3 days and having used antibiotics in the last 2 weeks. Women with BV were enrolled by clinical evaluation of the presence of all 4 Amsel criteria [4]: The healthy and the BV-positive groups did not differ in contraceptive use or menstrual cycle phase. All enrolled women had normal Pap smear results i. Vaginal fluids were retrieved bywashing with 10 mLof sterile saline. Vaginal flora, clue cells, and leukocyte counts were evaluated on the Gram-stained smear. Three different bacterial morphotypesâ€”lactobacilli, Gardnerella-like species including

G. The group of healthy control subjects had Nugent scores of 0â€”2. The clinically enrolled women with BV were all positive for clue cells and had Nugent scores of 5â€” Anti-Gvh IgA levels were evaluated in the vaginal fluids, according to a procedure described elsewhere [17], using the purified Gvh for coating of the microtiter wells. As in previous studies [17â€”19], a cutoff of milliunits optical density mOD at nm was adopted for the anti-Gvh IgA response this cutoff was calculated previously for a large healthy reference control group [19]. After the addition of 4-aminoantipyrine and potassium ferricyanide, the absorbance was read at nm. Specific activity was expressed as nanomoles of methoxyphenol produced, compared with a standard curve of pure methoxyphenol. A duplicate sample without the prolidase substrate served as sample blank. Absorbance mOD was read at nm. IL-8 was quantified in the vaginal fluid by sandwich-type ELISA, using commercial capture and conjugated detection antibodies. The vaginal fluid samples were tested in duplicate; if the reading was outside the standard curve, the sample was serially diluted to obtain values in the range of the reference curve. Samples below this limit were given the value 0. All samples except 2 Low, medium, and high levels of IL-8 were defined as those below the 25th percentile, between the 25th and the 75th percentile, and above the 75th percentile values, respectively. Examined parameter values were not normally distributed; thus, nonparametric statistical methods were used for the analyses. The Mann-Whitney U test was used to compare levels of vaginal factors between healthy and BV-positive women and between subgroups of patients with BV. The median level of IL-8 was Comparison of diagnostic, microbial, and immune factors in healthy and BV-positive women. The median and interquartile range 25th and 75th percentiles values for pH; Nugent score; prolidase, sialidase, anti-Gvh IgA, and IL-8 concentrations; and leukocyte counts found in vaginal fluid specimens of 85 healthy and 75 BV-positive nonpregnant women are shown in table 1. These parameters were compared between allBV-positive women and healthy control subjects, using the Mann-Whitney U test. As expected, BV-positive women had significantly higher occurrences of BV diagnostic markers i. Prolidase and sialidase levels and anti-Gvh IgA responses were significantly higher in BV-positive women. The leukocyte counts in the vaginal fluid smears were not significantly different for BV-positive women median, 5. Bacterial vaginosis BV diagnostic parameters, enzymatic activities, and immune factors in vaginal fluid from healthy and BVpositive women. View large Download slide Bacterial vaginosis BV diagnostic parameters, enzymatic activities, and immune factors in vaginal fluid from healthy and BVpositive women. Correlation of IL-8 concentration with other local immune factors and microbial activities. Analysis of BV subsets on the basis of IL-8 concentrations. In table 2 , we compared BV-positive women with high, medium, and low IL-8 concentrations. Sialidase levels were higher in medium, compared with high, IL-8 responders, although this difference did not reach statistical significance. Specifically, low IL-8 responders had 3. All such comparisons remained statistically significant when low and medium IL-8 responders were compared. Bacterial vaginosis BV diagnostic parameters, enzymatic activities, and immune factors in vaginal fluid of subgroups of BV-positive women, by interleukin IL -8 level Table 2. View large Download slide Bacterial vaginosis BV diagnostic parameters, enzymatic activities, and immune factors in vaginal fluid of subgroups of BV-positive women, by interleukin IL -8 level Analysis of BV subsets on the basis of anti-Gvh IgA levels. The innate immune factor concentrations were more elevated in women with positive anti-Gvh IgA levels. IL-8 concentrations were increased 6.

Chapter 4 : Cytokines, vol 4: Interleukin-8(NAP-1) and Related Chemotactic Cytokines

Interleukin 8 (IL-8) in the bronchoalveolar lavage fluid from patients with the adult respiratory distress syndrome (ARDS) and patients at risk for ARDS Philippe G. Jorens, Jo Van Damme, Wilfried De Backer, Leo Bossaert.

 Abstract Forty-eight patients were subdivided according to C-reactive protein CRP levels, resulting in 19 patients with normal 2. Anti-inflammatory cytokine levels were normal, except for Il, supporting previous indications that Il contributes to reducing bioavailable iron. Regression analysis suggested decreases in transferrin to be related to increases in Il-8 and an increase in ferritin to be related to a decrease in Il levels. Introduction Cytokine production is a feature of immune stimulation, and alterations in the cytokine profile can influence both the iron status and red blood cell profile. Chronic immune stimulation is often associated with a decrease in serum iron. The effects of cytokines on iron bioavailability are largely mediated through a reduction in duodenal absorption of iron and a shift in the handling of iron by the macrophage in favour of iron storage. The latter can, in time, lead to hypoferraemia [1 â€” 3] and haemosiderosis of the macrophage [2 , 4 , 5]. This reduction in bioavailable iron can contribute to the anaemia of chronic disease ACD. It is commonly accepted that duodenal absorption of iron is decreased during chronic immune stimulation [6], and that cytokines are involved [7]. With chronic immune stimulation the expression of enterocyte ferritin is upregulated, resulting in excessive sequestration and entrapment of iron within the enterocyte [10]. This newly acquired enterocyte iron will subsequently be expelled from the body during sloughing of the lining of the gastrointestinal tract. In addition, the numbers of the basolateral membrane iron exporter, ferroportin, are reduced thus blocking the entry of absorbed iron into the circulation. Ferroportin expression is downregulated by the acute phase protein, hepcidin. Hepcidin release is stimulated by the cytokine interleukin-6 [11]. Iron circulates between the iron-containing compartments intercellular iron shuttling bound to the plasma iron transport protein transferrin. Transferrin is a negative acute phase protein, and as such serum transferrin is reduced during immune stimulation [6] resulting in less iron being available for cellular processes. Ferritin, the major intracellular protein responsible for the storage of macrophage iron, plays a major role in the establishment and maintenance of an iron transfer block in the macrophage and thus in the hypoferraemic state of chronic immune stimulation. Ferritin up-regulation precedes the reduction in serum iron [15]. Cytokines not only upregulate ferritin expression, but also stimulate the macrophage to increase its uptake of iron by increasing the expression of the divalent metal transporter 1. In addition, the anti-inflammatory cytokines, interleukin-4 and interleukin, can upregulate transferrin receptor expression, resulting in an increase in transferrin receptor-mediated uptake of iron by the macrophage [6 , 18]. The macrophage obtains most of its iron by the degradation of haemoglobin and phagocytosis, and degradation of senescent erythrocytes is known to increase during chronic immune stimulation. Not only is haemoglobin iron obtained by degradation of red blood cells, but free plasma haemoglobin is taken up by the haemoglobin scavenger receptor, CD Interleukin and interleukin-6 augment macrophage haemoglobin acquisition by stimulating the expression of the haemoglobin scavenger receptor, CD [18]. In addition to increased uptake of iron by the macrophage during immune stimulation, release of iron is also reduced. Many proinflammatory mediated effects on iron homeostasis are counterbalanced by anti-inflammatory cytokines such as interleukin-4 and interleukin [18]. The aim of this study was to investigate the pro- and anti-inflammatory cytokine status and the possible relationship of these cytokines to the iron status and red blood cell profiles in patients with chronic immune stimulation. A diverse group of patients with chronic disease was divided into two groups based on their C-reactive protein levels and then evaluated in terms of their iron status, red blood cell profiles, and pro- and anti-inflammatory cytokines. Materials and Methods 2. Patients The study group consisted of 48 patients attending the Department of Internal Medicine, Kalafong Hospital, South Africa, for treatment of chronic diseases. Blood and bone marrow were collected from each patient. The diagnosis of the patients were diverse and included various types of infections tuberculosis TB , malaria, human immunodeficiency virus HIV ,

cancers lung, breast , pancytopenias as a result of bone marrow suppression or peripheral destruction of blood cells, organ failures including renal failure, heart failure and liver failure, anaemias with different etiologies, and various other pathologies. This resulted in an extremely heterogenous group of patients. The diagnosis and HIV status of all patients are presented in Table 1. Patients were subdivided based on their C-reactive protein levels. The mean of these values were calculated and used for statistical analysis. HCl-Ferrocyanide Iron Stains of Core Bone Marrow LR White Plastic Sections A piece of core bone marrow was obtained during the time the patients had their biopsies, taken for diagnostic purposes, and placed immediately in the fixative on ice. The fixative was prepared fresh immediately prior to the obtainment of bone marrow tissue. Once the solution had reached the proper temperature stirring was continued for 15 minutes. At this point, the solution was milky. One to two drops of 1 N NaOH was added, with stirring, until the solution cleared [20]. After 24 hours, the bone marrow tissue was washed 3 times for 20 minutes with the sodium phosphate buffer. It was then dehydrated as follows: Subsequently, the bone marrow tissue was infiltrated with a 1: LR White mixture for 30 minutes. The bone marrow tissue was infiltrated with LR White, twice for 30 minutes each. The slides were rinsed in deionised H2O before the staining procedure. After the staining step, the slides were rinsed in deionised H2O. Once again, the slides were rinsed in deionised H2O. Finally, the slides were air-dried on a hot plate and mounted with immersion oil and a cover slide. Statistical Analysis The ranksum test was employed on log transformed data. This was done due to the skewness of the data sets. Testing was done at the 0. Forward stepwise regression with as the entrance point was employed to investigate the relationship between each of the iron status and red blood cell profile parameters and the pro- and anti-inflammatory cytokines. The discrepancy between and adjusted was due to the small sample size. This resulted in a group of 19 patients with normal C-reactive protein 2. The average and SD for age for the group of patients with elevated C-reactive protein was The majority of patients were black females, with the exception of four males and three whites and six males and one white in the elevated C-reactive protein and normal C-reactive protein groups, respectively. The results for the pro- and anti-inflammatory cytokines are presented in Table 2. No significant differences were shown for the proinflammatory cytokines Il-2 and Il However, the T-helper cell type-2 cytokine, Il, was significantly higher in the group of patients with elevated C-reactive protein compared to the group of patients with normal C-reactive protein. Cytokine levels for patients with elevated C-reactive protein and patients with normal C-reactive protein. The iron status of the group of patients with elevated C-reactive protein was characteristic of patients with a chronic proinflammatory immune status. The serum iron markers and soluble transferrin receptor for the two groups of patients are shown in Table 3. Serum transferrin levels were significantly lower, serum ferritin significantly higher, and soluble transferrin receptor significantly lower in the group with elevated C-reactive protein. Serum iron markers and soluble transferrin receptor for patients with elevated C-reactive protein and patients with normal C-reactive protein. When the red blood cell profiles of the group with normal C-reactive protein and the group with elevated C-reactive protein were compared Table 4 , it was seen that both groups were anaemic, but that the MCV, MCH, and the MCHC were significantly lower in the group of patients with normal C-reactive protein. The RDW did not differ significantly between the groups, but was higher than normal for both groups. Red blood cell indices for patients with elevated C-reactive protein and patients with normal C-reactive protein. To assess total body iron stores, in order to distinguish between true iron deficiency and an iron transfer block, a Prussian blue iron stain was performed on the bone marrow aspirates and bone marrow cores. Results can be seen in Table 5. Iron stores and prevalence of iron transfer block for patients with elevated C-reactive protein and patients with normal C-reactive protein. Various correlations were shown between storage iron, bioavailable iron, and red blood cell production in the group of patients with normal C-reactive protein. None of these correlations could be demonstrated in the group of patients with elevated C-reactive protein refer to Table 6. Correlations between storage iron, bioavailable iron, and red blood cell production in patients with normal C-reactive protein levels and patients with elevated C-reactive protein. The dependence of various serum iron markers, soluble transferrin receptor, and red blood cell indices on pro- and anti-inflammatory cytokines in the group of patients with elevated C-reactive protein are presented in Table 7. Discussion C-reactive protein is an acute phase protein and rises sharply with the onset of inflammation reaching peak concentrations within 24â€”48

hours. Inflammatory processes accompanying tissue injury, infection, malignancy, autoimmune diseases, and cardiovascular diseases can all result in an increase in C-reactive protein levels [21]. C-reactive protein is synthesised and secreted by hepatocytes upon stimulation by acute phase protein-inducing cytokines such as Il-6 [22]. In patients with elevated C-reactive protein, the macrophage takes on a proinflammatory role, which is characteristic of a T-helper cell type-1 immune response. An increase in C-reactive protein is thus seen as an indicator of the involvement of the classically activated macrophage proinflammatory macrophage. C-reactive protein levels are considered by some as the most accurate reflection of the inflammatory state [23]. In the present study, patients with chronic disease were divided into two groups based on their C-reactive protein levels and then evaluated in terms of their iron status, red blood cell profiles, and pro- and anti-inflammatory cytokines. Iron status was evaluated by Prussian blue iron stains of bone marrow aspirates and cores, by levels of serum iron markers, and by red blood cell indices. The results are shown in Tables 3 , 4 , and 5. In the group of patients with high C-reactive protein levels, a high prevalence of iron transfer block was found when all factors were considered. As was expected, most of the patients with normal C-reactive protein did not have serum iron profiles characteristic of an iron transfer block. However, these patients had a high incidence of true iron deficiency. Chronic immune stimulation has a negative effect on red blood cell production. Immune-stimulated decreases in bioavailable iron contribute, but other factors, mostly cytokine-induced, are also involved. Such factors include suppression of the proliferation of erythroid progenitor cells, a decrease in the synthesis of erythropoietin, a decrease in the sensitivity of erythroblasts to erythropoietin, and shortened red blood cell life span [24 â€” 26]. The anaemia of chronic disease is, therefore, on the one hand, the result of a decrease in iron reaching the erythron and, on the other, that of a suppression of red blood cell synthesis [24 â€” 26]. In this study, anaemia was present in the majority of patients, irrespective of their C-reactive protein levels. In the patients with normal C-reactive protein the inclusion of a couple of patients with different red blood cell pathologies, such as macrocytic anaemia, resulted in a normal mean corpuscular volume for the group. However, both the mean corpuscular haemoglobin and mean corpuscular haemoglobin concentration were decreased, which is characteristic of the anaemia of true iron deficiency. In the patients with elevated C-reactive protein, the average for the mean corpuscular volume corresponded to that of a normocytic red blood cell profile. It is known that patients with the anaemia of chronic disease ACD often exhibit a normocytic, normochromic anaemia when they are initially seen in medical care facilities [6 , 27]. With further development of ACD, these patients develop a microcytic, hypochromic anaemia. In view of the iron status of the two groups, it would be reasonable to assume that the group with normal C-reactive protein had true iron deficiency anaemia, while the anaemia of the high C-reactive protein group was predominantly that of chronic disease.

Chapter 5 : Interleukin 8 - Wikipedia

Cytokine vol 4 Karger, Basel, p Google Scholar Baggiolini M, Walz A, Kunkel SL () Neutrophil-activating peptide-1/interleukin 8, a novel cytokine that activates neutrophils. J Clin Invest

Purified ExoS protein itself did not degrade IL We next show that IL-8 degradation by PAO1 was inhibited by the addition of serine protease inhibitors. The PAO1 genome encodes 28 different protease genes, including two serine proteases: To understand the significance of IL-8 degradation, we next evaluated neutrophil infiltration in lungs excised from mice intranasally infected with the P. Taken together, our results suggest that P. Presentation of two cases of infants with such symptoms; Conclusion of most cases of Pseudomonas aeruginosa sepsis as nosocomially acquired and occur in subjects Role of Interleukin in defense against pseudomonas aeruginosa infection in lungs. Pseudomonas aeruginosa may cause severe or even fatal infection in hosts with immunodeficiency. Interleukin IL is a newly discovered pro-inflammatory cytokine, which promotes the recruitment and activation of neutrophils in the respiratory tract by inducing release of Neutrophils provide the first line of defense against P. Aside from their defense conferred by phagocytic activity, neutrophils also release Induction of release and up-regulated gene expression of interleukin IL -8 in A cells by serine proteinases. Hypersecretion of cytokines and serine proteinases has been observed in asthma. Since protease-activated receptors PARs are receptors of several serine proteinases and airway epithelial cells are a major source of cytokines, the influence of serine proteinases and PARs on Circulating monocytes from healthy individuals and COPD patients. Although biofilm formation has been extensively studied in vitro on glass or plastic surfaces, much less is Airway epithelial cell signalling is critical to the activation of innate immune A pathogenetic role in antineutrophil cytoplasmic autoantibody-associated glomerulonephritis. In neutrophil trafficking, the role of interleukin-8 IL-8 is location dependent. Tissue IL-8 directs transmigration, whereas intravascular IL-8 frustrates this process.

Chapter 6 : Interleukin-8, a chemotactic and inflammatory cytokine.

Interleukin-8 (IL-8) is a chemokine that belongs to the CXC family. 57, 58 It is an autocrine factor, produced by normal hematopoietic progenitors, mature blood cells, and leukemic cells, that promotes cell survival and proliferation in response to hematopoietic cytokines, functions as a chemoattractant, and activates neutrophils.