DOWNLOAD PDF FACTOR III AND FACTOR IV

Chapter 1 : Factor V and Factor VIII | Oncohema Key

2. a preparation of factor VIII administered intravenously for the prevention or treatment of hemorrhage in patients with hemophilia A and the treatment of von Willebrand disease, hypofibrinogenemia, and coagulation factor XIII deficiency.

Kaufman Laura Popolo Thomas L. Ortel Factor V and factor VIII are two homologous nonenzymatic proteins that play a critical role in blood coagulation, an essential process that involves the sequential activation of plasma proteases in response to blood vessel injury. Factor V and factor VIII circulate in plasma in inactive forms that are devoid of coagulant activity. In their active state, factors Va and VIIIa serve as cofactors for their respective proteases factor Xa and factor IXa , resulting in a striking enhancement of their catalytic activity. To maximally express their function, factor VIIIa and factor Va need to assemble into enzyme complexes. This complex catalyzes the proteolytic conversion of the serine protease factor X to factor Xa. The thrombin-mediated conversion of soluble fibrinogen to insoluble fibrin generates a stable platelet-fibrin clot at the site of vascular injury. This is also underscored by the clinical findings, which indicate that conditions of factor V or factor VIII deficiency lead to parahemophilia and hemophilia A, respectively. The activation process has been the subject of intense investigation during the last two decades. Since proteolysis is an irreversible protein modification, it needs to be spatially and temporally controlled. Efficient inactivation mechanisms targeting the cofactors exist and are essential for normal hemostasis. One key reaction in down-regulating coagulation is the inactivation of factor Va by the anticoagulant-activated protein C APC. Cleavage of factor Va at specific sites converts it into factor Vai with a complete loss of cofactor activity. Although the knowledge of factor V and factor VIII and their regulation has progressed significantly over the last two decades, the molecular mechanisms by which protein cofactors factor V and factor VIII accelerate substrate cleavage remains to be fully defined. The difficulties in having homogeneous preparations of these factors were partially overcome by the advent of recombinant DNA technologies. However, the dynamics and interactions of these factors with partners ions, membranes, activators and inhibitors, plasma proteins are many, and their analyses require a reductionist approach and a rather complex process of critical integration and interpretation of the results obtained. The molecular models that were recently built on the basis of the crystal structures of factor VIII, factor Vai, and their interacting proteins proteases and substrate-proteases provide a background to gain insight into the mechanistic details of how the structure of these factors changes to fulfill their function. Quick 1 first reported the identification of a labile factor in plasma that was necessary for the rapid conversion of prothrombin to thrombin. At approximately the same time, Owren 2 identified a patient with a severe bleeding disorder parahemophilia , who lacked this factor. This protein, which was the fifth coagulation factor to be discovered, was designated factor V. Subsequent work established that activated factor V functions as a nonenzymatic cofactor in the prothrombinase complex. Transfusion of whole blood was shown to successfully treat a hemophilia-associated bleeding episode by In the early s, factor VIII was purified from human plasma 8 and subsequently the gene was cloned. At approximately the same time, the human factor V gene was isolated. Over the past three decades, considerable efforts have been made defining the cofactor activity and its regulation. The exons range in size from 72 to base pairs bp with the exception of exon 13, which spans 2, bp. The introns range in size from bp to The length of F5 mRNA is approximately 7 kb. A rich report of this gene and the surrounding genomic region is available at NCBI www. The top line shows the scale of F5 genomic sequence. The second line shows the intron-exon organization of F5 with the exons being represented by green boxes. For F8, the bar represents the scale, and the bottom of the figure shows the intron-exon organization with exons represented by green boxes. The genomic region between exons 22 and 23 is enlarged to show the direction of transcription of F8A and F8B see text. F8 is localized on human X chromosome Xq The exon length varies from 69 to bp except for exon 14 that is 3, bp and the last exon 26 that has 1, bp. There are some large intervening sequences including IVS22 that is 32 kb long. F8 mRNA is approximately 9 kb, of which the coding sequence covers 7, nucleotides. One transcript of 1. The orientation of this transcript is opposite to that of factor VIII and contains no intervening sequence. The two transcripts F8A and F8B originate within bases from each other. The sequences of F8A and F8B along with a

few kilobases of surrounding DNA are also present in two other areas of the X chromosome approximately kb telomeric to F8. Transgenic mice with a deletion of the F8B gene showed particular eye abnormalities, suggesting that migration of neural crest cells might have been perturbed during eye development. At the N-terminal, both precursors have a signal peptide, of 19 and 28 amino acids, respectively, that is cleaved upon translocation in the lumen of the endoplasmic reticulum ER. The B domain is encoded by an unusually large single exon spanning 3. In general, the B-domain sequence is about amino acids in length and rich in flexible amino acids e. A unique feature of both B domains is their unusual number of N-linked oligosaccharides. In the human factor V B-domain, two tandem repeats of a amino acid sequence and 31 tandem repeats of a nine-amino acid sequence are present FIGURE The significance of the tandem repeats structures that are present in the B domain of factor V, but not factor VIII, remains to be determined. The structural domains of the single-chain factor V are depicted in the top line by the labeled boxes: The location of potential disulfide bonds and asparagine-linked glycosylation sites is not shown for simplicity see Accession number P at UniprotKB: The violet diamonds indicate the location of putative sulfotyrosines. The thrombin cleavage sites are indicated by the black arrows at the top of the figure. The location of the APC cleavage sites are indicated by red arrows at the bottom of the scheme. The apparent molecular mass of the intermediates and final products following activation by thrombin and inactivation by APC are indicated. The heavy chain and light chain of thrombin-activated factor V Va form a calcium-dependent heterodimer. The numbering refers to the amino acid sequence devoid of the signal sequence. The analysis of homologies of the primary sequences of factors V and factors VIII from different species suggests that these genes evolved from an ancestral ferroxidase gene by triplication of the A domain, insertion of the B domain, and addition of the C domains to the primordial cofactor gene. Subsequently, the factor V and factor VIII genes possibly evolved by duplication and divergence of amino acid residues within the B domain, although the high number of N-glycosylation sites were preserved, while amino acid sequences within the A and C domains were conserved. Human megakaryocytes also have been shown to contain factor V mRNA and to express factor V 27 but it is believed that most or all of platelet factor V originates from the plasma pool by endocytosis. The storage of factor V within platelets appears to be important because, when platelets aggregate to form the primary hemostatic plug, they also provide both a surface for assembly of the prothrombinase complex as well as high local concentrations of released platelet factor V. In addition, residual platelet factor V supports thrombin generation in patients with severe factor V deficiency and mild bleeding symptoms. The structural domains of the full-length factor VIII are depicted in the top line by the labeled boxes: The black boxes represent regions enriched in acidic amino acids. The ball-stick symbol violet represents the positions of sulfotyrosine residues that were experimentally determined residues , , , , , The location of free cysteine residues, disulfide bonds, and asparagine-linked glycosylation sites is not shown see Accession number P at UniprotKB Database: Within the Golgi compartment in the cell, factor VIII is cleaved at two sites within the B domain to generate heavy-chain polypeptides of variable size 90 to kDa and the kDa light chain. The cleavage sites for activation by thrombin black arrows and inactivation by APC red arrows are shown at the point of the processed products. The apparent molecular mass kDa of the intermediates and final products are indicated. Initial immunochemical localization by light microscopic 34 or electron microscopic 35 examination detected the factor VIII antigen in hepatocytes. A significant portion of newly synthesized factor VIII is retained in the ER through interactions with two protein chaperone systems designed to prevent the exit of unfolded proteins from the ER. BiP expression is induced by glucose deprivation, inhibition of N-linked glycosylation, or the presence of malfolded protein within the ER. In addition, high-level factor VIII expression can also induce transcription of the BiP gene indicating the induction of the unfolded protein response for details, see Chapter 5. Substitution of phenylalanine at residue with serine within the hydrophobic sheet increased the secretion efficiency of factor VIII several-fold and this correlated with a reduced requirement for ATP for secretion. Finally, a portion of factor VIII forms high molecular weight aggregates immediately after synthesis. The figure depicts the pathway of biosynthesis of factor VIII from the primary translation product that is translocated into the lumen of the ER to the medium as determined by expression in culture cells. Rapid trimming of the two outermost glucose residues of the N-linked glycans

N-acetylglucosamine2-mannose9-glucose3 prepares protein-bound N-glycans for association with the two homologous ER lectins calnexin CNX and calreticulin CRT and exposure to the glycoprotein-specific oxidoreductase ERp57 to catalyze proper disulfide bond rearrangement see Chapter 5. Although the modalities of misfolded protein domain recognition and ER retention are not known, 50 , 51 the enzyme UDPglucose: Factor VIII contains eight disulfide bonds and factor V has seven putative disulfide bonds deduced by similarity. Interestingly, it has been recently reported that treatment with antioxidants improves secretion of factor VIII from cultured cells suggesting that folding of complex multidomain proteins can generate oxidative stress. The sum of these findings supports the notion that oligosaccharide processing plays a central role in directing factor VIII trafficking within the secretory pathway. Also within the Golgi apparatus, factor VIII is further processed by a modification of the asparagine-linked high mannosecontaining oligosaccharides to complex types, b addition of carbohydrate to multiple serine and threonine residues within the B domain O-glycosylation , and c addition of sulfate to six tyrosine residues within the heavy and the light chains 61 FIGURE In vitro reconstitution experiments demonstrated that vWF can directly promote reassembly of isolated heavy and light chains of factor VIII, 62 , 64 suggesting a possible role of vWF in facilitating factor VIII assembly. The recently reported three-dimensional 3-D structures of these factors identified the position of the high-affinity ion-binding sites and provided new interpretations on the role of ions in factor V and VIII structure and function. The two A domains sit on a platform formed by the two C domains, which are aligned in an edge-to-edge fashion, a feature that was found to be present also in the crystal structure of a recombinant single-chain B-domain-deleted human factor VIII FIGURE The van der Waals representation in the background shows the surface contour of the protein. The C domains are side-by-side and predict a role in membrane binding see text. Adapted from Adams TE, et al. The crystal structure of activated protein C-inactivated bovine factor Va: A high-affinity calcium-binding site and a copper-binding site were identified in factor Vai. Chain association is required for factor V function and is dependent on a divalent cation. Although calcium ion was believed to bridge the heavy and light chains, 74 the structure revealed that the high-affinity calcium-binding site is located entirely in the A1 domain 74 FIGURE The side chains of both Asp and Asp, along with the main-chain carboxyl oxygens of Lys93 and Glu, coordinate the calcium ion. The structural studies clearly indicate that chain association cannot directly be attributed to the coordination of calcium but rather calcium may play a role in the maintenance of the A1-C3 domain interface. The role of copper ion in factor V has always been uncertain. A single copper ion-binding site is located in the A3 domain of bovine factor Vai with ligands His, His, and Asp arranged in a trigonal planar coordination geometry. However, the structure of factor Vai suggested that copper ion provides additional stabilization of the A1-A3 interface rather than directly linking the two domains. The A1 domain and a2 acidic regions are colored in dark blue. The A2 domain and the a2 acidic region are in light blue. The A3 domain, the C1 domain, and the C2 domain are colored dark red, dark pink, and light pink, respectively.

Chapter 2 : Factor V and VIII Combined Deficiency

This gene encodes coagulation factor III which is a cell surface glycoprotein. This factor enables cells to initiate the blood coagulation cascades, and it functions as the high-affinity receptor for the coagulation factor VII. The resulting complex provides a catalytic event that is responsible for.

Maintenance doses of one half the initial dose may be given at these intervals. The frequency depends on the severity of bleeding, with more frequent dosing for serious bleeding. Increased oral or intravenous fluids are necessary to maintain renal output. Subsequent doses are adjusted according to the plasma factor levels. Repeat doses are administered for as long as needed based on repeat monitoring of appropriate clinical and laboratory measures. Dosages should be adjusted according to the extent and location of bleeding. RCof of approximately 3. Table 2 shows dosing recommendations for pediatric and adult patients. Dosing Guidelines for the Treatment of von Willebrand Disease treatment. Factor VIII-C levels should be monitored and maintained according to the guidelines for hemophilia A therapy Control of perisurgical hemostasis Dental and oral surgery: Intravenous, 40 IU per kg of body weight prior to surgery. A single dose is often sufficient for normal hemostasis when an antifibrinolytic agent, such as aminocaproic acid or tranexamic acid, is used as adjunctive treatment. Usual pediatric dose Size s usually available: Preparation of dosage form: The specific activity of AHF Porcine is more than 15 porcine units per mg of protein. The dry concentrate should then be dissolved with 20 mL of sterile water for injection. The vial should be shaken gently until the concentrate is dissolved, taking care to prevent foaming. Administration should begin within 3 hours after reconstitution. Partially used vials should be discarded. However, the rate at which recombinant AHF is administered should be guided by the comfort of the patient.

Chapter 3 : Factor XII Deficiency - NORD (National Organization for Rare Disorders)

Factor III Factor IV Laws and Violence superior and no plan rules Is the march of human society towards economic progress, greater freedom, democracy.

Genetics[edit] The gene for factor V is located on the first chromosome 1q It is genomically related to the family of multicopper oxidases , and is homologous to coagulation factor VIII. The gene spans 70 kb, consists of 25 exons, and the resulting protein has a relative molecular mass of approximately kDa. Structure[edit] Factor V protein consists of six domains: The A domains are homologous to the A domains of the copper-binding protein ceruloplasmin , and form a triangular as in that protein. A copper ion is bound in the A1-A3 interface, and A3 interacts with the plasma. The B domain C-terminus acts as a cofactor for the anticoagulant protein C activation by protein S. The protein is now divided to a heavy chain, consisting of the A1-A2 domains, and a light chain, consisting of the A3-C1-C2 domains. Both form non-covalently a complex in a calcium-dependent manner. This complex is the pro-coagulant factor Va. The molecule circulates in plasma as a single-chain molecule with a plasma half-life of 12â€”36 hours. On activation, factor V is spliced in two chains heavy and light chain with molecular masses of and , respectively which are noncovalently bound to each other by calcium. The thereby activated factor V now called FVa is a cofactor of the prothrombinase complex: The activated factor X FXa enzyme requires calcium and activated factor V to convert prothrombin to thrombin on the cell surface membrane. Factor Va is degraded by activated protein C , one of the principal physiological inhibitors of coagulation. In the presence of thrombomodulin , thrombin acts to decrease clotting by activating Protein C; therefore, the concentration and action of protein C are important determinants in the negative feedback loop through which thrombin limits its own activation. Role in disease[edit] Various hereditary disorders of factor V are known. Deficiency is associated with a rare mild form of hemophilia termed parahemophilia or Owren parahemophilia , the incidence of which is about 1: It inherits in an autosomal recessive fashion. Other mutations of factor V are associated with venous thrombosis. They are the most common hereditary causes for thrombophilia a tendency to form blood clots. The most common one of these, factor V Leiden , is due to the replacement of an arginine residue with glutamine at amino acid position RQ. It therefore remains active and increases the rate of thrombin generation. History[edit] Until the discovery of factor V, coagulation was regarded as a product of four factors: She had suffered from nosebleeds and menorrhagia excessive menstrual blood loss for most her life, and was found to have a prolonged prothrombin time , suggesting either vitamin K deficiency or chronic liver disease leading to prothrombin deficiency. However, neither were the case, and Owren demonstrated this by correcting the abnormality with plasma from which prothrombin had been removed. Most investigations were performed during the Second World War , and while Owren published his results in Norway in , he could not publish them internationally until the war was over. They appeared finally in The Lancet in Confirmatory studies from other groups led to their final approval several years later. VI was the factor that accelerated the conversion from prothrombin to thrombin. It was later discovered that factor V was "converted" activated by thrombin itself, and later still that factor VI was simply the activated form of factor V.

Chapter 4 : Factor V - Wikipedia

The FSSC-SA has a five-factor solution: Factor I (fear of danger and death), Factor II (fear of the unknown), Factor III (worries), Factor IV (fear of animals), and Factor V (situational fears). Comparing fears in South African children with and without visual impairments.

This factor enables cells to initiate the blood coagulation cascades, and it functions as the high-affinity receptor for the coagulation factor VII. The resulting complex provides a catalytic event that is responsible for initiation of the coagulation protease cascades by specific limited proteolysis. Unlike the other cofactors of these protease cascades, which circulate as nonfunctional precursors, this factor is a potent initiator that is fully functional when expressed on cell surfaces. There are 3 distinct domains of this factor: This protein is the only one in the coagulation pathway for which a congenital deficiency has not been described. Alternate splicing results in multiple transcript variants. The interaction with filamin A may translocate cell surface TF to cholesterol-rich lipid rafts, increasing cell surface TF activity as well as TF incorporation and release into microvesicles. Our study identifies a previously undescribed role of miRNA in venous thrombosis by regulating TF expression. Cell lines with intrinsically high TF expression were associated with decreased cancer stem cell activity. Knockdown of TF was associated with increased cancer stem cell activity. Overexpression of TF was associated with decreased cancer stem cell activity. Expression of TF did not affect cellular viability but may increase proliferation. The highest tissue factor activity was detected in microparticles from monocytes, lower activity - in microparticles from endothelial cells and THP-1 cells, and no activity - in microparticles from platelets and granulocytes. These results demonstrate that procoagulant microvesicles shed by head and neck squamous cell carcinoma line UMSCC81B induced a procoagulant effect in HUVECs through increased clotting activity and cell membrane surface expression of TF. Patients with early onset preeclampsia are characterised by an attenuated coagulation response characterised by reduced thrombin generation stimulated by low-dose TF and elevated plasma TFPI activity. The proinflammatory cytokine IL induces differential tissue factor expression and activity in monocyte subsets, as well as the release of procoagulant microvesicless. In this manner, IL may contribute to the formation of a prothrombotic state characteristic for cardiovascular disease. Pin1 is a fast-acting enzyme which may be utilised by cells to protect the phosphorylation state of TF in activated cells prolonging TF activity and release, and therefore ensuring adequate haemostasis. Circulating pentraxin nCRP has little pro-angiogenic effect but when dissociated into mCRP on the surface of endothelial cells it is able to trigger potent proangiogenic effects by inducing F3-gene upregulation and TF signaling. TF is an angiogenic-specific receptor and the target molecule for fVII-targeted therapeutics. It was demonstrated that the nature of the clot formed, as determined from the quartz crystal microbalance parameters, was highly dependent on the rate of clot formation resulting from the TF concentration used for activation. These parameters could also be related to physical clot characteristics such as fibrin fibre diameter and fibre density, as determined by scanning electron microscopic image analysis. Through induction of TF in vascular endothelial cells, IL could enhance their thrombotic capacity and thereby might impact on thrombus formation in the setting of atherosclerosis. Tissue Factor was highly expressed in Platelet tissue factor activity and membrane cholesterol are increased in hypercholesterolemia and normalized by rosuvastatin, but not by atorvastatin. Ticagrelor, but not clopidogrel, reduces arterial thrombosis via endothelial tissue factor suppression. The aim of this study was to evaluate the concentration of TF and its inhibitor TFPI in blood plasma, the impact of traditional and non-traditional cardiovascular risk factors on their concentration and the impact of both markers of haemostasis on the severity of subclinical atherosclerosis. TF is highly expressed in breast neoplasms, but does not predict survival or correlate with tumor size. TF levels were significantly elevated in type 2 diabetes mellitus both with and without cardiovascular complications when compared to the controls. We suggest that pathologic plasma TF activity, as marker of increased propensity of clot pathology, should be investigated. However, our data also indicate that TF regions outside of the putative lipid binding region may also contribute to PS-dependent decryption of TF. These findings suggest that cancer cell-derived extracellular vesicles mediate

coagulopathy resulting in ischemic stroke via TF-independent mechanisms. Circulating miR exhibits antithrombotic properties via regulating post-transcriptional TF expression, thereby impacting the hemostatic balance of the vasculature in diabetes mellitus. Low concentrations of TF and exogenous FXIa, each too low to elicit a burst in thrombin production alone, act synergistically when in combination to cause substantial thrombin production. The role of these molecules in the pathogenesis of this disease and in alterations of hemostatic and histopathological aspects of placentas need further studying. These findings suggest that activation of TF-pathway is an important component of dengue virus-related coagulation disorders. TF may have a critical role in the hypoxic podocyte injury. These results reveal a functional link between VWF and TF under whole blood flow conditions, in which surface-immobilized TF and VWF mutually contribute to mural thrombus formation, which is essential for normal hemostasis. By contrast, TF circulating in blood may be involved in systemic hypercoagulability, as seen in sepsis caused by severe microbial infection, in which neutrophil inflammatory responses may be active. These factors may play an important role in the development of chronic thromboembolic pulmonary hypertension. Microvesicle-associated tissue factor procoagulant activity, but not plasma TF antigen, may provide valuable additional information for the diagnostic work-up of women with suspected ovarian cancer. This brief review summarizes the contribution of the coagulation system and in particular the role of TF in brain hemostasis as well as to the pathophysiology of stroke and multiple sclerosis. The data obtained indicate that active tissue factor, TF is present in membrane microparticles produced in vitro by endothelial cells, monocytes, and THP-1 cells, but not in microparticles derived from granulocytes and platelets. Results indicate that granulocyte-colony stimulating factor receptor, tissue factor, and vascular endothelial growth factor receptor bound vascular endothelial growth factor expression as well as their co-expression might influence breast cancer biology. The findings of the study show an increased expression of tissue factor in the lesional and perilesional skin of patients with bullous pemphigoid. The expression of TF was not observed in biopsies from healthy people and dermatitis herpetiformis patients. High serum Tissue Factor levels are associated with Pancreatic Cancer. TF plays more fundamental roles in cancer biology. TF regulates tumor cell dormancy, is associated with cancer stem cell behavior, epithelial-to-mesenchymal transition, and dictates establishment of the tumor cell premetastatic niche. Insights into Platelet Tissue Factor. Soluble Tissue Factor" in the 21st Century: Tissue factor isoform and estrogen signaling share downstream targets in BrCa; concomitant asTF and estrogen signaling is required for BrCa cell proliferation. Data suggest that tissue factor thromboplastin functions in initiation phase of blood clotting cascade and contributes to regulation of hemostasis versus thrombosis. The most cell proliferation and cyclin D1 expression were seen in cells expressing wild-type or Aspsubstituted TF. Increased cellular apoptosis was seen in cells expressing Alasubstituted TF or pre-incubated with TF-rich microvesicles. B-Raf VE mutation in metastatic melanoma cells up-regulated tissue factor expression on cell membranes and promoted thrombin production Tissue factor is an endogenously synthesised protein that characterises megakaryocyte maturation and that it is transferred to a subset of newly-released platelets where it is functionally active and able to trigger thrombin generation. Association between micro particle-tissue factor activity, factor VIII activity and recurrent VTE in patients with acute pulmonary embolism. Hyperglycemia of short duration increases TLR4 and TF-procoagulant activity, key players in inflammation and thrombosis. Tissue factor-regulated vascular smooth cell migration and microvessel formation is under the control of the ER-protein PDIA2. Contribution of FXIa and platelet-derived polyphosphate in thrombin generation varies depending on surface tissue-factor level. Molecular dynamics simulation of tissue factor activation of factor VIIa. Common genetic variation in tissue factor was significantly associated with outcome of severe sepsis in Chinese Han population. Describe inhibition of tissue factor: Tissue factor TF is known to be the key element in the initiation of the extrinsic pathway of the coagulation cascade and appears to be a critical determinant of atherosclerotic plaque thrombogenicity. Pregnancy was not associated with changes in cell origin of circulating maternal microparticles or in the number of tissue factor-expressing microparticles. Neither genetic polymorphisms nor the plasma levels of TF seem to act as direct risk factors for venous thromboembolism. MiRmediated suppression of TF expression provides a novel molecular mechanism for the regulation of coagulation cascade data provide evidence that elevated levels of circulating TF are potential risk factors for

ischemic strokes. Alpha-1 proteinase inhibitor MR inhibits endogenous thrombin on cells co-expressing tissue factor. Microparticle-associated tissue factor activity did not differ between patients with acute deep vein thrombosis and healthy controls. Tissue factor TF and fibrinogen in peripheral artery disease patients undergoing endovascular revascularization can participate in the formation of restenosis. Overexpression of miRb inhibited TF expression and procoagulant activity. Colon tissue factor levels are increased in ulcerative colitis. Suggest that cell confluence and the type of flow are critical independent factors in the induction of TF and PECAM-1 phosphorylation in endothelial cells exposed to disturbed pulsatile flow and chemical stimuli. Tissue factor-rich endothelial microparticles released by microvascular endothelial cells can overcome the consequences of arterial occlusion and tissue ischemia by promoting postischemic neovascularization and tissue reperfusion. TF expression correlates with poor prognosis in glioma, but not in Glioblastoma multiforme. These studies reveal the functional contributions of residues in the C-terminal half of the tissue factor ectodomain that are implicated in interacting with phosphatidylserine headgroups. Patients with cirrhosis have increased levels of circulating microparticle tissue factor activity. TF expression levels in pretreatment biopsy samples are useful for predicting response to neoadjuvant chemotherapy in advanced esophageal cancer. This covers the expression and regulation of TFA by hepatocytes, the role of TFA in coagulation triggered by liver toxicity, and the contribution of coagulation activity to the progression of liver disease. Tissue factor inflammatory response regulated by promoter genotype and p38 MAPK in neonatal versus adult microvascular endothelial cells. This increases significantly with increase of the stage of the Child-Pugh score. TF expression was increased in clear cell ovarian cancer and endometroid cancer and this may explain the higher risk of venous thromboembolism in these subgroups. Data demonstrate that TF encryption is not limited to a specific cell type, and unlike previously thought, the majority of the TF expressed in cancer cells is not constitutively procoagulant. These results demonstrate that coagulation kinetics for circulating tissue factor particles are controlled by factor IX and X levels within the normal physiological range. Hypoxia-induced expression of TF in human breast cancer cells depends on Egr-1 and HIF-1alpha, and both of these proteins may play an important role in breast cancer metastasis, either directly or indirectly through the TF pathway. Targeting asTF may comprise a previously unexplored therapeutic strategy in BrCa that stems tumor growth, yet does not impair normal hemostasis Bivalirudin reduces periprocedural platelet activation and inhibits thrombin-induced tissue factor expression in vascular smooth muscle cells. Tissue factor promoted tumor growth may be attenuated by EPCR expression. The expression of tissue factor and tissue factor pathway inhibitor in prostate cancer cells themselves is unlikely to be the source of hypercoagulability in patients, but might precipitate chains of events that would produce such an effect. The reduction of TF disulfides with or without alkylation eliminates TF regulation of factor VIIa catalytic function in both membrane dependent FX activation and membrane independent synthetic substrate hydrolysis. Increased numbers of circulating tisse factor exposing microparticles were found in patients with IBD, but lack of association with coagulation system activation and disease activity questions their role in venous thromboembolism in this group. Presence of TF within microparticles enhances the interactions of endothelial cell-derived microparticles with extracellular matrices in an integrin-dependent manner, enhancing TF activity. The abnormal co-upregulated expression of TF and PAR-2 in eutopic and ectopic endometrium may affect the development and growth of endometriotic lesions. Study demonstrates the involvement of autophagic machinery in the extracellular delivery of TF in Neutrophil extracellular traps and the subsequent activation of coagulation cascades. TF inhibition caused basal cell apoptosis and necrosis. This was due to two parallel but interdependent TF-regulated processes: This review article presents the established knowledge of tissue factor expression in endothelial cells and current opinions on encrypted TF form and mechanisms of its activation. Our data demonstrate that ixolaris targets B16F10 cell-derived TF, resulting in the reduction of both the primary tumor growth and the metastatic potential of melanoma, as well as the inhibition of tumor angiogenesis. Transforming growth factor-beta1 markedly enhanced tissue factor expression in primary human lung fibroblasts. In this review, we aim to present a side-by-side evaluation of normally-spliced, full length TF flTF and asTF with regard to coagulant function, atherosclerosis, tumor progression and malignancy-associated thrombosis.

Chapter 5 : Tissue factor - Wikipedia

Tissue factor, also called platelet tissue factor, factor III, or CD is a protein encoded by the F3 gene, present in subendothelial tissue and www.nxgvision.com role in the clotting process is the initiation of thrombin formation from the zymogen prothrombin.

This haemostatic plug is a temporary formation, under physiological conditions, necessary to allow wound repair mechanisms repair the lesion. Coagulation is the process by which blood forms clots. It is an important part of haemostasis, the cessation of blood loss from a damaged vessel, wherein a damaged blood vessel wall is covered by a platelet and fibrin-containing clot to stop bleeding and begin repair of the damaged vessel. Disorders of coagulation can lead to an increased risk of bleeding haemorrhage or obstructive clotting thrombosis. Coagulation begins almost instantly after an injury to the blood vessel has damaged the endothelium lining of the vessel itself. Platelets immediately form a plug at the site of injury; this is called primary haemostasis. Secondary haemostasis occurs simultaneously: Proteins in the blood plasma, called coagulation factors or clotting factors, respond in a complex cascade to form fibrin strands, which strengthen the platelet plug. The coagulation factors are chemically heterogeneous, circulating in the blood or released from the tissues at the time of the vessel injury. Today, we know 12 factors numbered with Roman numerals I to XIII, excluding VI, which does not exist , and two factors that correspond to prekallikrein and kininogen. They are chemically heterogeneous substances, circulating in the blood or liberated from the tissues at the time of lesion of the vessel, whose activity is required for the normal development of blood clotting. Factor V is a protein of the coagulation system, rarely referred to as proaccelerin or labile factor. In contrast to most other coagulation factors, it is not enzymatically active but functions as a cofactor. Deficiency leads to predisposition for hemorrhage, while there are some mutations that predispose for thrombosis. All the four of them result then dangerous because lead to hypercoabulability disorders and deep vein thrombosis. The most common and best understood of these mutations is Factor V Leiden. Defects in this gene result in haemophilia A, a recessive X-linked coagulation disorder. Thrombin in turn cleaves fibrinogen to form fibrin, which polymerizes to form the dense meshwork that makes up the majority of a clot. Activated protein C aPC is a natural anticoagulant that acts to limit the extent of clotting by cleaving and degrading factor V. Factor V Leiden is an autosomal dominant condition that exhibits incomplete dominance and results in a factor V variated that cannot be as easily degraded by aPC activated Protein C. The gene that codes the protein is referred to as F5. Mutation of this gene - a single nucleotide polymorphism SNP - is located in exon Depending on the chosen start the position of the nucleotide variant is either at position or It also affects the amino acid position for the variant, which is either or Since this amino acid is normally the cleavage site for aPC, the mutation prevents efficient inactivation of factor V. When factor V remains active, it facilitates overproduction of thrombin leading to generation of excess fibrin and excess clotting. Factor VIII participates in blood coagulation. It is released into the bloodstream by the endothelial cells of the vascular networks: The factor VIII gene produces two alternatively spliced transcripts. Transcript variant 1 encodes a large glycoprotein, isoform a, which circulates in plasma and associates with von Willebrand factor in a noncovalent complex. This protein undergoes multiple cleavage events. Transcript variant 2 encodes a putative small protein, isoform b, which consists primarily of the phospholipid binding domain of factor VIIIc. This binding domain is essential for coagulant activity. After activation by thombin factor IIa , it dissociates from the complex and interacts with factor IXa in the coagulation cascade. Thrombin cleaves fibrinogen to fibrin which polymerizes to give crosslink with factor XIII in a blood clot.

Chapter 6 : Factor VIII Drug Information, Professional

Factor V deficiency is a rare blood clotting disorder that results in slow or prolonged blood clotting after an injury or surgery. The combination of factor V and factor VIII deficiencies is.

General Discussion Summary Factor XII deficiency is a rare genetic blood disorder that causes prolonged clotting coagulation of blood in a test tube without the presence of prolonged clinical bleeding tendencies. It is caused by a deficiency of the factor XII Hageman factor , a plasma protein glycoprotein. Specifically, factor XII is a clotting factor. Clotting factors are specialized proteins that are essential for proper clotting, the process by which blood clumps together to plug the site of a wound to stop bleeding. Although it is thought that factor XII is needed for proper blood clotting, when it is deficient, other blood clotting factors appear to compensate for its absence. Therefore, the disorder is thought to be benign and usually presents no symptoms asymptomatic ; it is usually only accidentally discovered through pre-operative blood tests that are required by hospitals. The disorder is sometimes known as Hageman factor deficiency or Hageman trait. However, when blood from a patient is subjected to a partial thromboplastin time test PTT , a test measuring clotting time, it takes an abnormally long time for the blood to clot. Serum prothrombin PT time, another test of blood clotting, is also abnormally long. The blood level of factor XII tends to vary greatly. According to some older medical reports, factor XII deficiency may predispose affected individuals to developing blood clots thrombi at an early age. For example, individuals may have a greater risk than the general population in developing deep vein thrombosis or acquired thrombotic disorders. However, such an association remains unproven. Researchers are now studying drugs to block inhibit factor XII as a potential therapy for individuals who are prone to developing blood clots. More research is necessary to determine the exact role that factor XII plays in the development or prevention of blood clots and its overall functions in the body. There are also reports in the medical literature that suggest an association between factor XII deficiency and repeated unexplained miscarriages in some affected women. However, such an association remains controversial and unproven. Causes Factor XII deficiency is inherited as an autosomal recessive disorder. Genetic diseases are determined by two genes, one received from the father and one from the mother. Recessive genetic disorders occur when an individual inherits the same abnormal gene for the same trait from each parent. If an individual receives one normal gene and one gene for the disease, the person will be a carrier for the disease, but usually will not show symptoms. The risk is the same for males and females. Investigators have determined that factor XII deficiency occurs due to mutations of the F12 gene located on the long arm of chromosome 5 5qqter. Chromosomes, which are present in the nucleus of human cells, carry the genetic information for each individual. Pairs of human chromosomes are numbered from 1 through 22, and an additional 23rd pair of sex chromosomes which include one X and one Y chromosome in males and two X chromosomes in females. Chromosomes are further sub-divided into many bands that are numbered. The numbered bands specify the location of the thousands of genes that are present on each chromosome. The F12 gene creates encodes factor XII, which is a clotting factor. The exact role that factor XII plays in the clotting process and any additional effects it has on the body are not fully understood. In addition to the clotting process, factor XII is believed to play a role tissue repair and the formation of blood vessels angiogenesis. Affected Populations Factor XII deficiency affects persons of Asian descent more often than individuals of other ethnicities. Males and females are affected in equal numbers. Since no symptoms are usually associated with factor XII deficiency, many individuals remain undiagnosed. The exact incidence of the disorder in the general population is unknown, but estimated to be approximately 1 in 1 million individuals. Related Disorders Symptoms of the following disorders can be similar to those of factor XII deficiency. Comparisons may be useful for a differential diagnosis: Hemophilia is a general term for a group of rare bleeding disorders. Most forms of hemophilia rare inherited blood clotting coagulation disorder caused by inactive or deficient blood proteins. There are three major forms of inherited hemophilia: Hemophilia A and B are inherited as X-linked recessive genetic disorders, while hemophilia C is inherited as an autosomal recessive genetic disorder. Therefore, while hemophilia A and B are fully expressed in males only, hemophilia C affects males and females in equal

numbers. Hemophilia A is the most common form of hemophilia and is characterized by a deficiency of factor VIII, one of several specialized proteins required for the blood to clot. Hemophilia may be classified as mild, moderate, or severe. The level of severity is determined by the percentage of active clotting factor in the blood normal percentage ranges from 50 to percent. People who have severe hemophilia have less than one percent of active clotting factor in their blood. There are also combined deficiencies of more than one factor. For more information on these disorders, choose the specific disorder name as your search term in the Rare Disease Database. Clotting factors are specialized proteins that are essential for the blood to clot properly. Specifically, individuals with factor XIII form blood clots like normal, but these clots are unstable and often break down, resulting in prolonged, uncontrolled bleeding episodes. Factor XIII also affects other processes in the body and is known to play a role in proper wound healing and pregnancy. The severity of factor XIII deficiency can vary greatly from one person to another. Some individuals may have no symptoms asymptomatic or only mild symptoms; other individuals may have severe, life-threatening complications. With early diagnosis and prompt treatment, the more serious complications of factor XIII deficiency can be avoided. Factor XIII deficiency is caused by mutations to one of two different genes. Factor XIII deficiency is inherited as an autosomal recessive disorder. Diagnosis Factor XII deficiency is often diagnosed accidentally during a routine blood clotting coagulation tests as in one done before surgery. In affected individuals, it will take longer for their blood to clot during these tests. Further tests can reveal low levels of factor XII in the blood. Clinical Testing and Work-up A diagnosis of factor XII deficiency may be suspected in individuals without clinical signs or a previous history of a bleeding disorder in whom specialized tests called screening coagulation tests known as activated partial thromboplastin time aPTT or prothrombin time PT are abnormal. These tests measure how long it takes the blood to clot. Individuals with abnormal results on these tests but no bleeding symptoms may then be screened for a condition known as antiphospholipid syndrome. A test will be run to detect a specific inhibitor called lupus anticoagulant, which is present in individuals with acquired antiphospholipid syndrome and can cause similar abnormal results on the aPTT or PT tests. A diagnosis of factor XII deficiency can be confirmed by a test called an assay. An assay is a test that measures the activity of coagulation factors. It can demonstrate a deficiency of factor XII. Standard Therapies Treatment for this disorder is usually not necessary since bleeding abnormalities only mild or nonexistent. Investigational Therapies Information on current clinical trials is posted on the Internet at www. All studies receiving U.

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Chapter 7 : Blood Transfusion : Clotting Factor Concentrates

Factor V (pronounced factor five) is a protein of the coagulation system, rarely referred to as proaccelerin or labile www.nxgvision.com contrast to most other coagulation factors, it is not enzymatically active but functions as a cofactor.

What is factor V deficiency? Factor V, or proaccelerin, is a protein made in your liver that helps convert prothrombin into thrombin. This is an important step in the blood clotting process. There are different levels of severity of factor V deficiency based on how little or how much factor V is available to the body. Factor V deficiency may also occur at the same time as factor VIII deficiency, producing more severe bleeding problems. What role does factor V play in normal blood clotting? Factor V is one of about 13 clotting factors responsible for normal blood coagulation, or clotting. Blood clotting occurs in stages: When one of your blood vessels is cut, it immediately constricts, or narrows, to slow blood loss. This is called vasoconstriction. Chemical messages are sent into the bloodstream to signal the body to release blood clotting factors and start the coagulation process. Blood platelets collect at the site of the wound and begin sticking to the wound and to each other. These form a soft platelet plug in your wound. This stage is called primary hemostasis. Once the platelets form a temporary plug, a complex chain reaction takes place among multiple blood clotting factors. Factor V appears about halfway through this chain of reactions and converts prothrombin into thrombin. Thrombin triggers fibrinogen to produce fibrin. Fibrin is the material that makes up the final blood clot. This new clot seals the broken blood vessel and creates a protective covering for tissue regeneration. This stage is called secondary hemostasis. After a few days, the fibrin clot starts to shrink, pulling the edges of the wound together to allow the damaged tissue to rebuild. As the underlying tissue is rebuilt, the fibrin clot dissolves. This results in prolonged bleeding. What causes factor V deficiency? Factor V deficiency may be inherited or acquired after birth. Hereditary factor V deficiency is rare. This form occurs in about 1 in 1 million people. Acquired factor V deficiency may be caused by certain medications, underlying medical conditions, or an autoimmune reaction. Conditions that might affect factor V include: The symptoms of factor V deficiency vary depending on the amount of factor V available to the body. The levels necessary to cause symptoms depend upon the individual. A certain level that may cause bleeding in one person may not clause bleeding in another person. In cases of severe factor V deficiency, the symptoms often include:

Chapter 8 : F3 coagulation factor III, tissue factor [(human)]

The Factor IV (Calcium) Coagulation Blood Test is performed to determine if an individual has deficient or decreased levels of Factor IV Clotting factors are proteins that help form blood clots at the site of blood vessel injury.

This factor enables cells to initiate the blood coagulation cascades, and it functions as the high-affinity receptor for the coagulation factor VII. The resulting complex provides a catalytic event that is responsible for initiation of the coagulation protease cascades by specific limited proteolysis. Unlike the other cofactors of these protease cascades, which circulate as nonfunctional precursors, this factor is a potent initiator that is fully functional when expressed on cell surfaces. There are 3 distinct domains of this factor: This protein is the only one in the coagulation pathway for which a congenital deficiency has not been described. TF is the cell surface receptor for the serine protease factor VIIa. The best known function of tissue factor is its role in blood coagulation. Together with factor VIIa, tissue factor forms the tissue factor or extrinsic pathway of coagulation. Both pathways lead to the activation of factor X the common pathway which combines with activated factor V in the presence of calcium and phospholipid to produce thrombin thromboplastin activity. Cytokine signaling[edit] TF is related to a protein family known as the cytokine receptor class II family. The members of this receptor family are activated by cytokines. Cytokines are small proteins that can influence the behavior of white blood cells. This serves as a probably rigid template for factor VIIa binding. TF is expressed by cells which are normally not exposed to flowing blood such as sub-endothelial cells e. This can change when the blood vessel is damaged by for example physical injury or rupture of atherosclerotic plaques. The inner surface of the blood vessel consists of endothelial cells. Endothelial cells do not express TF except when they are exposed to inflammatory molecules such as tumor necrosis factor-alpha TNF-alpha. Another cell type that expresses TF on the cell surface in inflammatory conditions is the monocyte a white blood cell. Thromboplastin[edit] Historically, thromboplastin was a lab reagent, usually derived from placental sources, used to assay prothrombin times PT time. Thromboplastin, by itself, could activate the extrinsic coagulation pathway. When manipulated in the laboratory, a derivative could be created called partial thromboplastin, which was used to measure the intrinsic pathway. This test is called the aPTT , or activated partial thromboplastin time. It was not until much later that the subcomponents of thromboplastin and partial thromboplastin were identified. Thromboplastin contains phospholipids as well as tissue factor, both of which needed in the activation of the extrinsic pathway, whereas partial thromboplastin does not contain tissue factor. Tissue factor is not needed to activate the intrinsic pathway.

Chapter 9 : Deficiency Of Factor V And Factor VIII

Combined factor V and factor VIII deficiency is an inherited bleeding disorder that is caused by low levels of factors V and VIII. Because the amount of these factors in the body is lower than normal, the clotting reaction is blocked prematurely and the blood clot does not form.

Overview Factor VII deficiency is a blood clotting disorder that causes excessive or prolonged bleeding after an injury or surgery. Factor VII is a protein produced in the liver that plays an important role in helping your blood to clot. The normal blood clotting process occurs in four stages: Vasoconstriction When a blood vessel is cut, the damaged blood vessel immediately constricts to slow blood loss. Then, the injured blood vessel releases a protein called tissue factor into the bloodstream. The release of tissue factor acts like an SOS call, signaling blood platelets and other clotting factors to report to the scene of the injury. Formation of a platelet plug Platelets in the bloodstream are the first to arrive at the injury site. They attach themselves to the damaged tissue, and to each other, forming a temporary, soft plug in the wound. This process is known as primary hemostasis. Formation of a fibrin plug Once the temporary plug is in place, the blood clotting factors go through a complex chain reaction to release fibrin, a tough, stringy protein. Fibrin wraps itself in and around the soft clot until it becomes a tough, insoluble fibrin clot. This new clot seals the broken blood vessel, and creates a protective covering for new tissue growth. Wound healing and destruction of the fibrin plug After a few days, the fibrin clot starts to shrink, pulling the edges of the wound together to help new tissue grow over the wound. As the tissue is rebuilt, the fibrin clot dissolves and is absorbed. If factor VII does not function properly, or there is too little of it, the stronger fibrin clot cannot form properly. What causes factor VII deficiency? Factor VII deficiency may be either inherited or acquired. The inherited version is quite rare. Fewer than documented cases have been reported. Both of your parents must carry the gene in order for you to be affected. Acquired factor VII deficiency, in contrast, occurs after birth. It can occur as a result of medications or diseases that interfere with your factor VII. Drugs that can impair or reduce factor VII function include: