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Using Factor VII in Hemophilia Gene Therapy

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1. Introduction

Human blood at physiological conditions is kept as fluid through precise system called homeostasis, if damage to the vessel, causing the system will be restored by vessel wall. Cases no regulation or homeostasis disorders, thrombosis (intravascular coagulation) or bleeding occur. In normal conditions, the secretion of vascular endothelial heparin-like and trmbomodulin molecules prevent blood coagulation and secretion of nitric oxide and prostacyclin prevent platelet aggregation and blood brings the liquid keeps. Homeostasis has three stages: vasoconstriction, platelet plug formation and blood coagulation, blood coagulation are reactions in which plasma zymogens become active enzymes that create the clotting reaction. Coagulation reactions will be set with inhibitory and stimulatory mechanisms. Coagulation is a regulatory process that keeps the blood flowing. Blood coagulation has two external and internal pathways (Figure 1), tissue factor and FVII form the external pathway, internal pathway is formed of FVIII, FIX and FXI (Ramanarayana et al., 2011; Ellison, 1977).

2. Hemophilia

Hemophilia had recognized in the fifth century BC, first the Jews law passed that when a woman has two dead boys doing the circumcision her third son should not be circumcised, they showed the mother will transmit the disease to her sons (History of hemophilia, 2011). Genetic and hereditary pattern of hemophilia was carefully described in 1803 by the American physician John Conrad Otto. He supposed that the bleeding was occurring due to lack of blood anti hemophilic factor (Cahill & Colvin, 1997). Glossary of hemophilia was developed for this disease in 1828 at the University of Zurich. Anti-hemophilia globin was discovered in 1937 by Patek and Tylor at Harvard University (History of Hemophilia Disease, 2011). The two forms of hemophilia A and B were distinguished in 1952 by Pavlosky, the Brazilian physician. Both diseases are sex-dependent and occur in males (Cahill & Colvin, 1977).

3. Causes hemophilia

Hemophilia is a genetic disorder happens in coagulation FVIII (hemophilia A) or FIX (hemophilia B) and are related to the X chromosome. Hemophilia A is a disease due to genetic defects in coagulation FVIII (Furie et al., 1994; White & Shoemaker, 1989) It is identified by Hoyer and Breckenridge (Hoyer & Breckenridge, 1968) and then by Denson for the first time (Denson et al., 1969). They showed that there was not FVIIIa in the plasma of

the most people with hemophilia. Hemophilia B caused by genetic defects occur in the coagulation FIX; the FIX deficiency will inhibit the activation of FX by FVIIa through external coagulation pathway (Furie et al., 1994; Thompson, 1986). About half The patients who suffer from severe hemophilia A there is a large inversion in intron 22 of their FVIII mRNA (Figure 2) which it is repeated (Arruda et al., 1995; Deutz-Terlouw et al., 1995; Okamoto et al., 1995; Pieneman et al., 1995; Van de Water et al., 1995; Goodeve et al., Jenkins et al., 1994; 1994; Naylor et al., 1993; Naylor et al., 1992). Different alleles of the VNTR (di nucleotides) have observed in intron 13 of FVIII in people with hemophilia A (Kochhan et al., 1994).

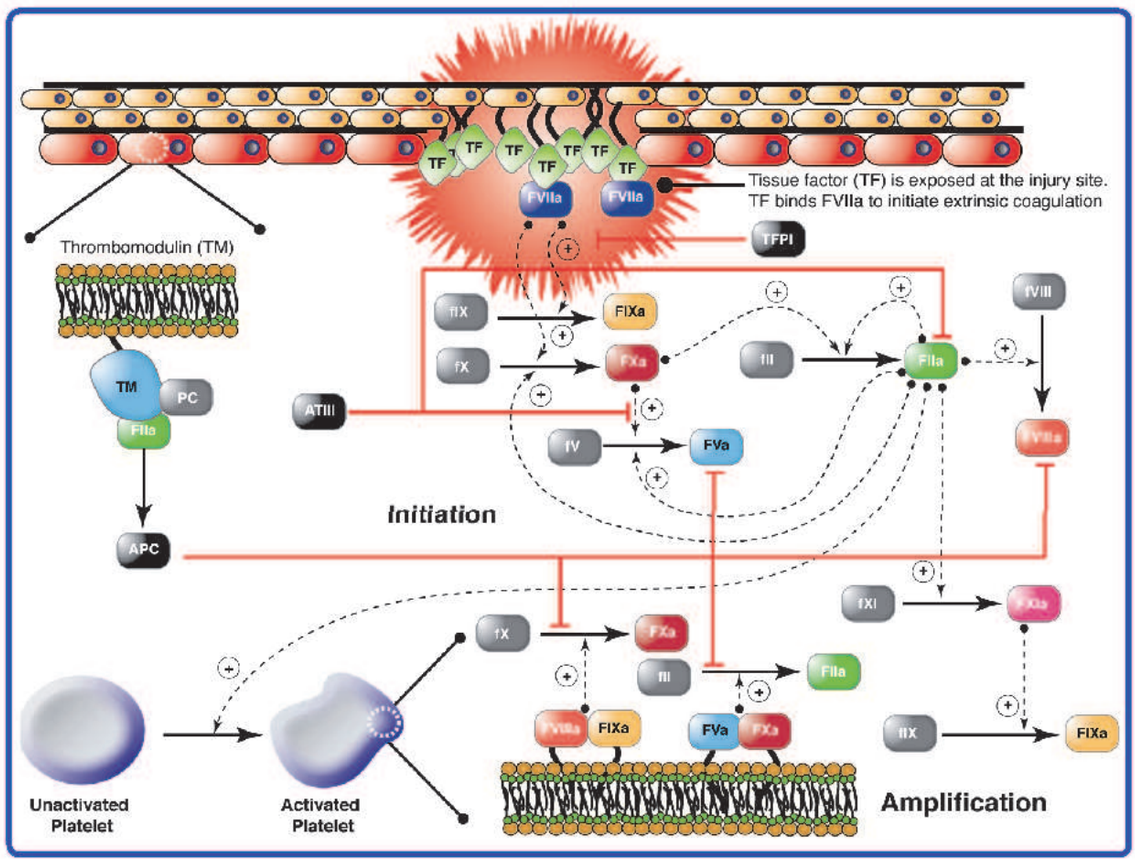

Fig. 1. External and internal pathways of blood coagulation process. (Reference http://www.varnerlab.org/coagulation)Read phonetically

Hemophilia A is occurring one for 5000-10000 birthday boys and hemophilia B one for 20,000 to 34,000 birthday boys (Dimitrios et al., 2009). The bleeding in joints of hemophilia patients the wound bleeding is longer continued (Petkova et al., 2004). The position of FVIII gene is Xq28 and of FIX is Xq27.1 location on distal long arm of chromosome X (Figure 3). The FVIII gene has 186 kb organized in 26 exons (about 9 kb) (Figure 4). There are detected some gene mutations on FVIII as insertion, deletions or point mutations which involved in the reduced or cut up in FVIII activation (Ramanarayana et al., 2011; Salviato et al., 2002; Cahill & Colvin, 1997; Arruda et al., 1995; Naylor et al., 1991; Higuchi et al., 1989; Youssoufian et al., 1987; Gitschier et al., 1985;). The FVIII organized in A, B and C domains

(Figure 5), which B domain is highly glycosylated and do not involve in FVIII activities (Eaton et al., 1986).

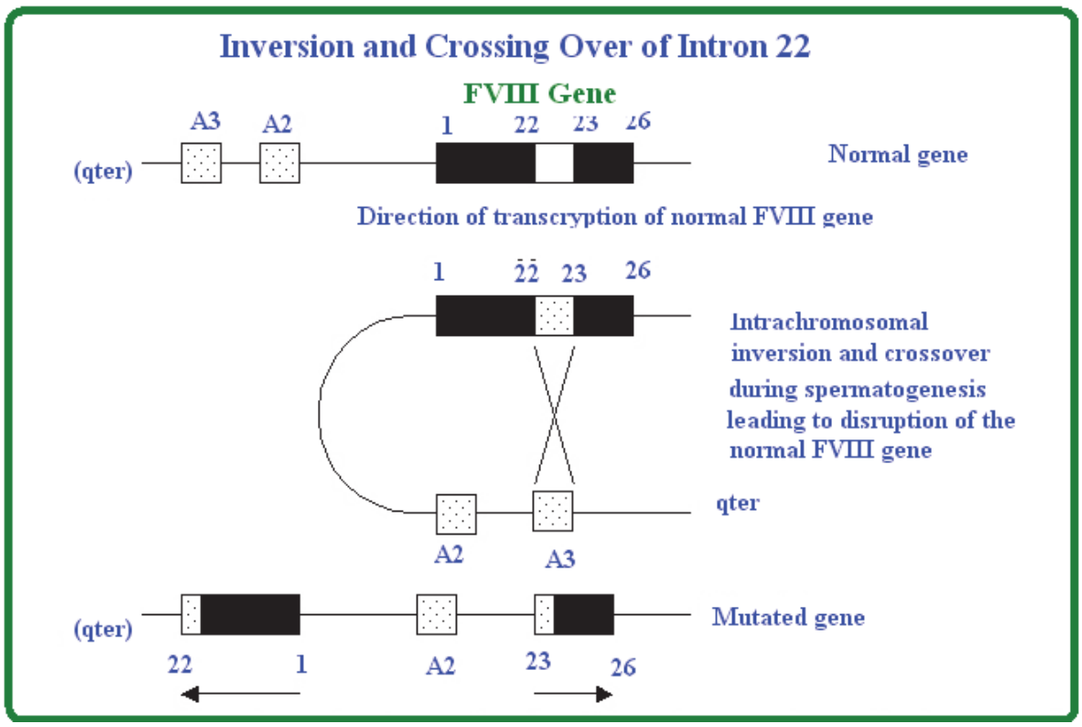

Fig. 2. Genetic mutation in intron 22 of FVIII (Schwartz et al., 2011)

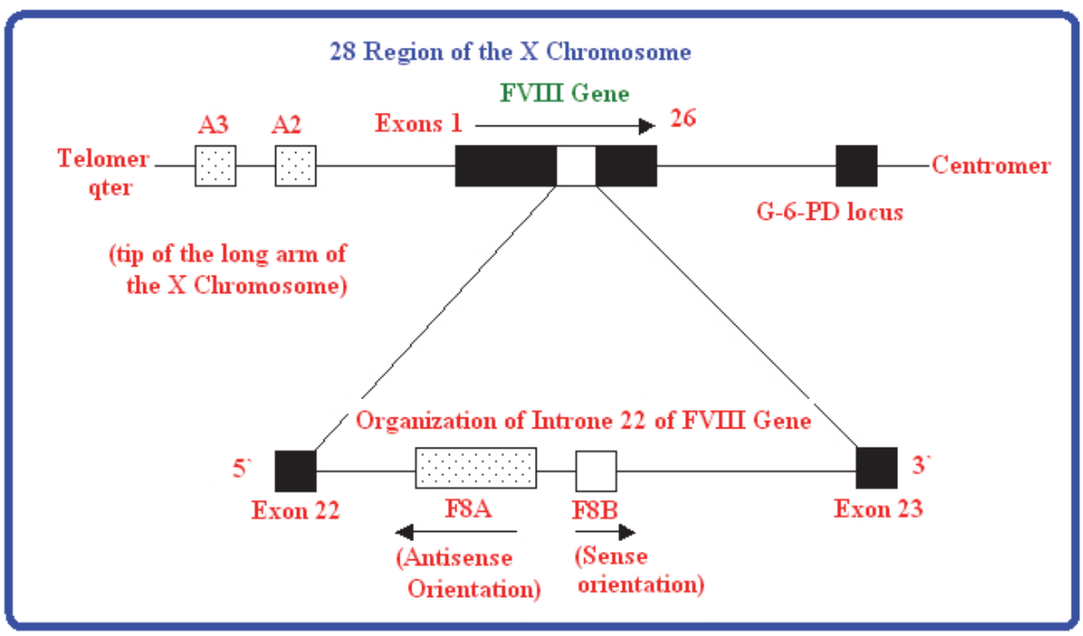

Fig. 3. The Map of FVIII on the long arm of chromosome X (Schwartz et al., 2011)

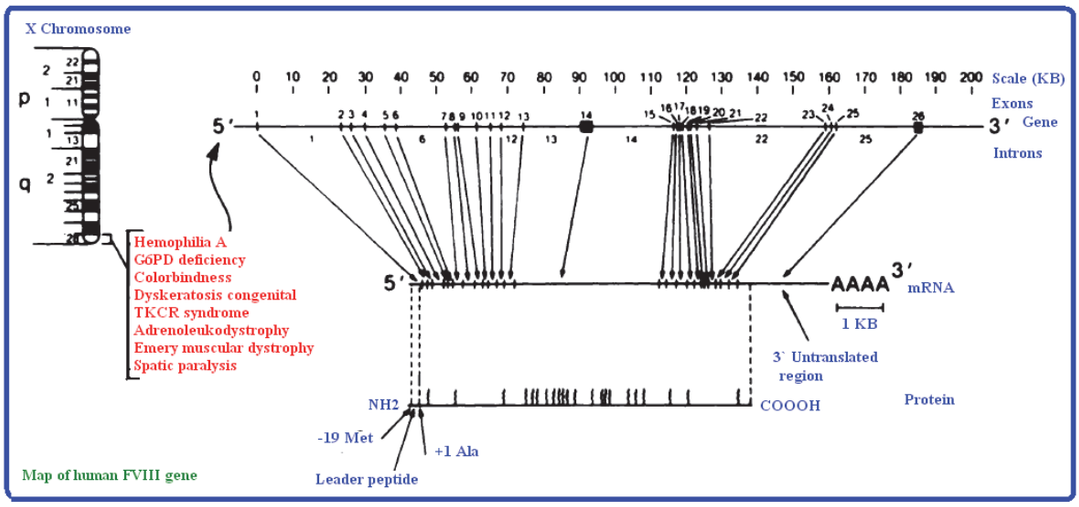

Fig. 4. Genetic map of FVIII (White & Shoemaker, 1989)

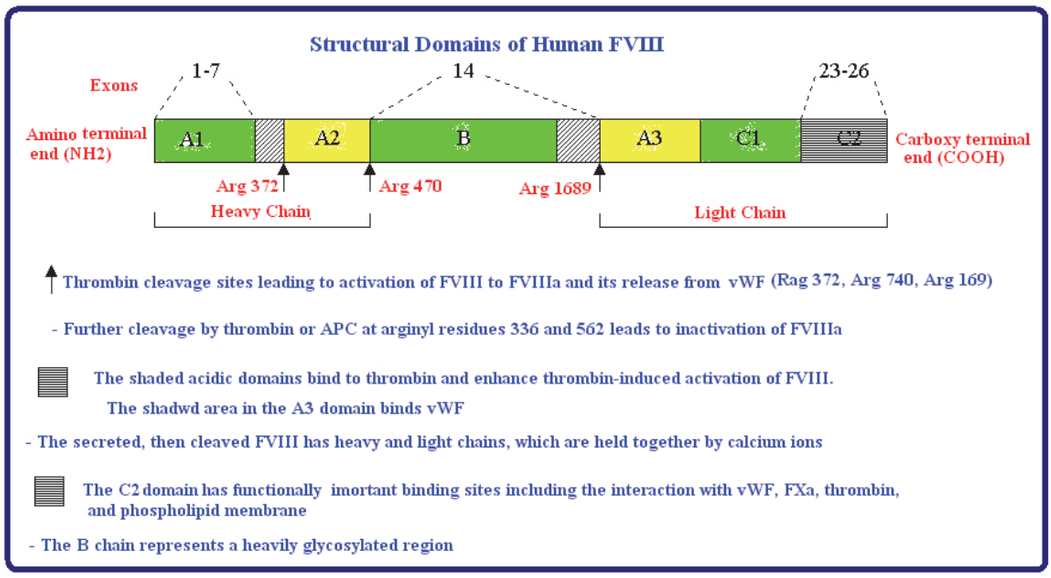

Fig. 5. The domains organization of FVIII (Schwartz et al., 2011)

4. Diagnosis of hemophilia

Laboratory diagnosis of hemophilia is done based on activated partial thromboplastin time (aPTT), prothrombin time (PT), platelet count and bleeding time. There is an abnormally in the initial section of internal coagulation pathway at the prolonged aPTT and normal PT. The normal aPTT should not be reject the FVIII deficiencies (hemophilia A), the aPTT is not enough sensitive too reduced amount of FVIII C. Prolonged PT alone, or PT and aPTT do not specify of hemophilia A, the liver diseases, overdose of warfarin or heparin and the distribution intravascular coagulation (DIC) can cause this coagulophaty. Thrombocytopenia alone cannot cause of hemophilia A. The nature and severity of bleeding is performed with cell blood counts (CBC) and differentiation also check for blood in the

stool and urine (Schwartz et al., 2011). Knights and Ingram in 1967 were used thromboplastin time assay for hemophilia A and B differentiation. Based on their test when alumina is added to normal plasma do not see the harm of FVIII, but FIX is deleted, remove the alumina from plasma FIX will re- back up. If thromboplastin time is increased in males with a history of prolonged bleeding, test is repeated after adding or removing alumina from the plasma. If thromboplastin time is shorter than the control, the patient is suffering from hemophilia A, but if thromboplastin time is shortened after the removal of the alumina, patient is suffering from hemophilia B (Knights & Ingram, 1967). Stites et al (1971) and Essien and Ingram (1967) were distinguished hemophilia A and B by FVIII inhibitory antibodies.

The test results in children and adults are different. Clotting Index and coagulability in hemophilia patients significantly lower than non-hemophilia one. In this test, coagulability of FVIII treated blood varies by the replaced FVIII type. rFVIII clotting index is lower than of derived plasma one (Goldenberg et al., 2006). Firshein and colleagues were diagnosed prenatal hemophilia A using radioimmunometric by fetal plasma and fetoscope by amniotic fluid at second trimester in pregnancy women (Firshein et al., 1979), other researchers were developed radoimmunometric method for measurements of FVIII antibody (Hoyer et al., 1985; Hellings et al., 1982; Ljung R, Holmberg, 1982). Antonarakis et al were analyzed FVIII gene for possibility detection of prenatal and hemophilia carrier through gene cloning method (Antonarakis et al., 1985), the problems and limitations of these methods were evaluated by other researchers (Graham et al., 1985). The PCR RFLP method was used for prenatal diagnosis and hemophilia A carrier for the first time in 1990s (Rudzki et al**.,** 1996; Herrmann et al., 1988; Kogan et al., 1987;). Missense and nonsense point mutations in FVIII gene of hemophilia A patient, prenatal and carrier hemophilia A were detected using DGGE method (Gitschier, 1989). Ball and colleagues were used oral cells, urine and hair follicles samples to identify prenatal and carrier hemophilia A (Ball et al., 1990). Various polymorphism and mutations have been detected in FVIII gene of hemophilia A patients (Wacey et al., 1996' Antonarakis et al, 1995; Naylor et al., 1991; Baranov et al., 1990; Gécz et al., 1990; Jedlicka et al., 1990; Sadler et al., 1990; Surin et al., 1990; Wehnert et al., 1990a; Wehnert et al., 1990b). Establishment the PCR technique in diagnostic laboratories was a large change in DNA analysis of FVIII gene for detecting carriers and individuals with hemophilia A (Song et al., 1993; Feng, 1991; Wadelius et al., 1991; Wu, 1991). Detection of unknown mutations is performed by universal mutation detection system methods such as SSCP (Arruda et al., 1995; Pieneman et al., 1995; David et al., 1994). Hemophilia diagnosis with PGD method was used by Michaelides (2006) and colleagues For the first time in 2006; they were diagnosed two point mutations in FVIII gene of donor (IVF) blastomere. Acquired hemophilia due to FVIII autoantibody is a rare disease and occurs one in a million, yearly; its mortality is 20 percent (Shetty et al., 2010).

5.1 Treatment of hemophilia A

Hemophilia treatment doing by replacing the natural (Brackmann & Gormsen, 1977) or recombinant FVIII (Kaufman, 1991) via intravenous injection. The half life of transfused FVIII in normal individuals or patients with hemophilia is 8 to 12 hours (White & Shoemaker, 1989). Using recombinant serum proteins in the treatment of hemophilia began in 1990 (Liras, 2008), but Homate P / humate-P is a derived pasteurized human plasma which was approved in Germany in 1981 and used administered intravenous injection for

25 years to control bleeding in patients with hemophilia A and von Willebrand disease (Berntorp, 2009; Carter & Scott, 2007; Czapek et al, 1988). The main presentation following hemophilia treatment is creating inhibitory antibodies against the FVIII which observed 5% in patients with hemophilia B and 40 -20 percent in patients with severe hemophilia A (Hong & Stachnik, 2010; Kempton et al., 2010; Eckhardt et al., 2009; Ghosh & Shetty, 2009; von Auer et al., 2005; Sharathkumar wt al., 2003; Scharrer, 1999; de Biasi et al., 1994). Complication inhibitory antibodies seem to produce with plasma-derived FVII severe than with recombinant one (Lusher, 2002; Lusher, 2000), also with FVIII (Qadura et al., 2009; Delignat et al., 2007; Goudemand et al., 2006; Yoshioka et al., 2003; Fijnvandraat et al, 1997). The B cell epitopes mutated, produced FVIII inhibitory antibody is reduced, and some one proposed that this phenomenon is safe vaccine for people with hemophilia (Parker et al, 2004). Antibody production against FVIII has been studied in hemophilia patients and indicates that most nonsense mutations and large deletions in FVIII gene and chromosomal recombination lead to produce FVIII inhibitory antibody (Schwaab et al., 1995). Treatment of hemophilia by FVIII overdose administration is effective for producer antibodies hemophilia patients (Scandella et al., 2000).

The OBI (BDD- rpFVIII) was introduced by Ipsen and Inspiration Biopharmaceuticals Inc Company and passed clinical trial phases 1 and 2. It shows porcine FVIII biochemical properties and procoagulant activity and less immunogenicity than plasma derived pFVIII (Toschi, 2010).

In 1960 Los Angeles Red Cross Blood Center was treated hemophilia patients using anti hemophilic globin (Rapaport et al., 1960). 1-Deamino-8-d-arginine vasopressin (DDAVP) (a FVII autologous) have been used instead of plasma derived factors for treatment of hemophilia A and B (Mannucci et al., 1977). Hultin and colleagues were used cyclophosphamide as immunosuppression drug for antibody producer hemophilia patients (Hultin et al., 1976). Lian et al. were treated hemophilia using cyclophosphamide, vincristine and prednisone (CVP) (Lian et al., 1989). Blatt et al were removed FVIII inhibitory antibody with prothrombin complex concentrates (PCC) (Blatt et al., 1977). Paleyanda and colleagues were transferred FVIII cDNA into pig lactate system; the pig was produced FVIII more than 10 times as normal plasma (**Paleyanda** et al., 1997). Specific thrombin anticoagulant Bivalirudin (Krolick, 2005) and monoclonal antibody Retoximab (Franchini, 2007; Wiestner et al., 2002) are also used for hemophilia treatment and patients with FVIII autoantibody, respectively. Idiotype vaccines will neutralize anti human FVIII antibody in hemophilia A patients (Lacroix-Desmazes et al., 2002).

Production and characterization of recombinant FVIII for the treatment of hemophilia was conducted in 1984 for the first time (Toole et al., 1984; Wood et al., 1984). Use of recombinant proteins to replace clotting factors and treatment of hemophilia opened a new arena in treatment of disease. Circulating blood factors are the first generation recombinant proteins and second generation drugs made by recombinant DNA and protein engineering technology cause changes in proteins for specific applications, like FVIIa (Levy & Levi, 2009; Pipe, 2008). FVII alone or in combination with its analogues have been used to reduce bleeding (Lauritzen el al., 2008a; Lauritzen et al., 2008b; Allen et al., 2007). Use of recombinant FVIIa for hemophilia patients with FVIII antibody (Obergfell et al., 2010; Margaritis, 2010; Margaritis et al., 2010), also people who have bleeding into the joint or prevent bleeding in surgery is economically efficient (Stephens et al., 2007).

5.2 Gene therapy of hemophilia A

For the first time in 1996, Connelly et al were administrated intravenous hemophilia dog by adenovirus containing hFVIII gene in which related protein was detectable in plasma for two weeks (Connelly et al., 1996a). Connelly and colleagues were injected adenovirus containing BDD- hFVIII gene through the tail artery into mice; hFVIII was detected in plasma by ELISA method (Connelly et al., 1999; Connelly et al. 1995). Dwarki and colleagues were transfected fibroblast by retrovirus containing BDD- FVIII gene, transfected fibroblasts were transferred into mice, human FVIII was observed in plasma after one week (Dwarki et al., 1995). Connelly et al were transferred adenovirus containing hFVIII gene into mice, hFVIII was stable in mouse for five months. (Connelly et al., 1996b). Ill et al were prepared suitable plasmid with necessary elements for FVIII expression in liver cells (Ill et al., 1997). Zhang et al were prepared a mini-adenovirus containing FVIII -equipped human albumin gene promoter for hemophilia A gene therapy. This structure was transferred to cell line; the hFVIII was consistently produced in mouse transferred ell line (Zhang et al., 1999). Gene therapy of hemophilia were done by liver cell transfected by adeno associated viruses or lentiviral viruses containing FVIII and FIX. Also use non-viral vector is also considered. Antibody production in gene therapy of hemophilia with FVIII and FIX can be depended on vector serotype (viral), expression rate (a long time, especially in the liver), the promoter used, method of gene delivery and transduced cell types (Margaritis et al., 2009; Ohmori et al., 2008; VandenDriessche et al., 2003; Chuah et al., 2001).

To overcome adenovirus toxicity phenomena, Andrews and colleagues were used adenovirus defected early genes E1, E2a, E3, E4 (four-generation defected vector), and transferred albumin promoter –controlled FVIII gene into mice, but was not suitable for use in vivo (Andrews et al., 2001). Chuah et al were inhibited bleeding in hemophilia A SCID mice using intravenous injection of adenovirus carrying BDD -FVIII gene (Chuah et al., 2003). Shi et al believed that platelet/ megakaryocyte is a target for hemophilia A gene therapy, they were transferred equipted specific platelet glycoprotein IIb promoter BDD-hFVIII to Domi cells, hFVIII was biosynthesised (Shi et al., 2003). Sarkar and colleagues were transferred AAV carrying hFVIII to deficient FVIII mice through portal, intravenous and spleen injections, they observed secreted hFVIII in transgenic animals but no in neonatal animal (Sarkar et al., 2003). Scallan et al were transferred FVIII gene into mice by AAV2 vector. The construct was equipped with liver cell specific promoter (Scallan et al., 2003). Kang and colleagues were used liver specific promoter equipted FIV retrovirus containing BDD- hFVIII gen for intravenous injection in hemophilia mice, hFVIII was secreted in mice for months without anti FVIII antibody production (Kang et al., 2005). Kumaran et al were treated hemophilia mice by cell therapy, a mixture of hepatocytes, liver endothelial sinusoids and liver kupffer cells was injected into mice peritoneum, FVIII was observed in mouse blood (Kumaran et al., 2005). Jiang et al were transferred FVIII in to hemophilia dog by AAV types 2, 5, 6 and 8, their report indicated that the performance of virus types 2 and 5 for gene therapy is more than viruses type 6 and 8 (Jiang et al., 2006). Sarkar et al believed that gene therapy duration in the dog with AAV8 containing FVIII have prolonged up to two years (Sarkar et al., 2006). Durable gene therapy based on AAV containing FVIII have also been reported by McCormack and colleagues (McCormack et al., 2006). Shi and colleagues findings suggest that targeted FVIII gene expression by platelets specific promoter is effective in the treatment of hemophilia A (Shi et al., 2006). Shi and colleagues were suggested that ectopic expression of FVIII in platelets with lentiviral virus via bone

marrow gene therapy is effective for human hemophilia treatment They were transferred lentiviral vector containing FVIII - Induced glycoprotein IIb platelet specific promoter into null mice bone marrow, the permanent secretion of FVIII in platelets lysates mice was observed. (Shi et al., 2007). Liu and colleagues were targeted rDNA of HL7702 hepatocytes by non-viral vector pHrneo containing FVIII gene for treatment of hemophilia (Liu et al., 2007). Doering has been transferred swine FVIII gene into mouse bone marrow mesenchymal cells for hemophilia treatment (Doering, 2008). Ishiwata and colleagues have been treated hemophilia mice using AAV8 vector containing canine BDD -FVIII gene (Ishiwata et al., 2009). Sabatino and colleagues report indicated that canine BDD- FVIII dogs is stable than human BDD- FVIII, it can be considered in the hemophilia treatment (Sabatino et al., 2009). Doering et al were transferred hFVIII - sFVIII hybrid in to hematopoietic stem cells with lentiviral vector; cells expressed FVIII more than 100-8 times of cells transfected with hFVIII only (Doering et al., 2009). Zatloukal and colleagues report suggested that expressed FVIII would be observed if the adenovirus containing FVIII -transfected fibroblasts or mayoblasts move into liver or spleen cells, but do not observe in the transfected muscle cells (Zatloukal et al., 1995). Because there are no acceptable phenotypic correction of hemophilia mice, Liars was used induced pluri potent stem cell therapy technology, these cells suggested converting into all cells and can be transfected by recombinant AAV or lentiviral vectors (Liars, 2011). Studies conducted so far suggest that blood factors gene therapy with AAV in animal muscle (dogs and mice) was healthy for FIX, but did not sufficiently much success for FVIII (Haurigot et al., 2010; Wang & Herzog, 2005). It is believed that the clinical correction of hemophilia B depends on the dose of vector transfer into muscular hosts (mice and dogs) (Hagstrom et al., 2000; Kay et al., 2000).

5.3 Hemophilia gene therapy with factor VII

Activated FVII is used as recombinant factor VII (rFVII) can go around process dependent coagulation FVIII and FIX (Mackman et al., 2007), it helps blood coagulation through extrinsic pathway. It is an ideal choice in the treatment of patients with FVIII producing antibodies and hemophilia patients to be considered (Johannessen etal., 2000; Lauritzen et al., 2008a). FVII is used in patient`s surgery with hemophilia A (Lauritzen et al., 2008a) also effective in term of homostatic process (Hedner et al., 2000; Kenet et al., 1999). The VIIa (Novoseven; rhFVIIa) has been achieved great success in treating patients with hemophilia. On the FVIII or FIX defects or presence of inhibitory antibodies, FVIIa – tissue factor complex will activate coagulation FX. FVIIa can activate coagulation cascade which cause clot formation and bleeding is inhibited (Hong & Stachnik, 2010; Levy & Levi, 2009). The main drug problems are short half-life (3-6 hours) and highly price (Ramanarayana et al., 2011; Puetz, 2010; Agersø et al., 2011;), more than one full dose of medication, especially for homeostasis regulation during surgeries are required. Hence, research groups around the world are trying different methods of gene transfer to express stable FVIIa in cells without the need to drug re administration (Ramanarayana et al., 2011). After biosynthesis of rhFVII as zymogen, it will be cut by proteases and biologically active through purification process (Huntington, 2009). The produced protein will breaks down at Arg152 and Ile153 to FVIIa. It is proposed that FVII gene transfer eliminates short half-life of rFVII and FVIII inhibitory antibody production (Ramanarayana et al., 2011). Emamgholipour et al (2009) and Margaritis (2010) established furin enzyme digestion site between Arg152 and Ile153 to generate FVIIa from FVII zymogene break down inside the targeted cell during FVII gene therapy strategy (Figure 6). Margaritis and colleagues were successfully corrected canine hemophilia B with this method

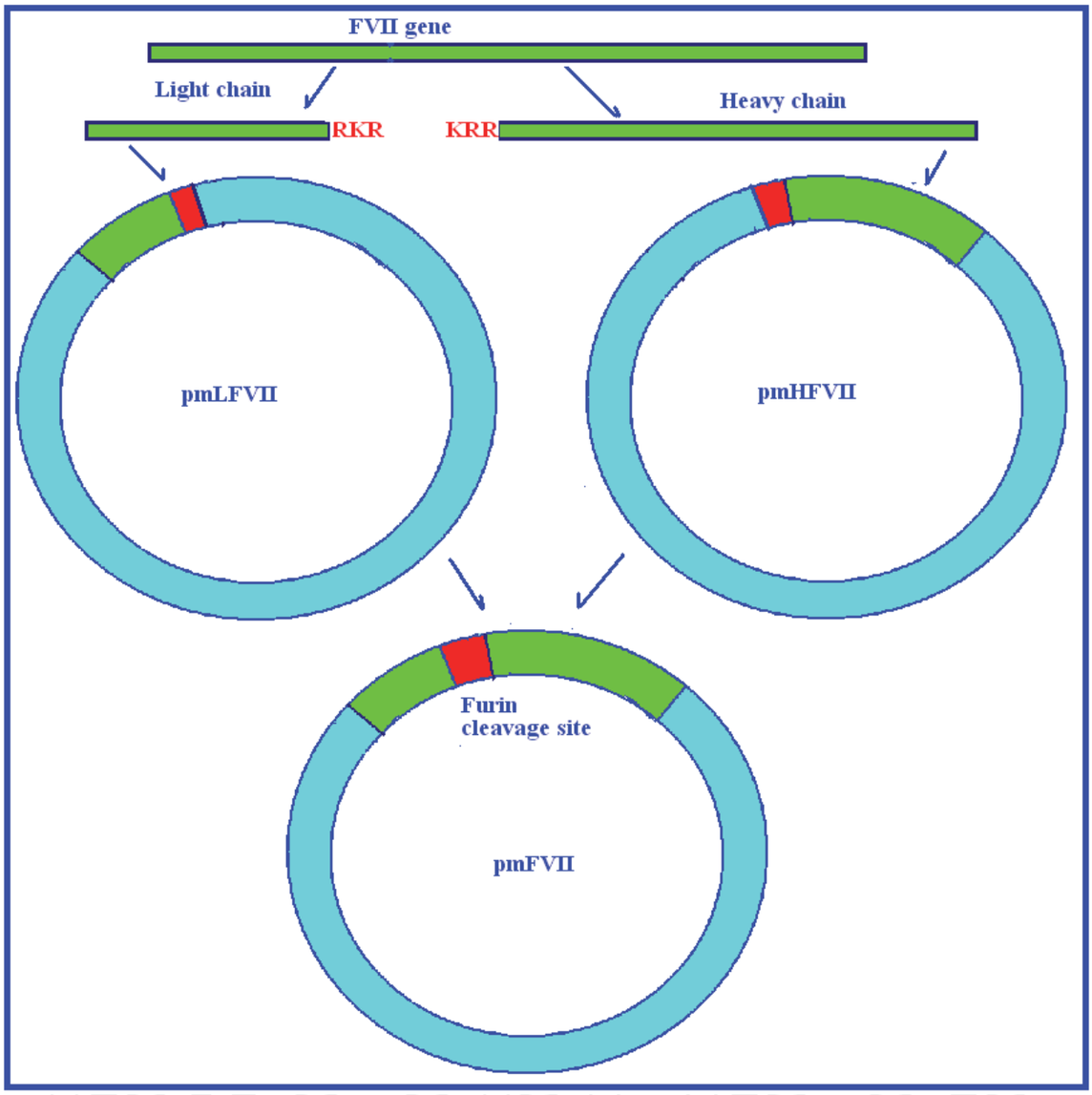

Fig. 6. Mutagenesis method to create furin digestion site on the FVII protein (Proposed based on Emamgholipour et al., 2009; Margaritis, 2010)

(Margaritis et al., 2004). Margaritis and colleagues were injected the mice through gene therapy by AAV contained FVII gene, FVII was produced in host cells (Margaritis et al., 2004). Miller et al were injected mice muscle myoblasts with plasmids coding FVIII and FVII cDNA (muscle specific elements and poly A were placed on both sides of genes); they were observed FVII and related antibody after 4-5 days. They believed that post translation modification process was occurred in the muscle cells (Miller et al., 1995). Tomokiyo and colleagues showed that the composition of plasma FVIIa and FXa in the treatment of monkeys hemophilia B more effective than FVIIa alone (Tomokiyo et al., 2003). Ohmori et al have been used ectopic expression FVIIa in platelets to hemophilia A treatment, they were transferred SIV containing platelet glycoprotein Ib alpha specific promoter into bone marrow cells, was lead to FVII expression on the platelets surface. This construct was

corrected mouse hemophilia A phenotype (Ohmori et al., 2008). Margaritis have been treated canine hemophilia by AAV containing FVII through the portal vein (Margaritis et al., 2009). To overcome the repeated injection problem, Obergfell and colleagues were studied hemophilia treatment and suggested permanent expression of FVII in canine hemophilia model through gene therapy method (Obergfell et al., 2010).

6. Conclusion

There are some reported of FVIII and FIX gene transfer by viral vectors in animal models, but no evidence so far reported successful treatment of human hemophilia gene therapy by this method. Researchers have used FVII to overcome antibody production in treatment of FVIII deficiency. Despite several reports of curing hemophilia A with FVII in animals, there is no yet successful reported in human.

Methods proposed for the future: reviewing the history of hemophilia gene therapy by viral vectors, identified several reasons that cannot be sure of the viruses used for gene transfer:

1) Application of viruses is associated with inappropriate chromosomal insertion and makes the undesirable point mutations (Nakai et al., 2003; Miller et al., 2002). 2) Viruses are carcinogens (Check, 2003). 3) The viruses will cause the host immune response (Lefesvre et al., 2003) which is temporarily being transgene. 4) Because viruses genome are great than non-viral vectors the sequences of the viruses cannot be controlled by reseaechers. 5) Preparation of this vector requires a lot of time and money. Although non-viral gene transfer is less efficient than virus vector but have been told no above disadvantages and their use for gene transfer in human can be safer than viruses. Vectors are suggested to be prepared as non-viral vector for targeting the rDNA locus of human genome by homologous recombination method, and as ex vivo gene transfer in humans to be done with them.

7. Acknowledgment

This work was supported by Iran National Science Foundation (project no.843083) and was done in Cellular and Molecular Biology Research Center of Shahid Beheshti University of Medical Sciences, the author's thanks directors.

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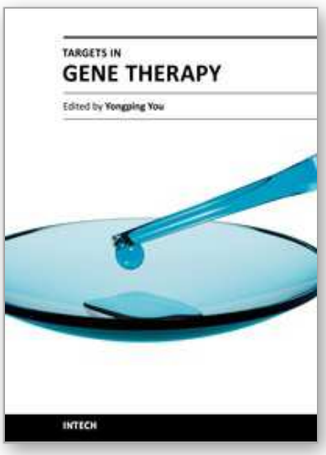

Targets in Gene Therapy

Edited by Prof. Yongping You

ISBN 978-953-307-540-2

Hard cover, 436 pages

Publisher InTech

Published online 23, August, 2011

Published in print edition August, 2011

This book aims at providing an up-to-date report to cover key aspects of existing problems in the emerging field of targets in gene therapy. With the contributions in various disciplines of gene therapy, the book brings together major approaches: Target Strategy in Gene Therapy, Gene Therapy of Cancer and Gene Therapy of Other Diseases. This source enables clinicians and researchers to select and effectively utilize new translational approaches in gene therapy and analyze the developments in target strategy in gene therapy.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Bahram Kazemi (2011). Using Factor VII in Hemophilia Gene Therapy, Targets in Gene Therapy, Prof. Yongping You (Ed.), ISBN: 978-953-307-540-2, InTech, Available from: http://www.intechopen.com/books/targets-in-gene-therapy/using-factor-vii-in-hemophilia-gene-therapy

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