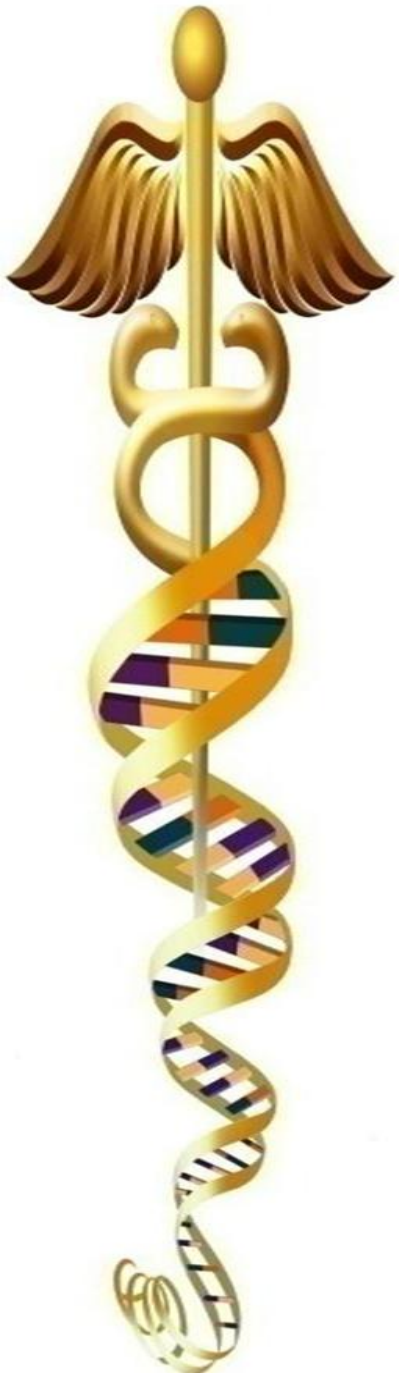

HEPATIT –C
OLGULARINDA CALISMA PLANI

ARZU DIDEM YALCIN, MD.
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PROJECT

1. **National:** The Determination and Evaluation of Pollination in Antalya City Center.(Çevre bakanlığı projesi proje no:19.2001/2006-2011)

2. **International:** Analysis of immunity and specific treatment in healthy elderly. Differences In Humoral And Cellular Immunity In Young And Old Individuals (Devlet Planlama teşkilatı projesi, proje no:2006K 120-430)(in cooperation with Transplant Research Division,Toronto Hospital, University Health Network,Toronto, Ontario, Canada)

ADVISOR:Prof. R. Gorczynski PhD. MD

3. **National:**Serum sTRAIL use for the assessment of the efficacy of BevacizumAb treatment in metastatic colon cancer.

ADVISOR:Prof. Dr. Burhan Savaş PhD. MD

4. **National:**Investigation of Amonium Inhalation Effects on Rat Respiratory Mucosa by Immunohistochemical and Electron Microscopy and Effects of Amonium Inhalation on Antioxidant Enzyme Activities in Rat Erythrocytes.

Effects of Amonium Inhalation on Plazma Vitamin C and Ceruloplasmin in Rats.Akdeniz Üniversitesi araştırma fonu projesi.proje no:9401010302)

ADVISOR:Prof. Dr. Saadet Gümüşlü. PhD.

5. **National:**Metronomik Tedavi Alan Metastatik Kanser Hastalarında Serum sTRAIL ve VEGF Düzeylerinin Önemi.

ADVISOR:Prof. Dr. Burhan Savaş PhD. MD

6. **International:** SIROCCO, ANTI IL-5, PHASE-3(BENRALIZUMAB ,MEDI-560)

ADVISOR: EUGENE R. BLEECKER ,Astra Zenecca , Sweeden.

7. **International:PAMPERO,** ANTI IL-5, PHASE-3 (BENRALIZUMAB ,MEDI-560)

ADVISOR: William Walter BUSSE, Astra Zenecca , Sweeden.

8. **International:** ALTO, an international non-interventional registry on the quality of life of patients with grass pollen-induced Allergic rhinitis Treated with ORALAIR®

ADVISOR: Xaviere CARTRY, Stallergen

MY EXPERIENCE on OMALIZUMAB in 4 years

1. Yalcin AD, Gorczynski RM et al.Total antioxidant capacity, hydrogen peroxide, malondialdehyde and total nitric oxide concentrations in patients with severe persistent allergic asthma: its relation to omalizumab treatment. Clin. Lab. 2012;58(1-2) ***(2011-APSR, China, ORAL PRESENTATION).***

2. Yalcin AD, et al. Serum soluble TRAIL levels in patients with severe persistent allergic asthma: its relation to Omalizumab treatment.Med Sci Monit2012;18(3) ***(2011-APSR, China, ORAL PRESENTATION).***

3. Yalcin AD, Gumuslu S, et al. Systemic Levels Of Ceruloplasmin Oxidase Activity In Allergic Asthma And Allergic Rhinitis. Immunopharmacology and Immunotoxicology,2012;34(6*) (2011, WAO-MEXICO).*

4. Yalcin AD, Bisgin A. The Relation of sTRAIL Levels and Quality of Life In Omalizumab Using Severe Persistent Allergic Asthma Patients. Med Sci Monit 2012;18(8) ***(2012 DECEMBER -WISC. WAO-OUTSTANDING ABSTRACT AWARD).***

5. Yalcin AD, Anti-IgE Therapy in Severe Allergic Conditions. Jour Allergy and Therapy.2012;3 *2011-EAACI, London ,ENGLAND).*

6. Yalcin AD, et al. Clinical Course and Side Effects of Omalizumab in Patients with Severe Persistent Asthma. Clin. Lab. 2013;59:71-77. *(2012-WAO, India).*

7. Yalcin AD, Gorczynski RM. IL-8, IL10, TGF-β and GCSF levels were increased in severe persistent allergic asthma patients with the anti-IgE treatment. Mediators of inflamations 2013 ***(2012-Canada ,WORLD ASTMA ORAL PRESENTATION).***

8. Yalcin AD, Strauss LG. Effects of Omalizumab on Eosinophil cationic peptid, 25-hydroxyvitamin-D, IL-1β, and sCD200 in a cases of Samter's syndrome: 36 Months follow-up.Immunopharmacology and Immunotoxicology. *(2013-EAACI, Italy).*

9. Yalcin AD, Gorczynski RM, Cilli A, Strauss L . Omalizumab Therapy Increases Blood Glucose Levels in Severe Persistent Allergic Asthma Patients with Diabetes Mellutus: 18 Months follow-up. Clin. Lab. 2013;59. *(2013-EAACI, Italy).*

10. Yalcin AD, Strauss LG, Gumuslu S,Cilli A, Hert F. Omalizumab is effective in treating severe asthma in patients with severe cadiovascular complications. Expert opinion on biological therapy .2013*. (2013-EAACI, Italy).*

11. Yalcin AD, D-dimer levels decreased in severe allergic asthma and chronic urticaria patients with the omalizumab treatment. Expert opinion on biological therapy .2014. WAO,BRAZIL.2014.

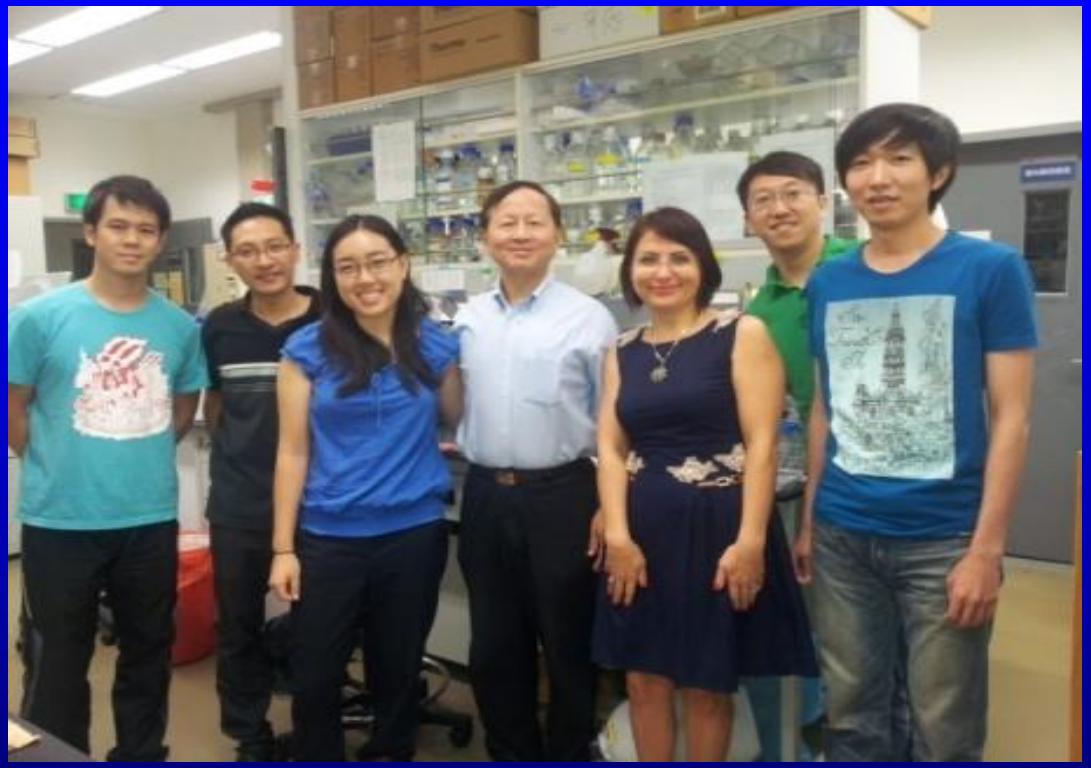
12. Yalcin AD, Genc GE, Celik B, Gumuslu S. Anti- IgE monoclonal antibody (omalizumab) isExpert opinion on biological therapy 2013 effective in treating Bullous Pemphigoid and effects on soluble CD200. Clin Lab (2013 APCAAI, Taiwan)

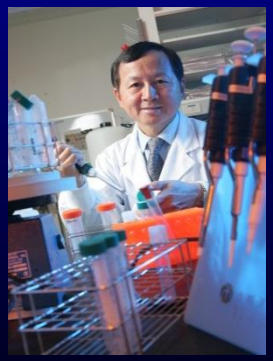
13. Yalcin AD, Bisgin A. A case of heterozygous factor V Leiden and prothrombin G20210A carrier and irregular emphysema/severe allergic asthma of successful Anti-IgE therapy without any arteriothrombotic event and Increases of serum Protein C and S levels. European jour of Immunology (2013 APCAAI, Taiwan)

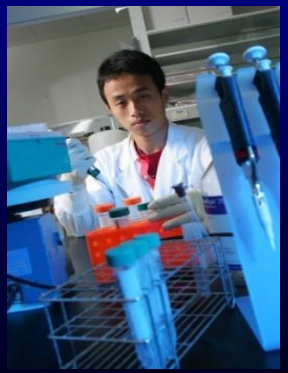
14. **Yalcin AD.** Evaluation of Homocysteine, Eosinophil Cationic Peptide, 25(OH) Vitamin D, and Immune Modulator OX-2 Levels in Moderate Allergic Asthma Patients: Association with Biological Treatment (Anti-IgE)& Disease Activity. jour Clin pharmacy and tharaupetics. WAO,BRAZIL.2014

15. Yalcin AD. An Overview on the Effects of Anti-IgE (Omalizumab) Therapies. Med sci Monit 2014. WAO,BRAZIL.2014

Academia Sinica, Genomics Research Center, Taipei, Taiwan

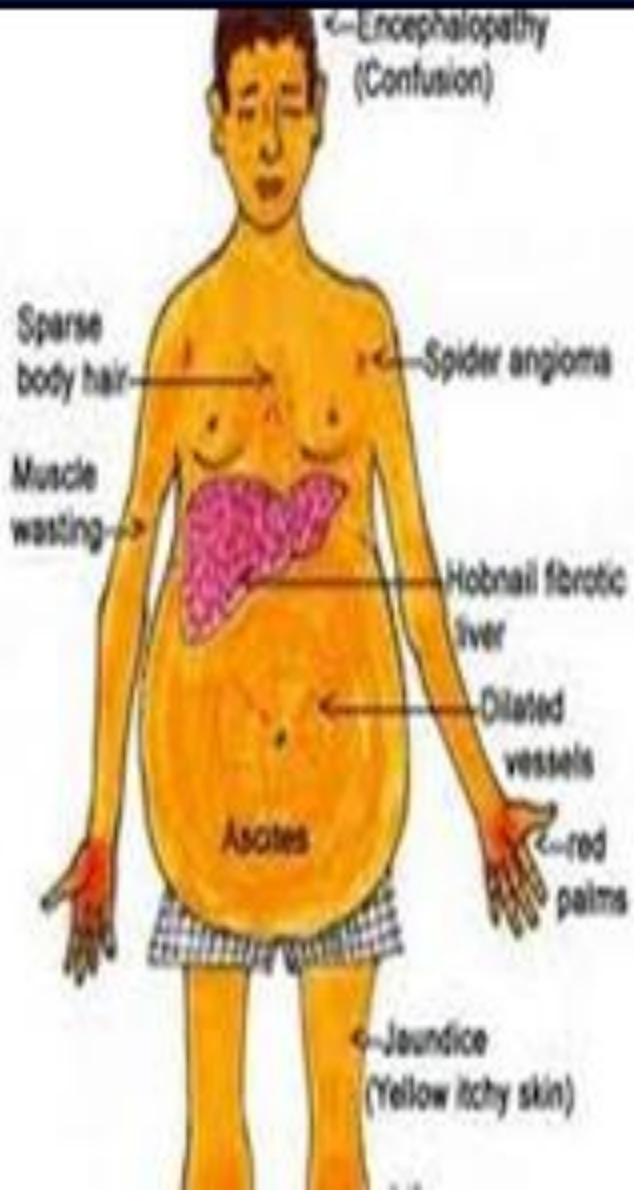


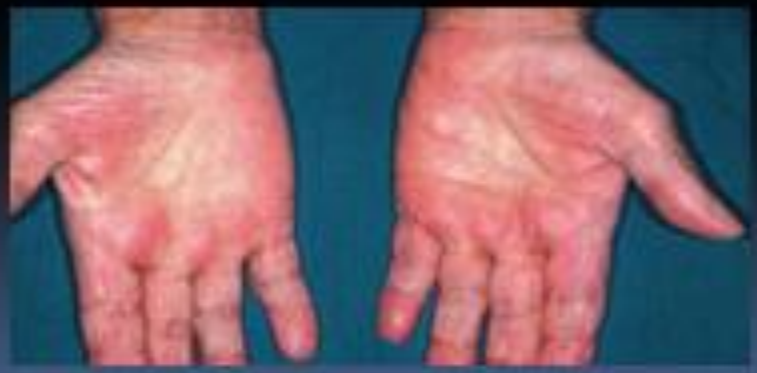




Signs (red color:our patients signs)

- Loss of hair (alopecia) +
- Icterus +, Itching+
- Parotid enlargement
- Fetor hepaticus +
- Loss of axillary & pubic hair +
- Spider nevi +
- Gynecomastia
- Atrophy of breasts in females +
- Wasting of muscles +
- Bleeding tendencies : deficiency of clotting
- Fever
- Hyperpigmentation





- Glossitis, cheilitis
- Palmar erythema +
- Clubbing +
- Dupuytren's contracture
- Ascites +
- In 70 % cases liver is enlarged, firm if not hard and nodular
- Splenomegaly +
- Caput medusae +
- Delirium
- Constructional apraxia
- Flapping tremors
- Inversion of sleep rhythm
- Edema +
- Hernia +
- Testicular atrophy

- Coagulopathy : Factor deficiency +
  Fibrinolysis +
  Thrombocytopenia +
- Bone Disease : Osteopenia/Osteoporosis/ +

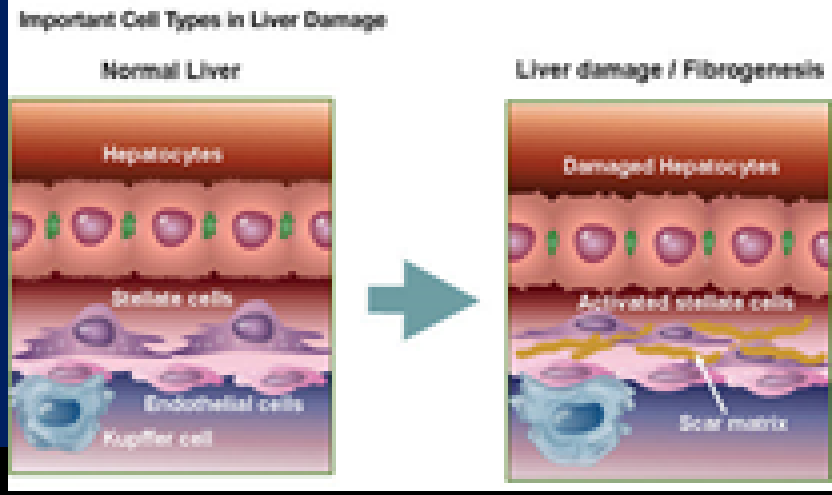
Splenomegaly +, Hypersplenism +
Thrombocytopenia +, Anemia +

Dilated Abdominal Veins, Caput Medusae +,
Ascitis +.

Спис (С)	С-I	С-II
FVC (%)	62 / 87	
FEV1 (%)	56 / 72	
PEF (%)	65 / 73	
MEF 25-75 (%)	31 / 34	
ACT	7 / 20	
SOA	27 / 16	
feNO	68/ 57	
ECP	79 / 38	

Case (C)	C-I
Laboratory Markers	Pre–AntiIgE / Post–AntiIgE
Sedimentation	23/71
Platelet (mm3)	70.000/ 65.000
MPV (fL)	8.4 / 9.2
aPTT	24.9 / 27,9
PT	14.8/ 15,14
INR	1.29/1.34
D-dimer (U/L)	**720/ 541**

Hepatocellular death
Regeneration
Progressive fibrosis



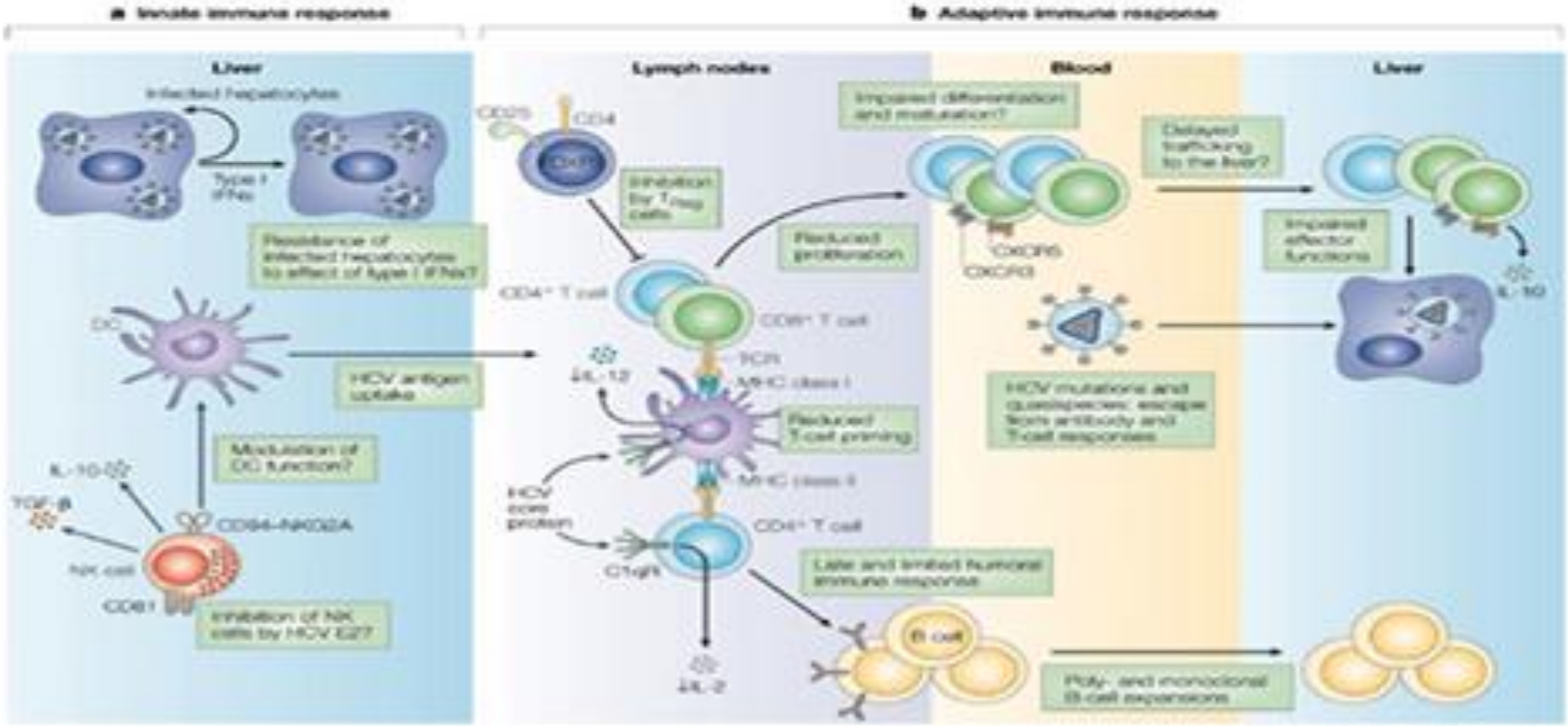
The induction of fibrosis occurs with activation of hepatic stellate cells, resulting in formation of increased amounts of collagen & other components of extracellular matrix.

- Stimuli : 1.Chr.inflam – cytokines like TNF, Lymphotoxin, IL-1
  2.Cytokine production by injured Kupffer cells, endothelial cells, hepatocytes, bile duct epithelial cells
  3.Disruption of ECM
  4.Direct stimulation of stellate cells by toxins

The standard therapy is a combination of Pegylated interferon alfa-2a (pegylated with a branched 40 kDa PEG chain; commercial name Pegasys) and ribavirin (bocepravir, teleprevir).

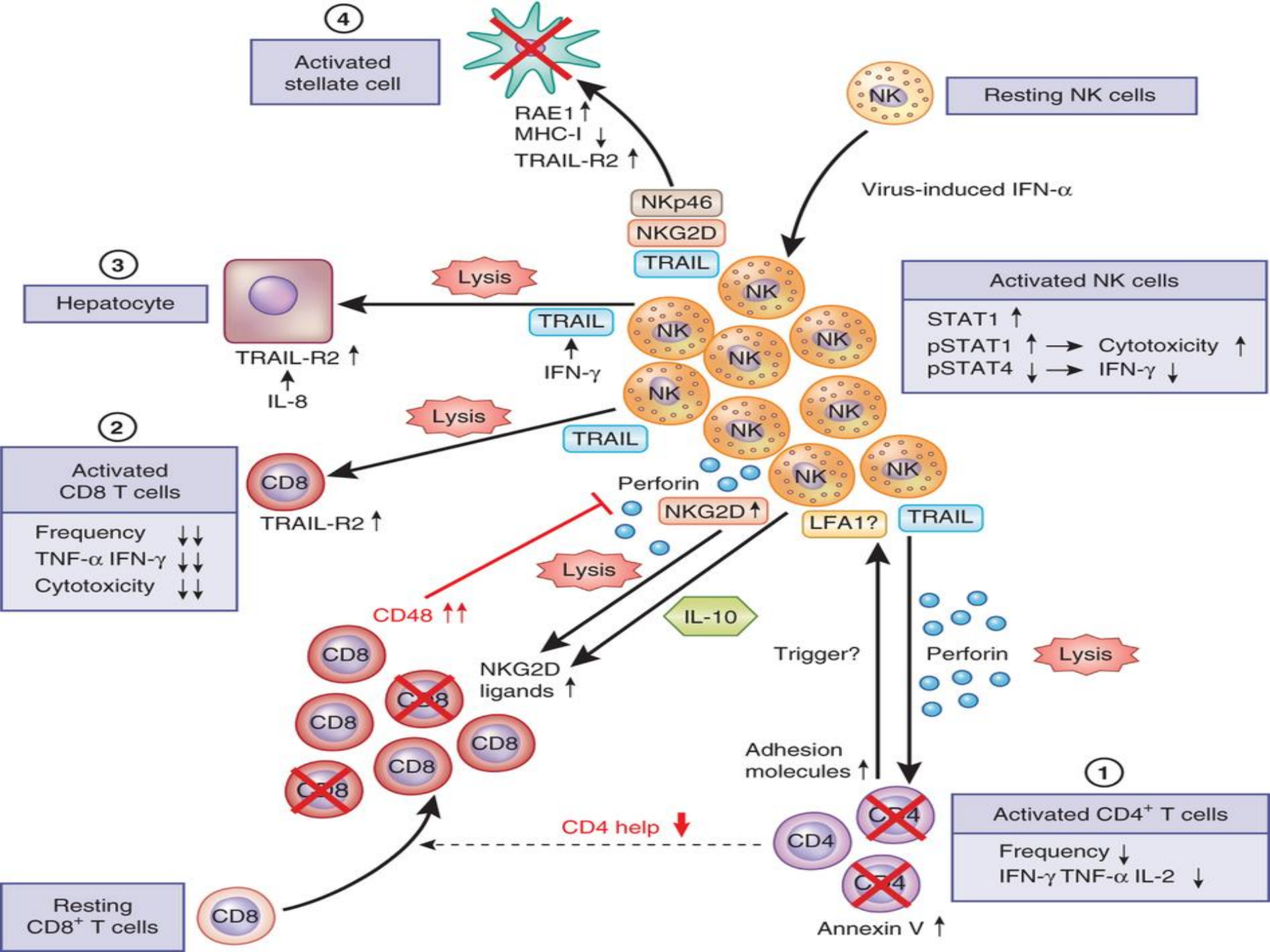
- Overall, 50–80% of people treated are cured. Those who develop cirrhosis or liver cancer may require a liver transplant. Hepatitis C is the leading reason for liver transplantation, though the virus usually recurs after transplantation.
- No vaccine against hepatitis C is available.

| Rosen, HR (2011-06-23). "Clinical practice. Chronic hepatitis C infection". NEJM 364 (25): 2429–38.

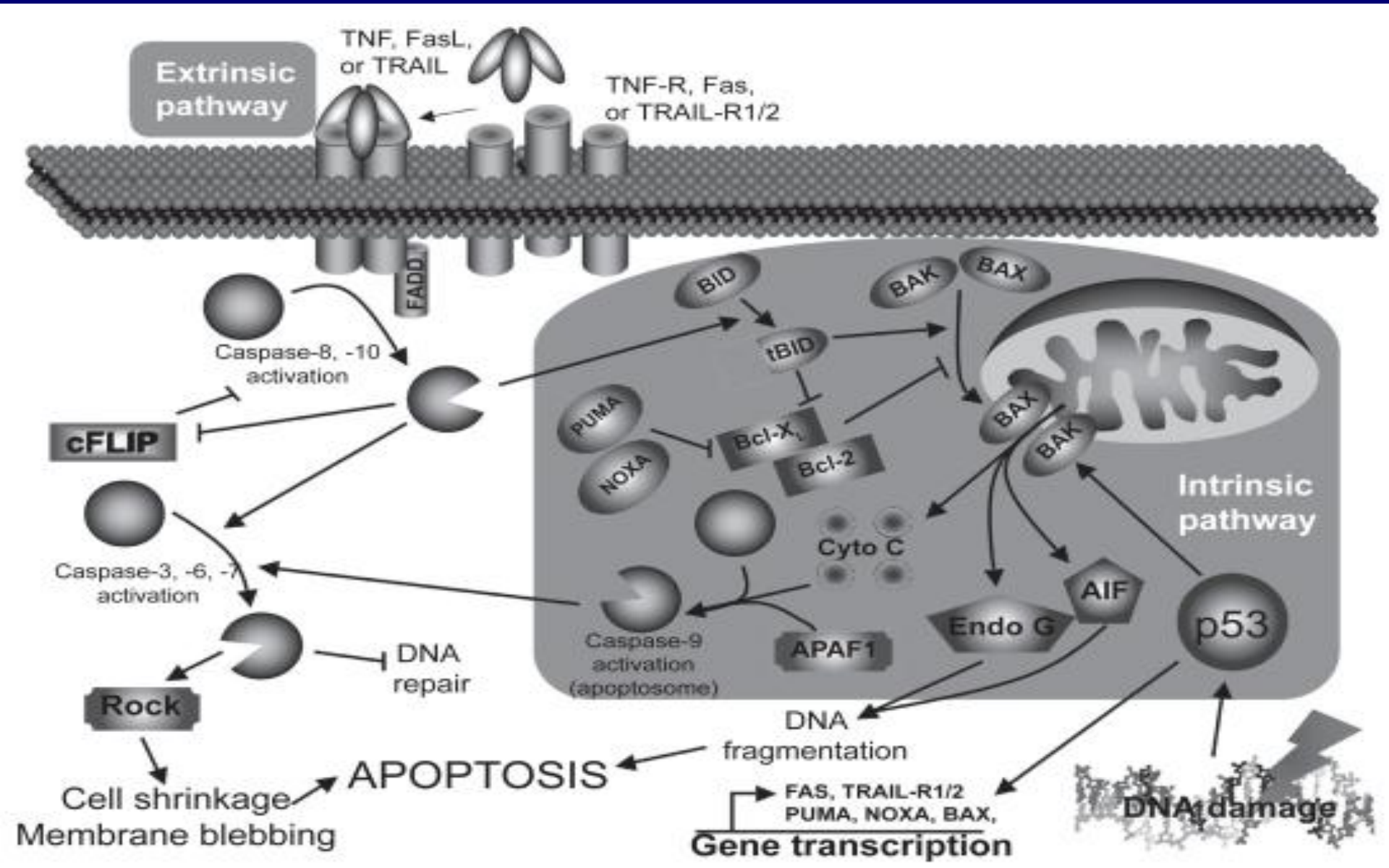


Hayashi N, Mita E. Involvement of Fas system-mediated apoptosis in pathogenesis of viral hepatitis. J Viral Hepat. 1999 Sep;6(5):357-65.
Fischer R, Baumert T, Blum HE. Hepatitis C virus infection and apoptosis. World J Gastroenterol. 2007 Sep 28;13(36):4865-72.

- Pathway of viral clearance occurs via the ligands and receptors of the TNF-α family: TNFα/TNF-receptor 1, CD95/CD95Ligand and TRAIL/Trail receptor-1 and -2, respectively.
- It was shown that lymphocytes that recognize the viral antigen on hepatocytes became activated and expressed cytolytic Fas ligand, while hepatocytes in the vicinity of lymphocytes exhibited enhanced Fas expression and become susceptible to FasL-mediated death .Ligand binding induces the formation of signal complex, resulting in the activation of caspase-8, which culminates apoptosis of hepatocyte

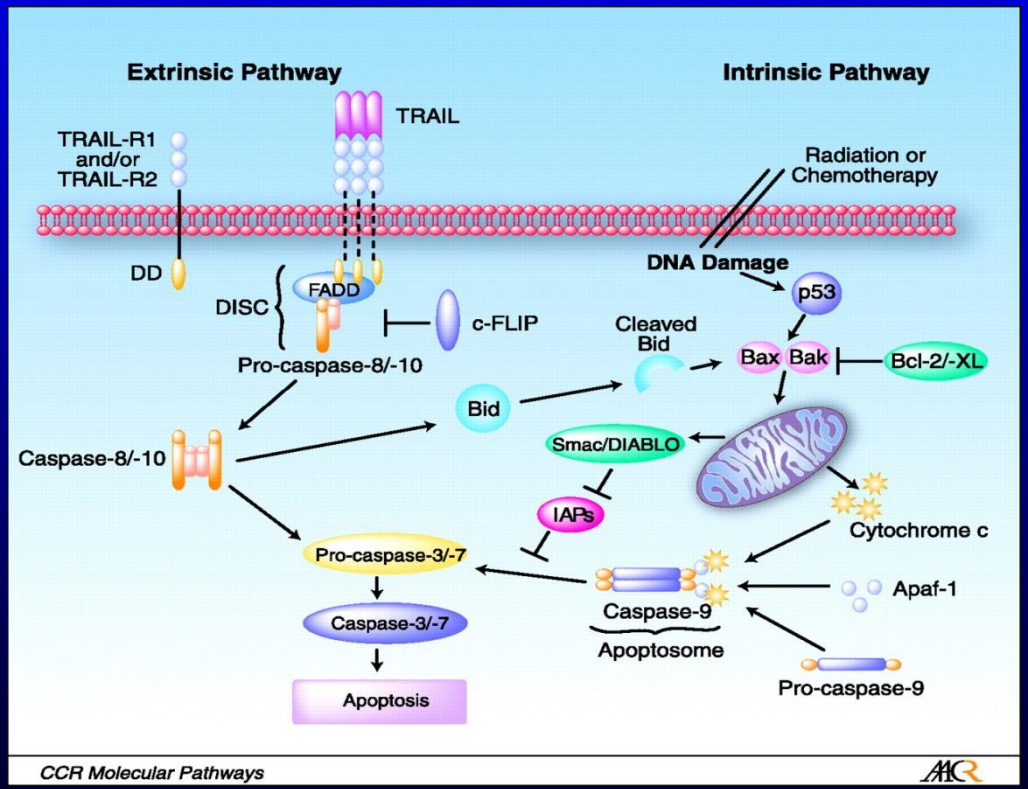

4
Activated stellate cell
RAE1 ↑
MHC-I ↓
TRAIL-R2 ↑
NK
Resting NK cells
Virus-induced IFN-α
NKp46
NKG2D
TRAIL
3
Hepatocyte
Lysis
TRAIL-R2 ↑
IL-8
TRAIL
IFN-γ
Activated NK cells
STAT1 ↑
pSTAT1 ↑ → Cytotoxicity ↑
pSTAT4 ↓ → IFN-γ ↓
2
Activated CD8 T cells
Frequency ↓↓
TNF-α IFN-γ ↓↓
Cytotoxicity ↓↓
Lysis
TRAIL
CD8
TRAIL-R2 ↑
Perforin
NKG2D ↑
LFA1?
TRAIL
CD48 ↑↑
Lysis
IL-10
CD8
NKG2D ligands ↑
Trigger?
Perforin
Lysis
Adhesion molecules ↑
1
Activated CD4+ T cells
Frequency ↓
IFN-γ TNF-α IL-2 ↓
CD4 help ↓
CD4
Annexin V ↑
Resting CD8+ T cells
CD8

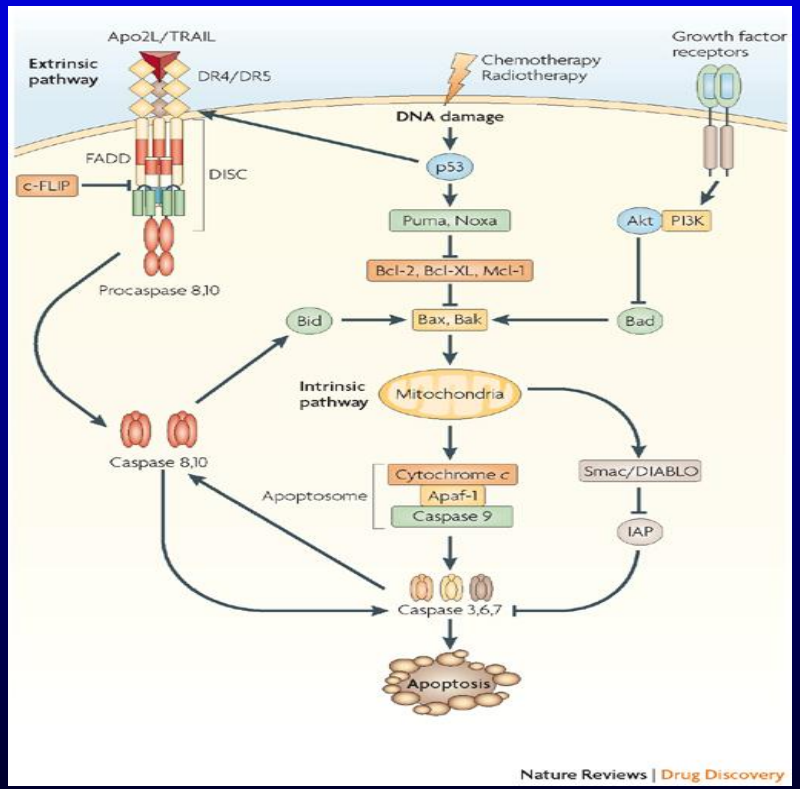
- Tennenberg SD,**Endothelium down-regulates Fas, TNF, and TRAIL-induced neutrophil apoptosis.** Surg Infect (Larchmt). 2002



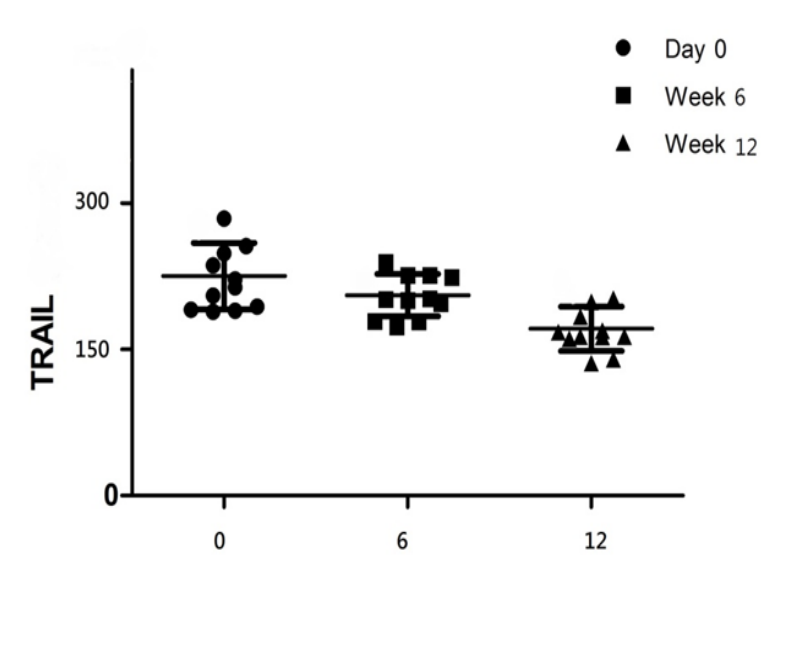
Circulating Apo 2L levels decreased in hepatitis-C with the peg- interferon-2 alpha treatment

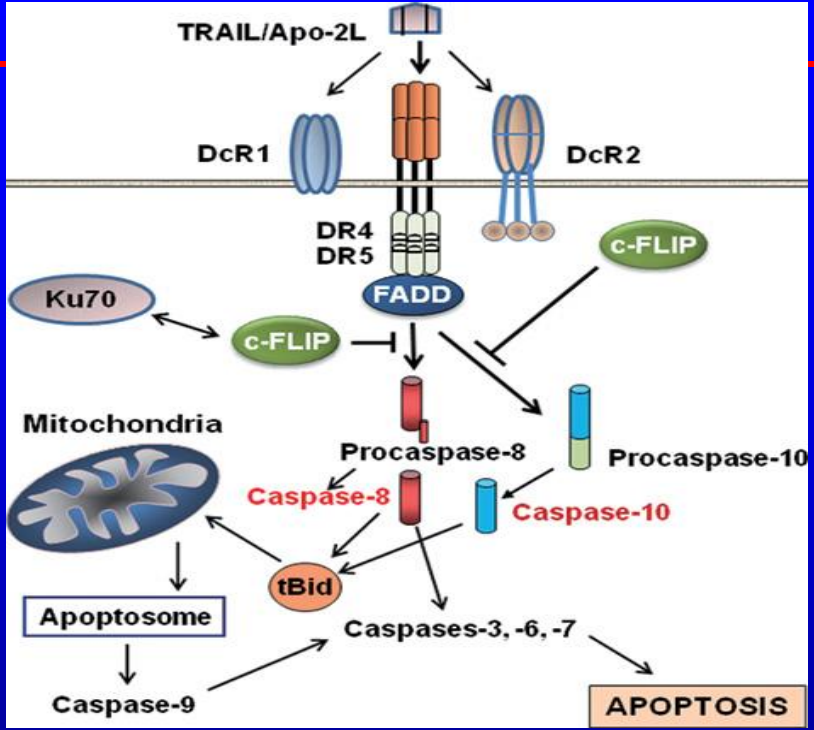
➢Arzu Didem Yalcin, Betul Celik, Sukran Kose,.Ata Nevzat YALCIN.





Parametreler	PRE-INTERFERON(IA) (n=11)	POST-6.hafta (IB) (n=11)	POST-12.hafta (IC) (n=11)
TRAIL(Apo 2L) (pg/mL)	250.24± 12.9	223.23± 8.41	183.39± 8.12
HCVRNA (IU/mL)	1583350.8 ± 395745.6	4705.08 ± 1638.8	711.8 ± 518.7
HGB (g/dL)	12.9 ± 0.5	11.9 ± 0.9	11.1 ± 0.7
WBC (mm^3)	7783. 4 ± 731.3	4008.9 ± 118.6	3216.67 ± 282.80
Platelet (mm^3)	175889.9 ± 13361.7	142496.8 ± 12010.39	135996.8 ± 12565.9
GGT (U/L)	59.3 ± 1.7	37 ± 2.1	35 ± 0.1
MPV (um^3)	11.8 ± 0.1	11.23 ± 0.43	11.27 ± 0.32
ALT (U/L)	82.5 ± 5.2	43.8 ± 6.5	27.6 ± 3.5
AST (U/L)	57.33 ± 17.00	30.33 ± 6.42	27.42 ± 2.89
AFP (ng/mL)	4.65 ± 0.69	3.67 ± 0.39	2.93 ± 0.40



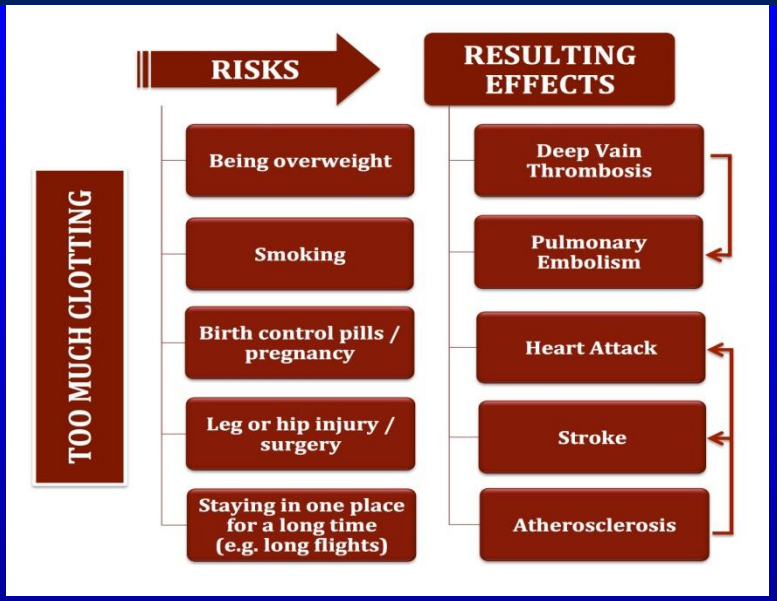


➢**FIGURE LEGENDS**

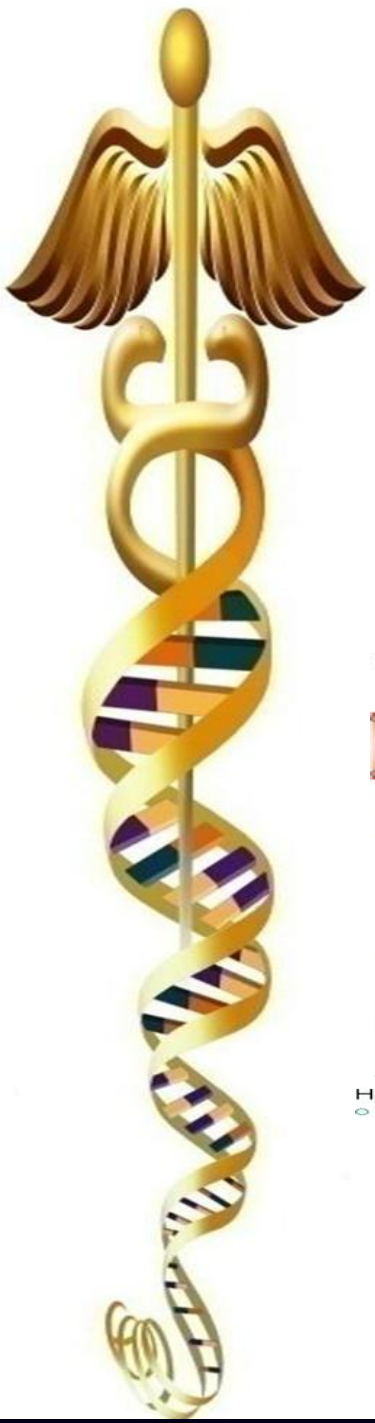
➢**Figure 1: sTRAIL levels.**

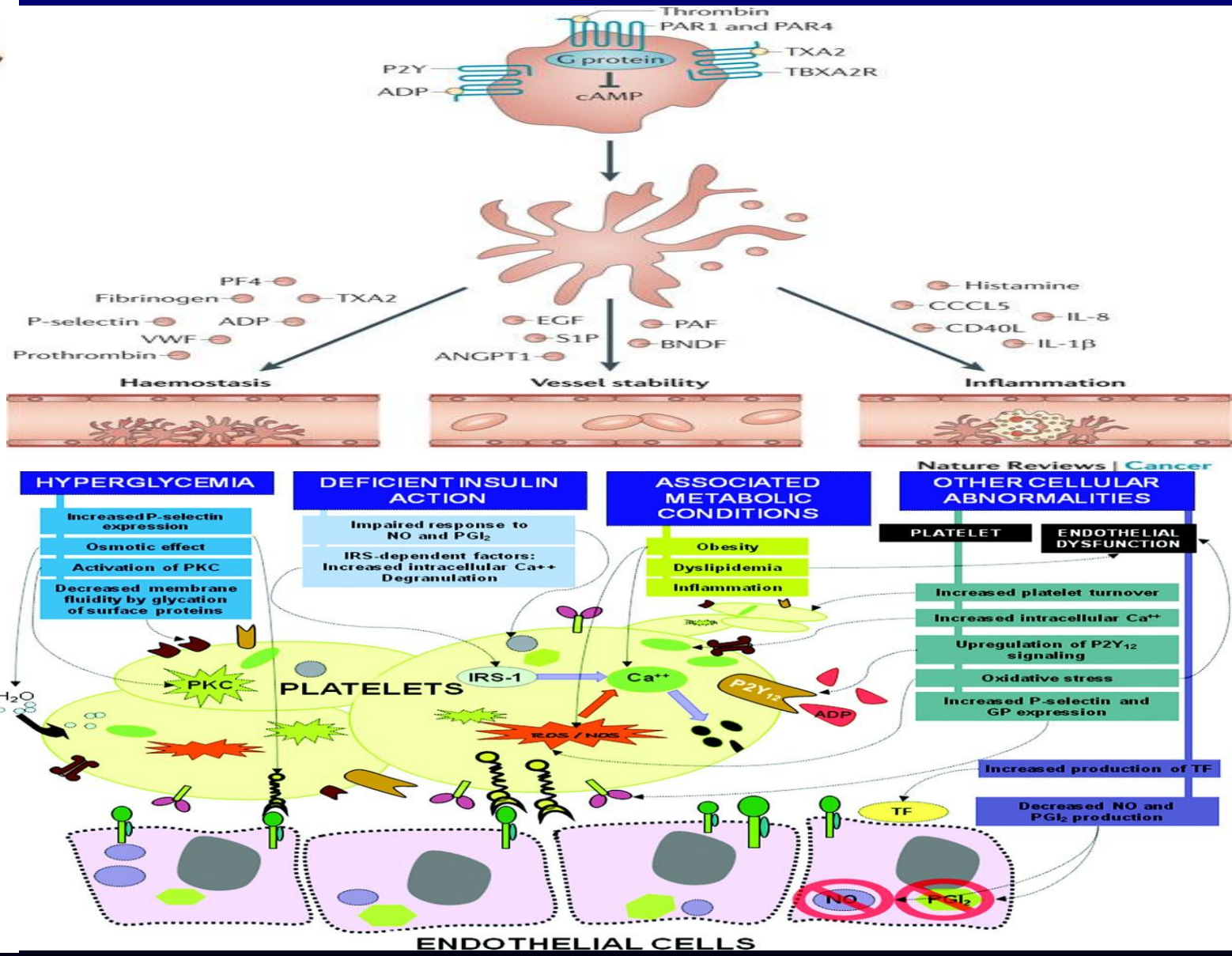
➢ **Group IA (mean±SEM): 250.24± 12.9**
Group IB (mean±SEM): 223.23± 8.41,
Group IC (mean±SEM): 183.39± 8.12

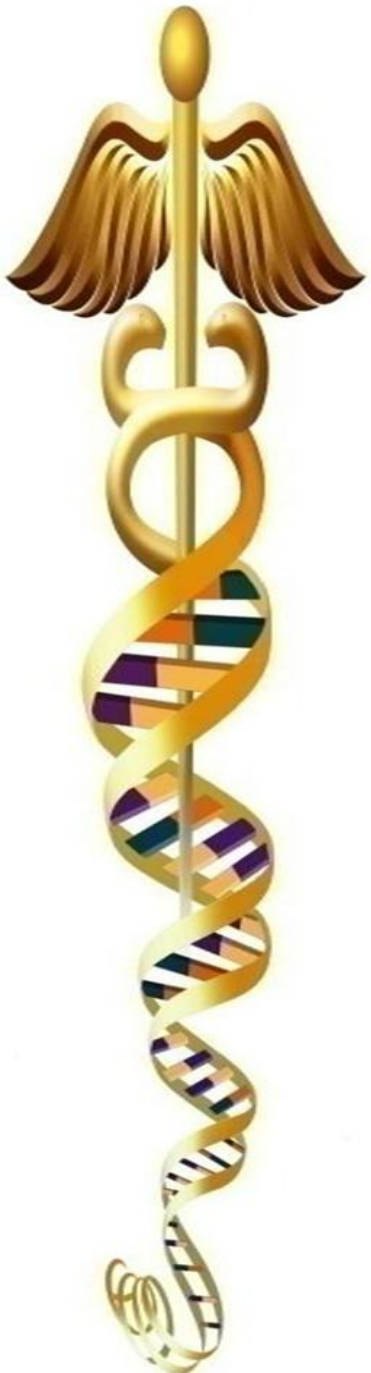
- http://www.youtube.com/watch?v=PsgmiIheTAo



1. PLATELETS



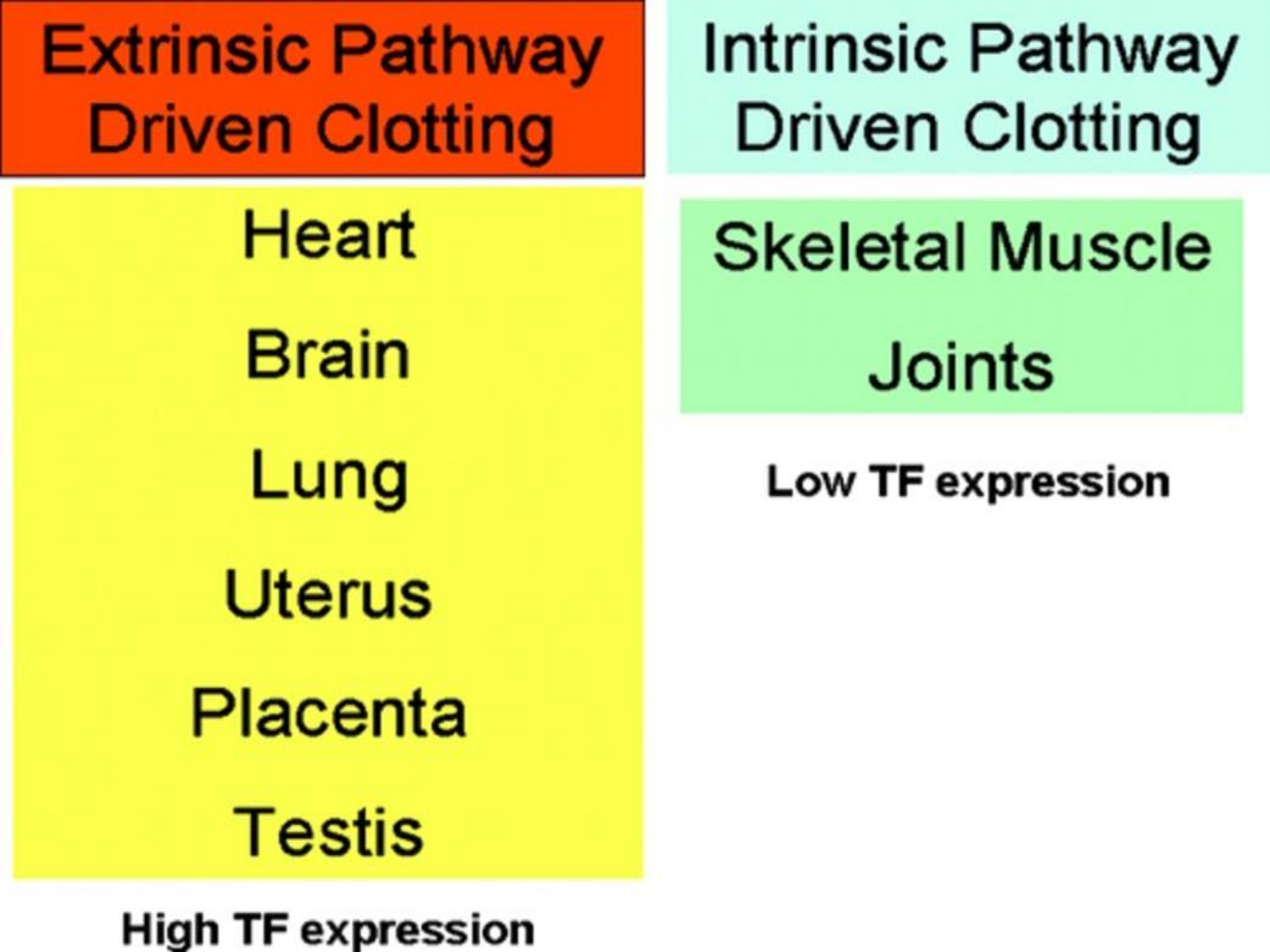

Thrombin
PAR1 and PAR4
G protein
cAMP
P2Y
ADP
TXA2
TBXA2R
PF4
Fibrinogen
TXA2
P-selectin
ADP
VWF
Prothrombin
EGF
S1P
ANGPT1
PAF
BNDF
Histamine
CCCL5
IL-8
CD40L
IL-1β
Haemostasis
Vessel stability
Inflammation
Nature Reviews | Cancer
HYPERGLYCEMIA
Increased P-selectin expression
Osmotic effect
Activation of PKC
Decreased membrane fluidity by glycation of surface proteins
DEFICIENT INSULIN ACTION
Impaired response to NO and PGI2
IRS-dependent factors: Increased intracellular Ca++ Degranulation
ASSOCIATED METABOLIC CONDITIONS
Obesity
Dyslipidemia
Inflammation
OTHER CELLULAR ABNORMALITIES
PLATELET
ENDOTHELIAL DYSFUNCTION
Increased platelet turnover
Increased intracellular Ca++
Upregulation of P2Y12 signaling
Oxidative stress
Increased P-selectin and GP expression
PKC
PLATELETS
IRS-1
Ca++
P2Y12
ADP
ROS / NOS
H2O
Increased production of TF
Decreased NO and PGI2 production
TF
NO
PGI2
ENDOTHELIAL CELLS



2.COAGULATION PROTEINS

Table 1-1. Coagulation Factors

Name	Description	Function
Fibrinogen (Factor I)	Molecular Weight (MW) = 340,000 daltons (Da); glycoprotein	Adhesive protein that forms the fibrin clot
Prothrombin (Factor II)	MW = 72,000 Da; vitamin K-dependent serine protease	Activated form is main enzyme of coagulation
Tissue factor (Factor III)	MW = 37,000 Da; also known as thromboplastin	Lipoprotein initiator of extrinsic pathway
Calcium ions (Factor IV)	Necessity of Ca++ ions for coagulation reactions described in 19th century	Metal cation necessary for coagulation reactions
Factor V (Labile factor)	MW = 330,000 Da	Cofactor for activation of prothrombin to thrombin
Factor VII (Proconvertin)	MW = 50,000 Da; vitamin K-dependent serine protease	With tissue factor, initiates extrinsic pathway
Factor VIII (Antihemophilic factor)	MW = 330,000 Da	Cofactor for intrinsic activation of factor X
Factor IX (Christmas factor)	MW = 55,000 Da; vitamin K-dependent serine protease	Activated form is enzyme for intrinsic activation of factor X
Factor X (Stuart-Prower factor)	MW = 58,900 Da; vitamin K-dependent serine protease	Activated form is enzyme for final common pathway activation of prothrombin
Factor XI (Plasma thromboplastin antecedent)	MW = 160,000 Da; serine protease	Activated form is intrinsic activator of factor IX
Factor XII (Hageman factor)	MW = 80,000 Da; serine protease	Factor that nominally starts aPTT-based intrinsic pathway
Factor XIII (Fibrin stabilizing factor)	MW = 320,000 Da	Transamidase that cross-links fibrin clot
High-molecular-weight kininogen (Fitzgerald, Flaujeac, or William factor)	MW = 110,000 Da; circulates in a complex with factor XI	Cofactor
Prekallikrein (Fletcher factor)	MW = 85,000 Da; serine protease	Activated form that participates at beginning of aPTT-based intrinsic pathway


Extrinsic Pathway Driven Clotting
Intrinsic Pathway Driven Clotting
Heart
Brain
Lung
Uterus
Placenta
Testis
High TF expression
Skeletal Muscle
Joints
Low TF expression

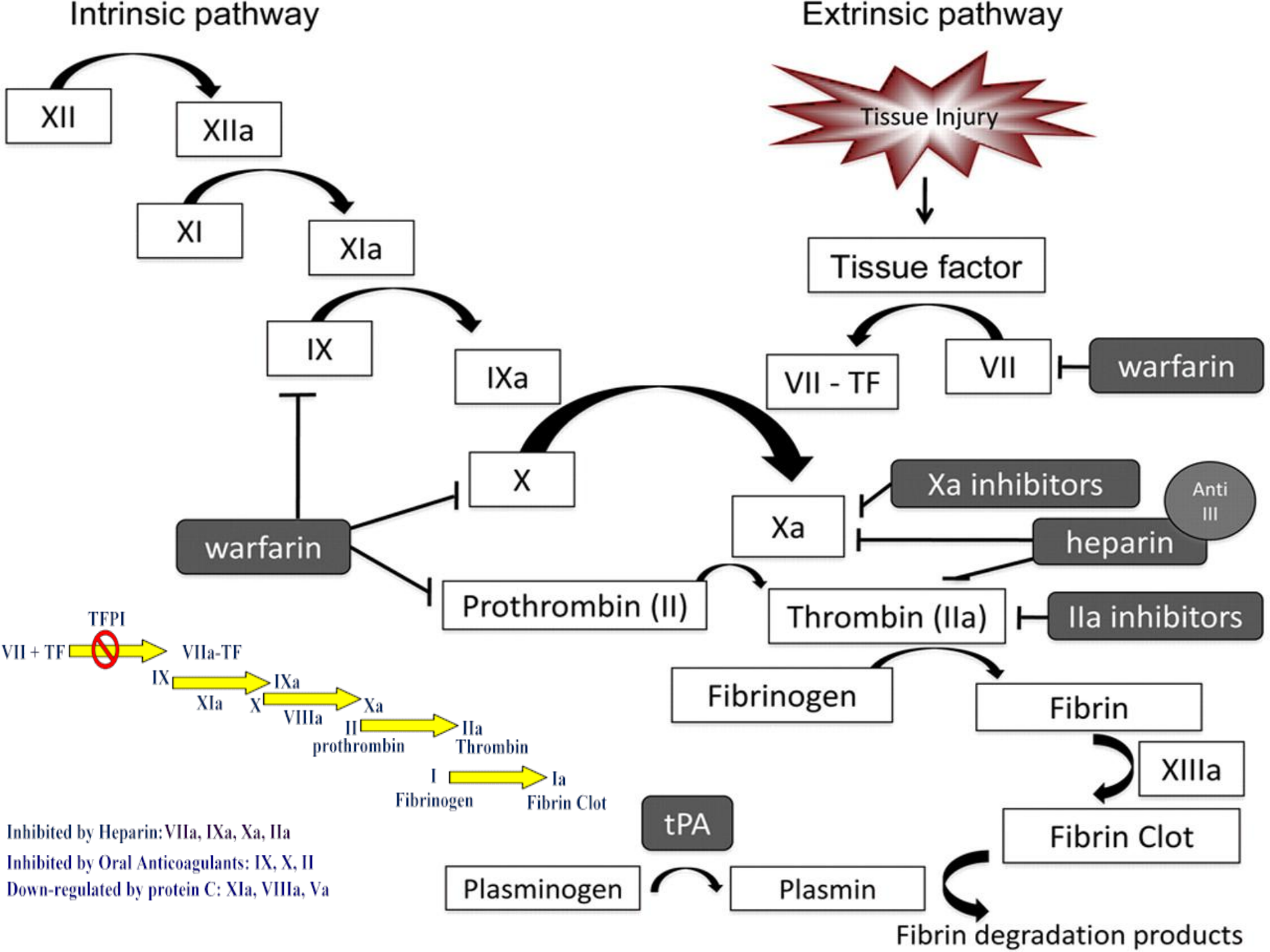
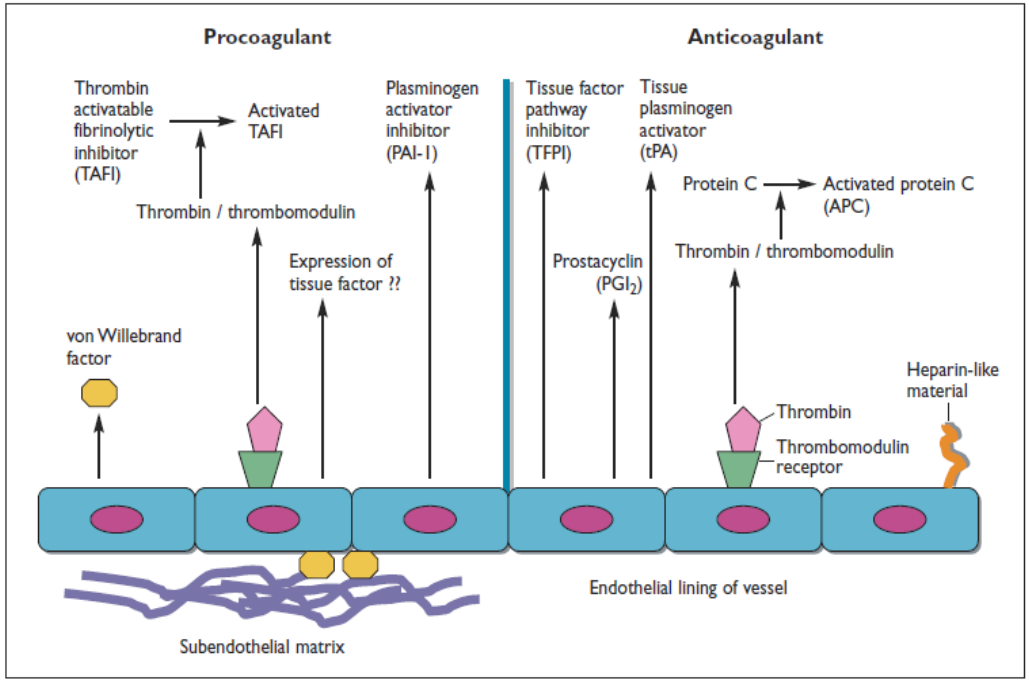
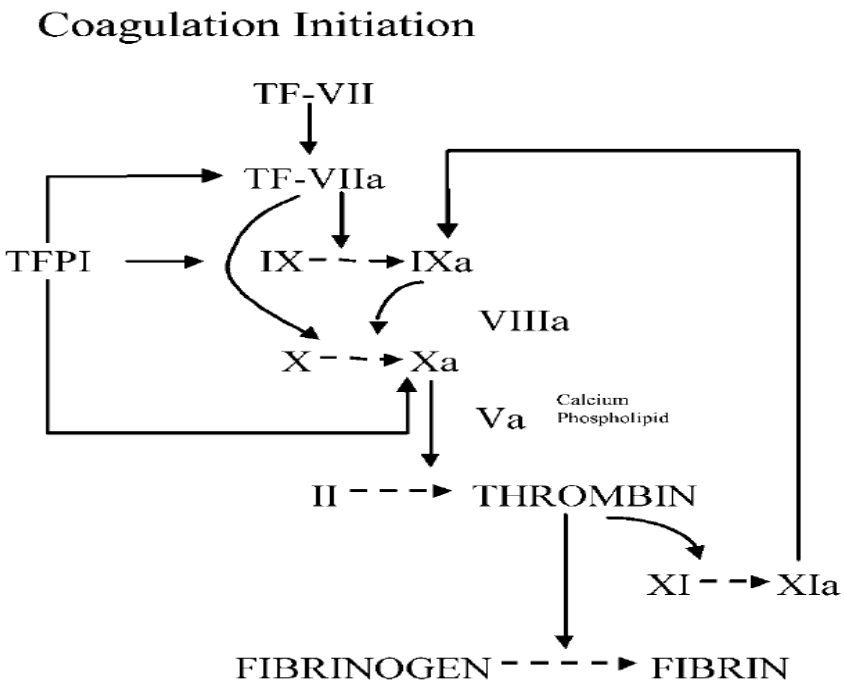
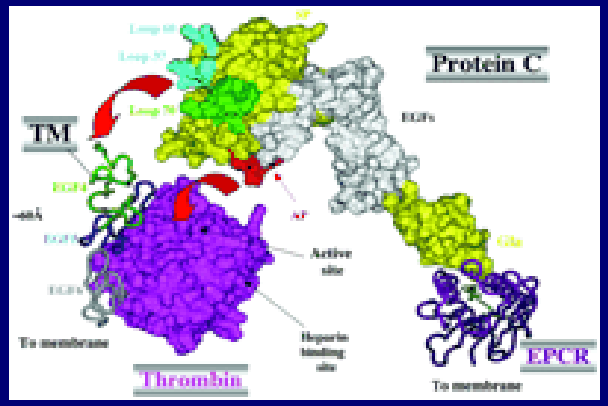

Intrinsic pathway
Extrinsic pathway
XII
XIIa
XI
XIa
IX
IXa
X
Xa
Tissue Injury
Tissue factor
VII - TF
VII
warfarin
Xa inhibitors
Anti III
heparin
warfarin
Prothrombin (II)
Thrombin (IIa)
IIa inhibitors
Fibrinogen
Fibrin
XIIIa
Fibrin Clot
tPA
Plasminogen
Plasmin
Fibrin degradation products
TFPI
VII + TF
VIIa-TF
IX
XIa
IXa
X
VIIIa
Xa
II
prothrombin
IIa
Thrombin
I
Fibrinogen
Ia
Fibrin Clot
Inhibited by Heparin: VIIa, IXa, Xa, IIa
Inhibited by Oral Anticoagulants: IX, X, II
Down-regulated by protein C: XIa, VIIIa, Va

Table 1-2. Coagulation Factor Inhibitors

Name	Description	Function
Tissue factor pathway inhibitor (TFPI)	Molecular Weight (MW) = 33,000 daltons (Da)	Inhibits the tissue factor/factor VIIa complex
Protein C	MW = 62,000 Da; vitamin K-dependent serine protease	Activated form cleaves coagulation cofactors Va and VIIIa
Protein S	MW = 75,000 Da; vitamin K-dependent protein	Cofactor for protein C
Antithrombin	MW = 58,000 Da	Serpin that directly inhibits several of the serine proteases; requires heparin as a cofactor

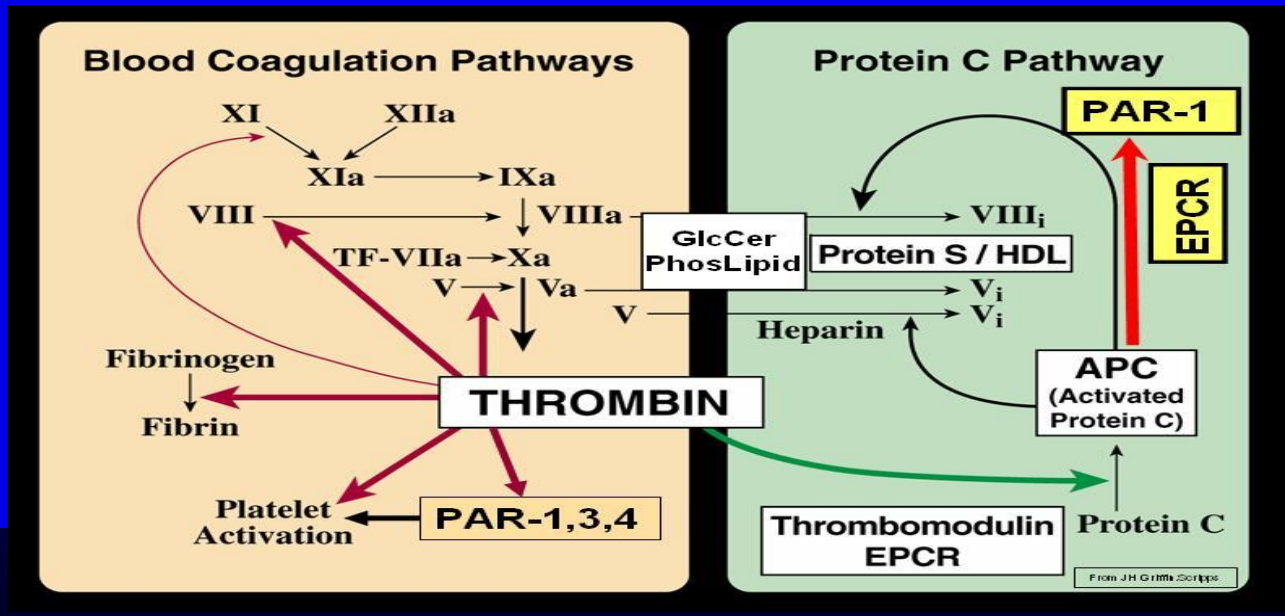






PROTEIN C

Through mechanisms downstream of PAR-1 activation, APC has been shown to exhibit anti-inflammatory and anti-apoptotic properties via up-regulated gene expression of anti-apoptotic and anti-inflammatory mediators , down-regulation of pro-inflammatory cytokines



➢. Kerschen, E. J.,. (2007) J. Exp. Med. 204 2439–2448.

Tissue factor pathway inhibitor

TFPI is a plasma Kunitz-type serine protease inhibitor, which modulates initiations of coagulation induced by TF. In a factor (F) Xa-dependent feedback system, TFPI binds directly and inhibits the TF–FVII/FVIIa complex.

TFPI also circulates in complex with plasma lipoproteins.

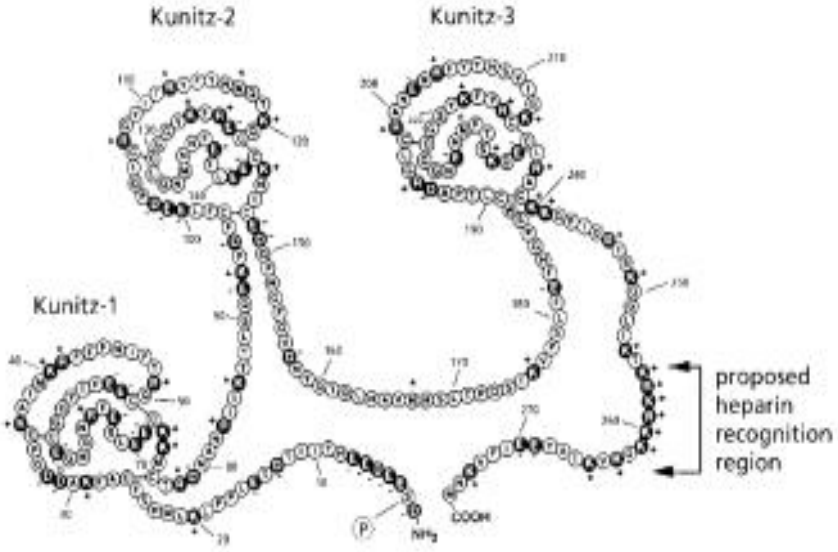
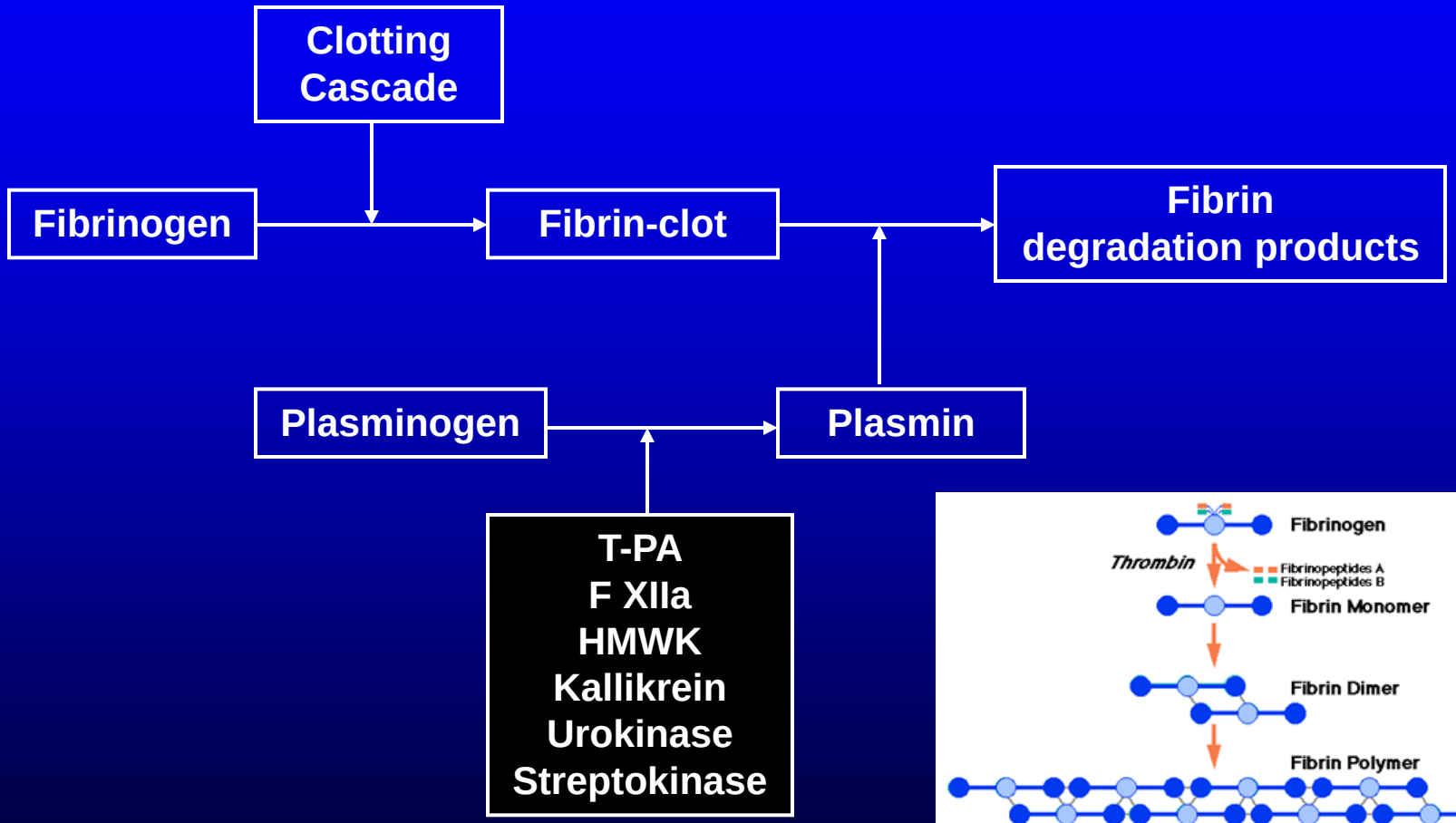
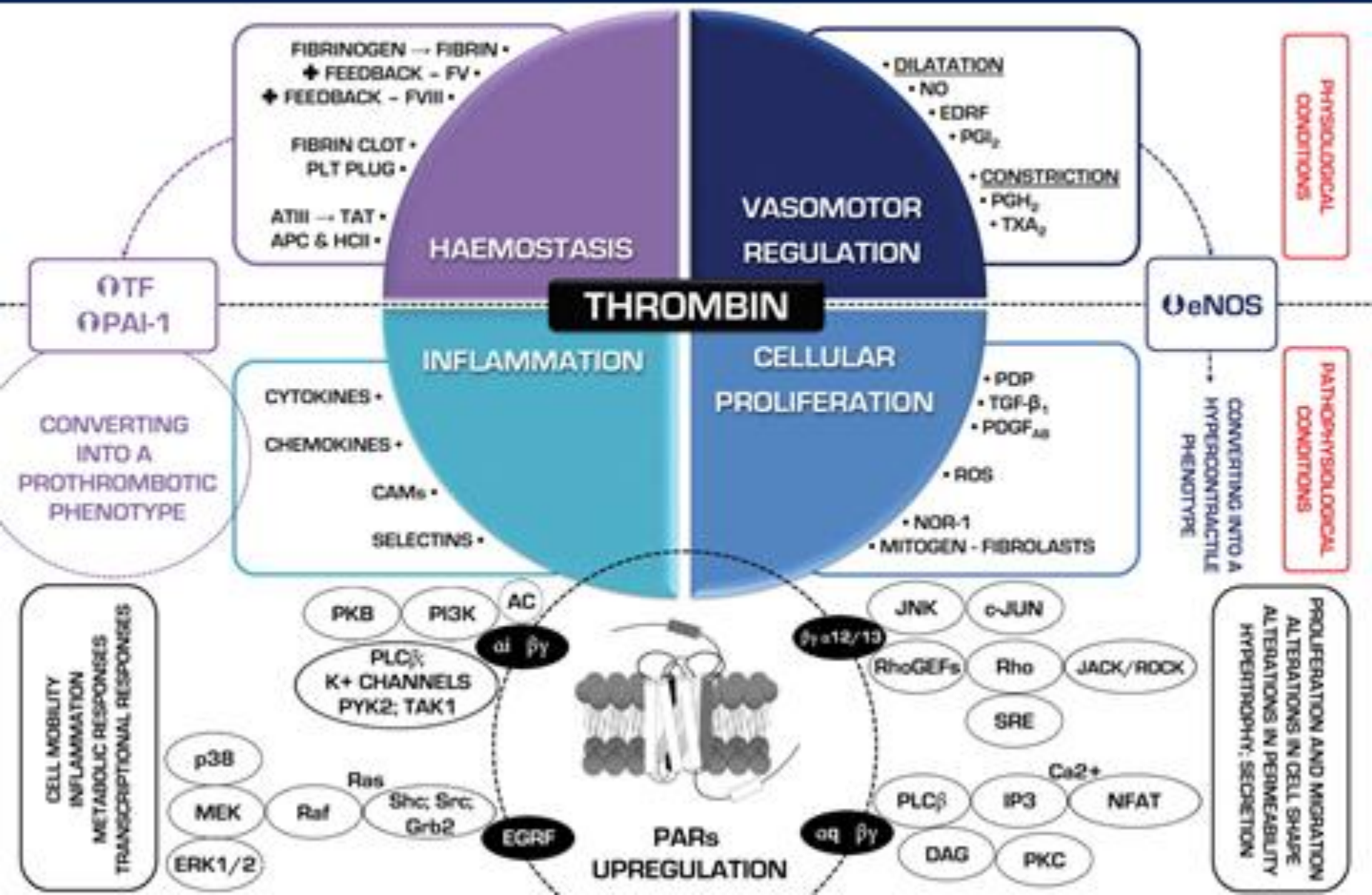


Figure 2. Model of tissue factor pathway inhibitor (TFPI), showing the Kunitz-type domains and the positively- and negatively-charged amino acid groups. The arrows point to the site of heparin binding at the C-terminal end of the TFPI [21]. Reproduced with permission from Brose GJ, Tissue factor pathway inhibitor and the current concept of blood coagulation. *Blood Coagul Fibrinolys* 1995;6:7–13

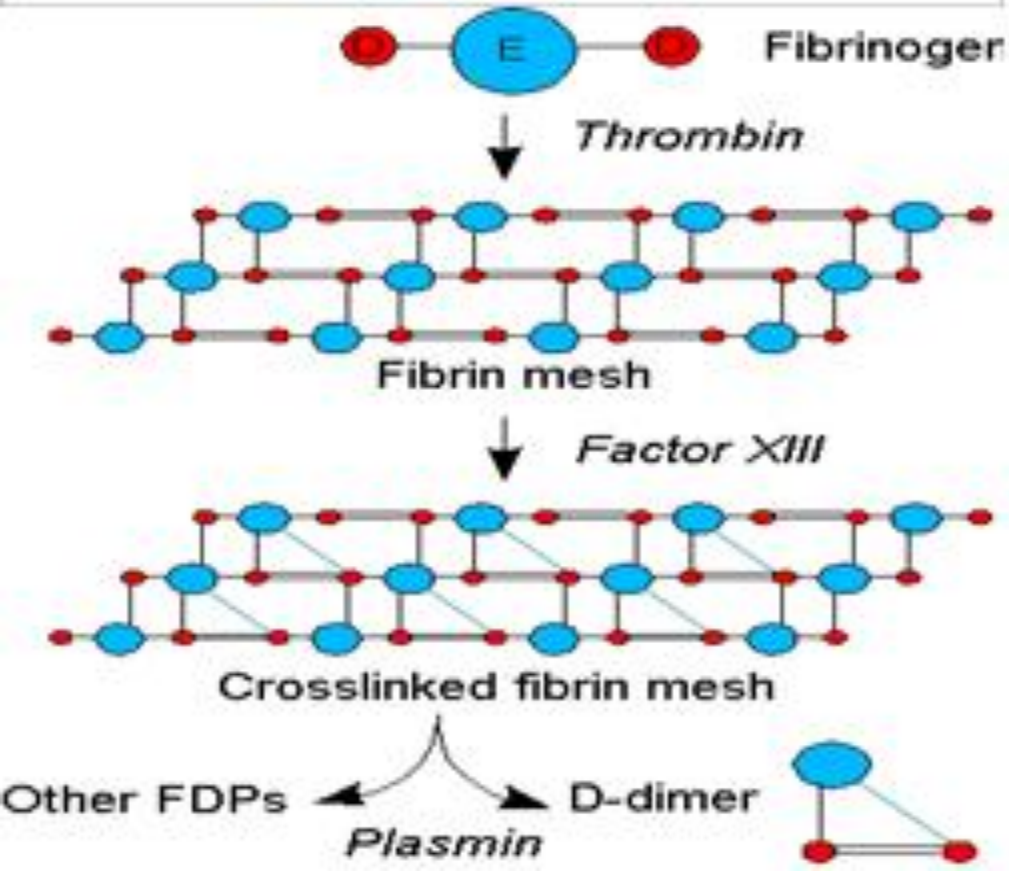
The Fibrinolytic System

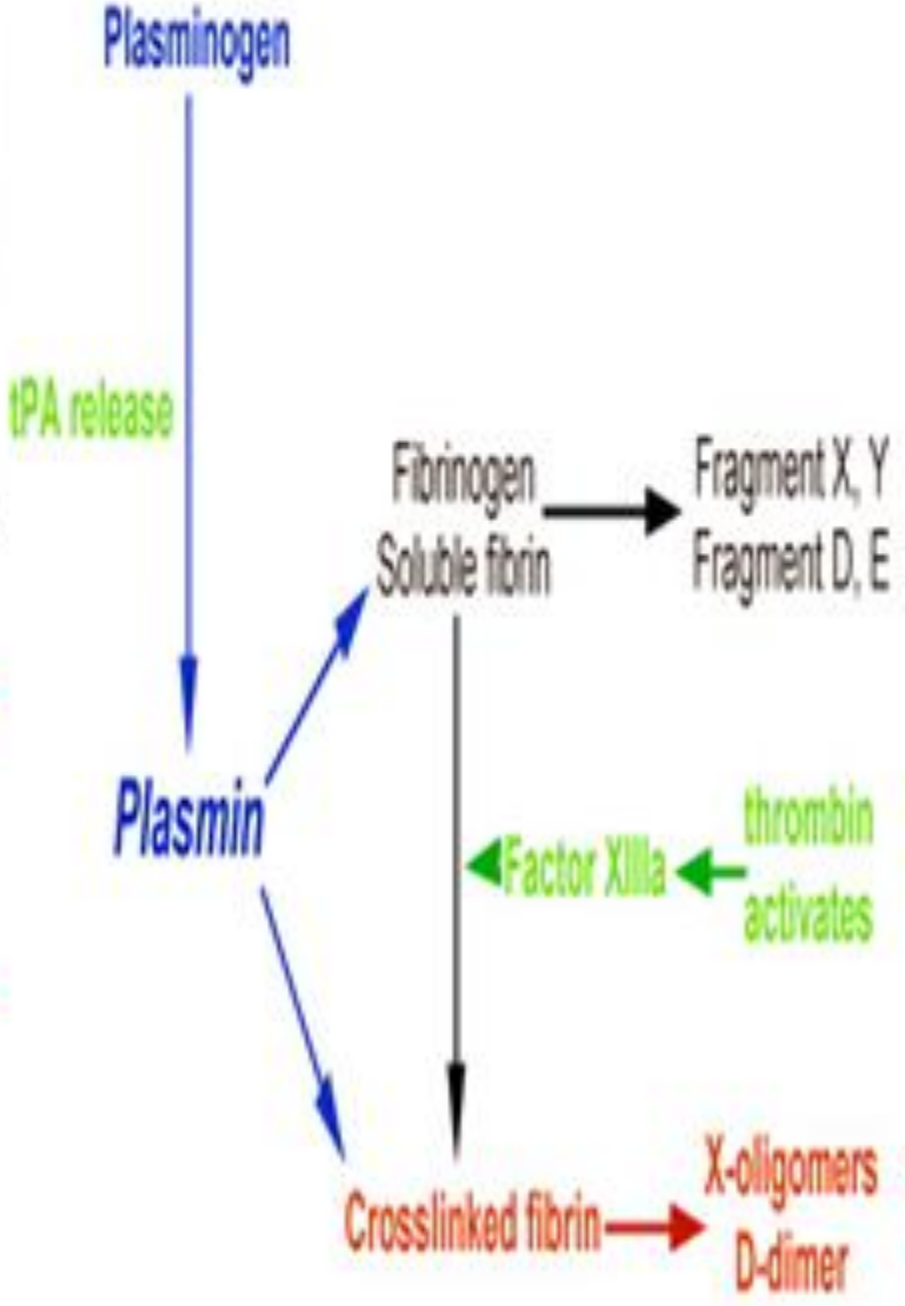


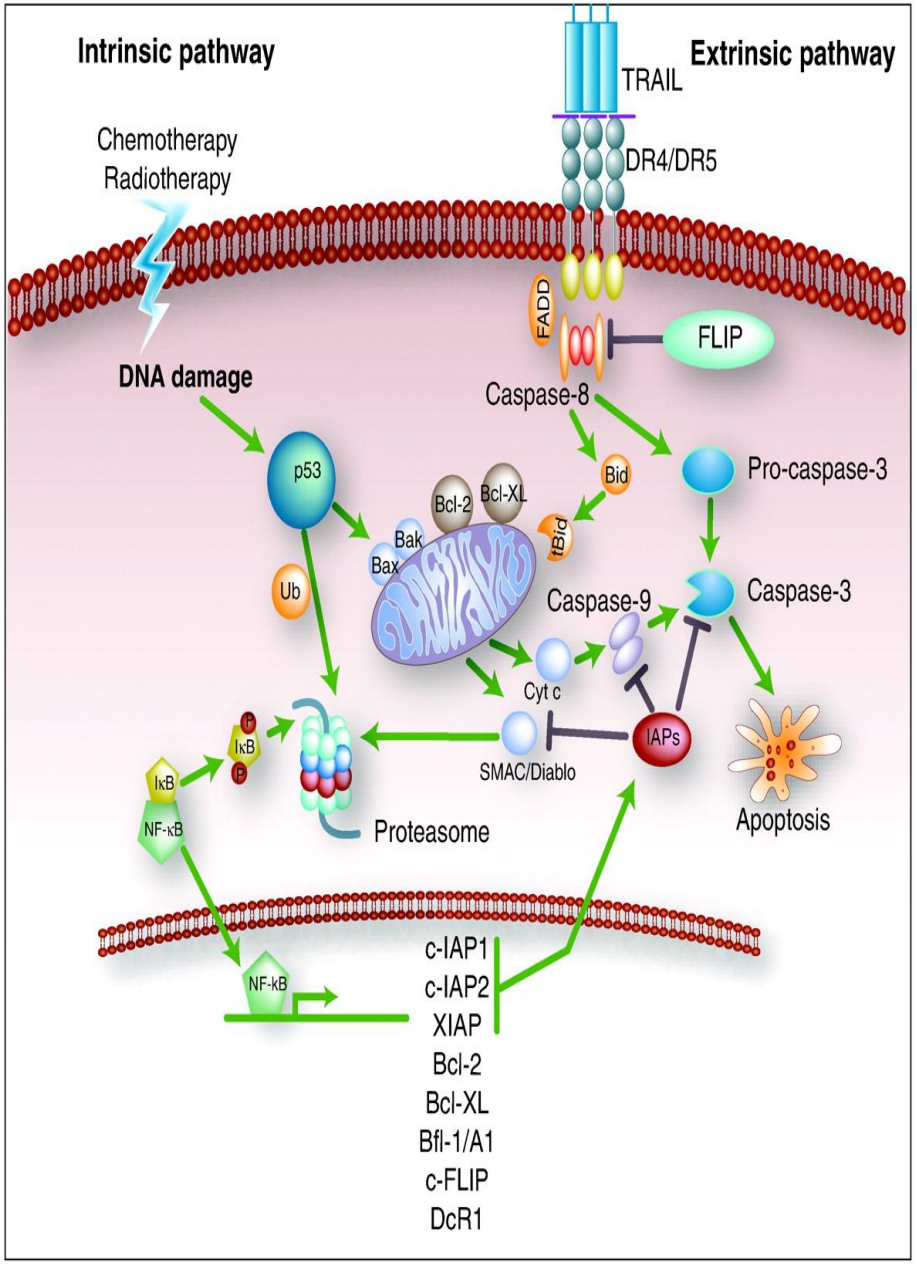
D-dimer

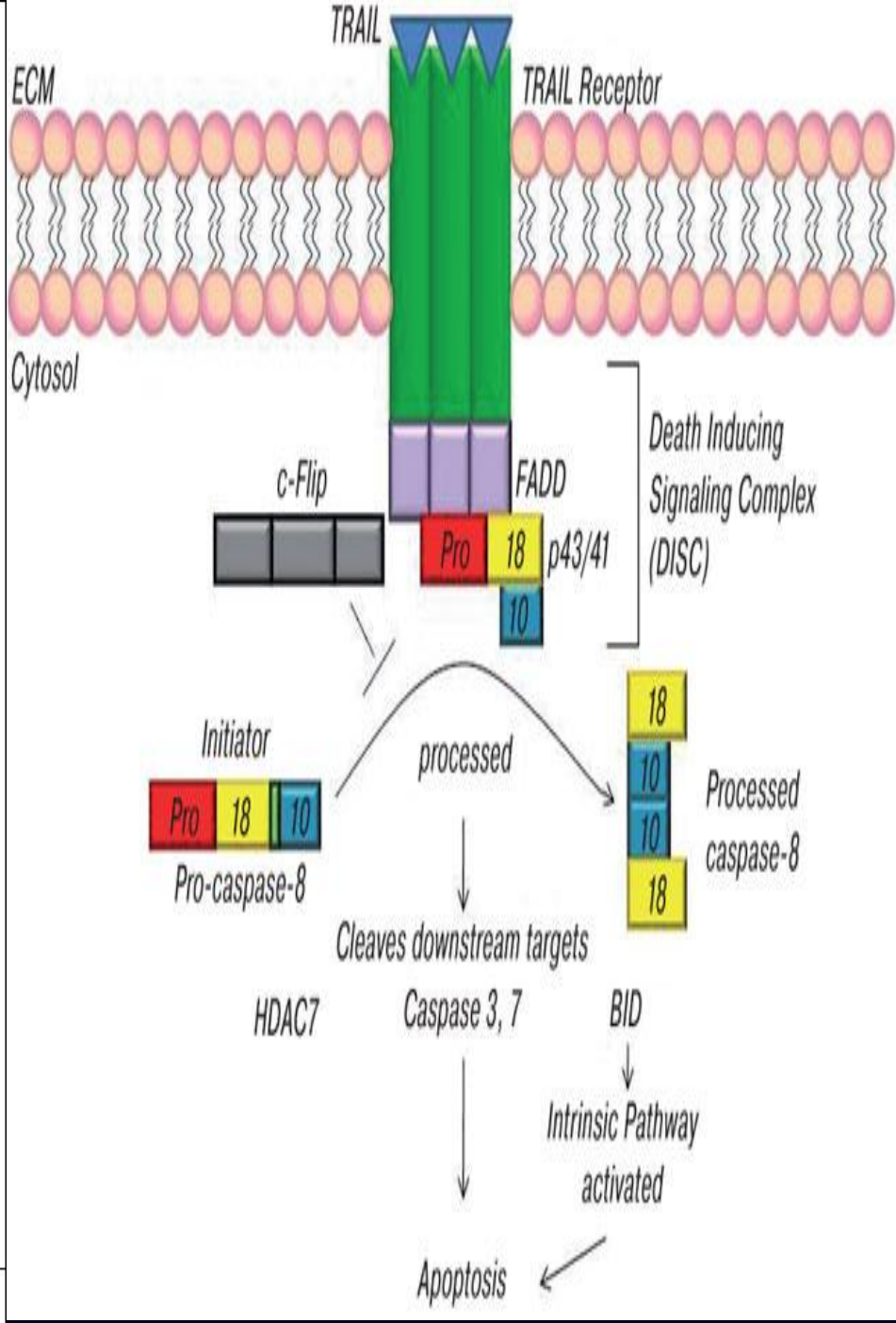

FIBRINOGEN → FIBRIN •
✚ FEEDBACK – FV •
✚ FEEDBACK – FVIII •
FIBRIN CLOT •
PLT PLUG •
ATIII → TAT •
APC & HCII •
HAEMOSTASIS
VASOMOTOR REGULATION
• DILATATION
• NO
• EDRF
• PGI2
• CONSTRICTION
• PGH2
• TXA2
PHYSIOLOGICAL CONDITIONS
THROMBIN
ϴTF
ϴPAI-1
ϴeNOS
CONVERTING INTO A PROTHROMBOTIC PHENOTYPE
INFLAMMATION
CELLULAR PROLIFERATION
CYTOKINES •
CHEMOKINES •
CAMs •
SELECTINS •
• PDP
• TGF-β1
• PDGFAB
• ROS
• NOR-1
• MITOGEN - FIBROLASTS
CONVERTING INTO A HYPERCONTRACTILE PHENOTYPE
PATHOPHYSIOLOGICAL CONDITIONS
PKB
PI3K
AC
αi βγ
PLCβ
K+ CHANNELS
PYK2; TAK1
JNK
c-JUN
βγ α12/13
RhoGEFs
Rho
JACK/ROCK
SRE
p38
MEK
ERK1/2
Ras
Raf
Shc; Src; Grb2
EGRF
PARs UPREGULATION
Ca2+
PLCβ
IP3
NFAT
DAG
PKC
αq βγ
CELL MOBILITY
INFLAMMATION
MEDIATION
METABOLIC RESPONSES
TRANSCRIPTIONAL RESPONSES
PROLIFERATION AND MIGRATION
ALTERATIONS IN CELL SHAPE
ALTERATIONS IN PERMEABILITY
HYPERTROPHY; SECRETION

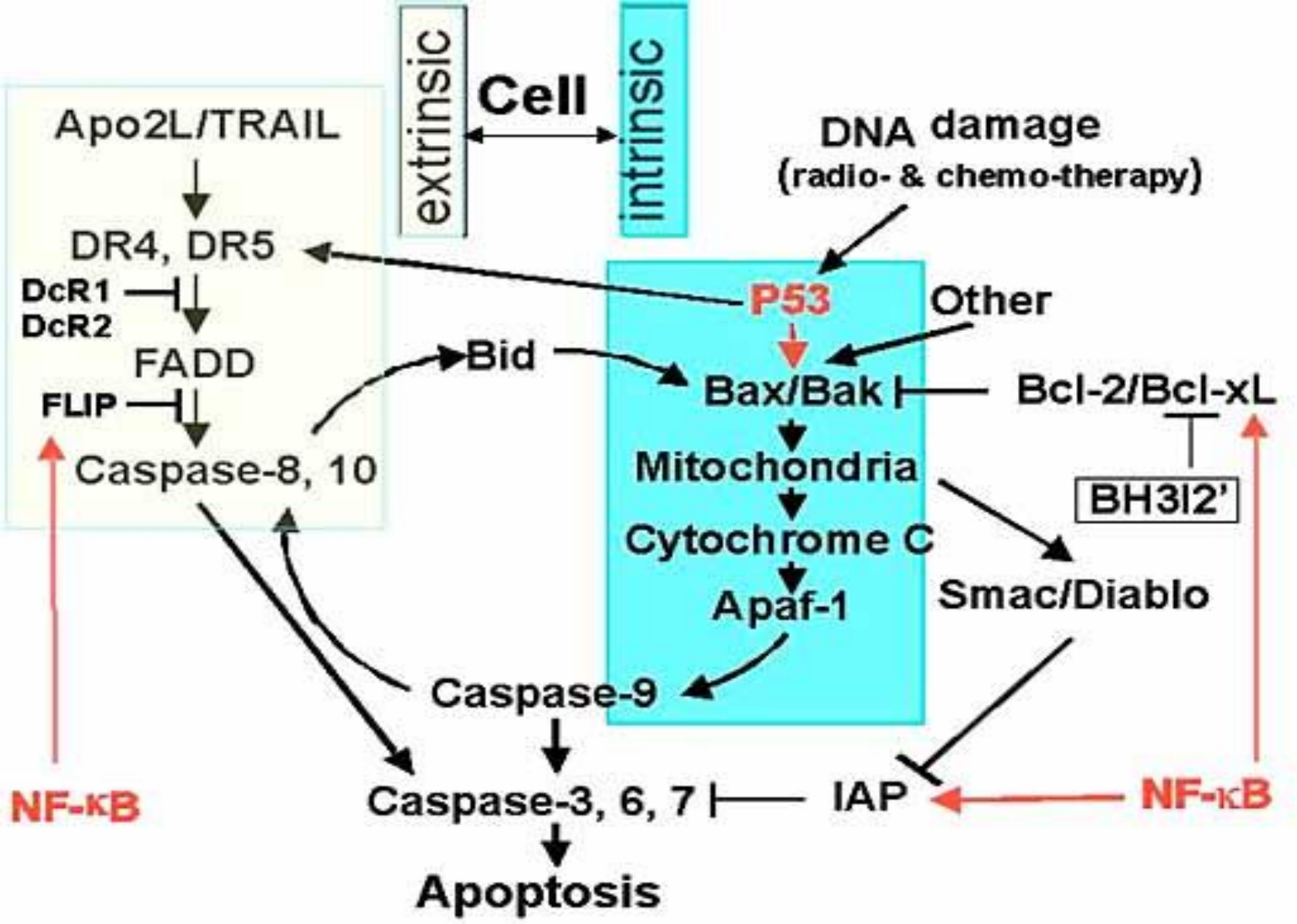

D-Dimer
Thrombin
Fibrinogen
Soluble Fibrin + FP A+B
XIIIa
Plasminogen Activators
Fibrin (Cross-linked)
Plasmin
Plasminogen
D-Dimers


Fibrinoger
Thrombin
Fibrin mesh
Factor XIII
Crosslinked fibrin mesh
Other FDPs
D-dimer
Plasmin

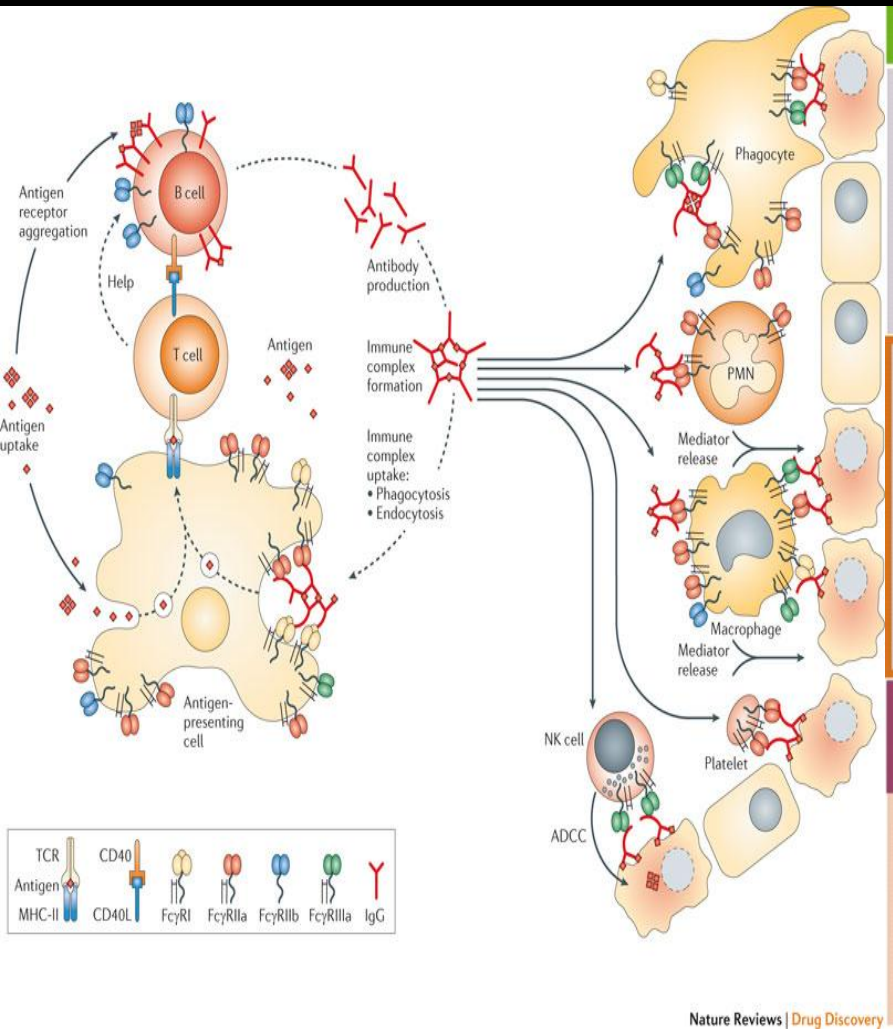

Plasminogen
tPA release
Plasmin
Fibrinogen
Soluble fibrin
Fragment X, Y
Fragment D, E
Factor XIIIa
thrombin
activates
Crosslinked fibrin
X-oligomers
D-dimer

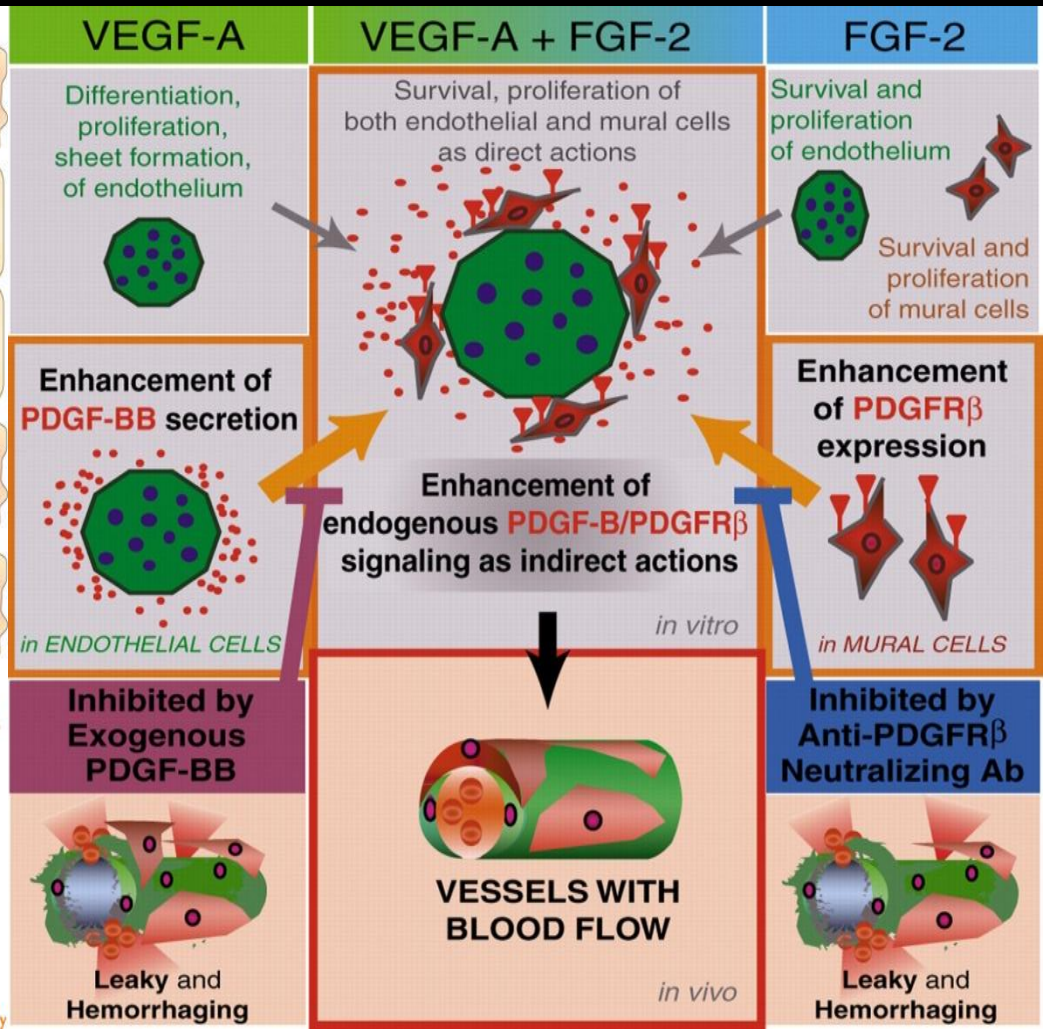

Intrinsic pathway
Extrinsic pathway
TRAIL
DR4/DR5
Chemotherapy
Radiotherapy
FADD
FLIP
DNA damage
Caspase-8
p53
Bid
Pro-caspase-3
Bcl-2
Bcl-XL
Bak
Bax
tBid
Ub
Caspase-9
Caspase-3
Cyt c
IAPs
SMAC/Diablo
IκB
NF-κB
Proteasome
Apoptosis
NF-κB
c-IAP1
c-IAP2
XIAP
Bcl-2
Bcl-XL
Bfl-1/A1
c-FLIP
DcR1

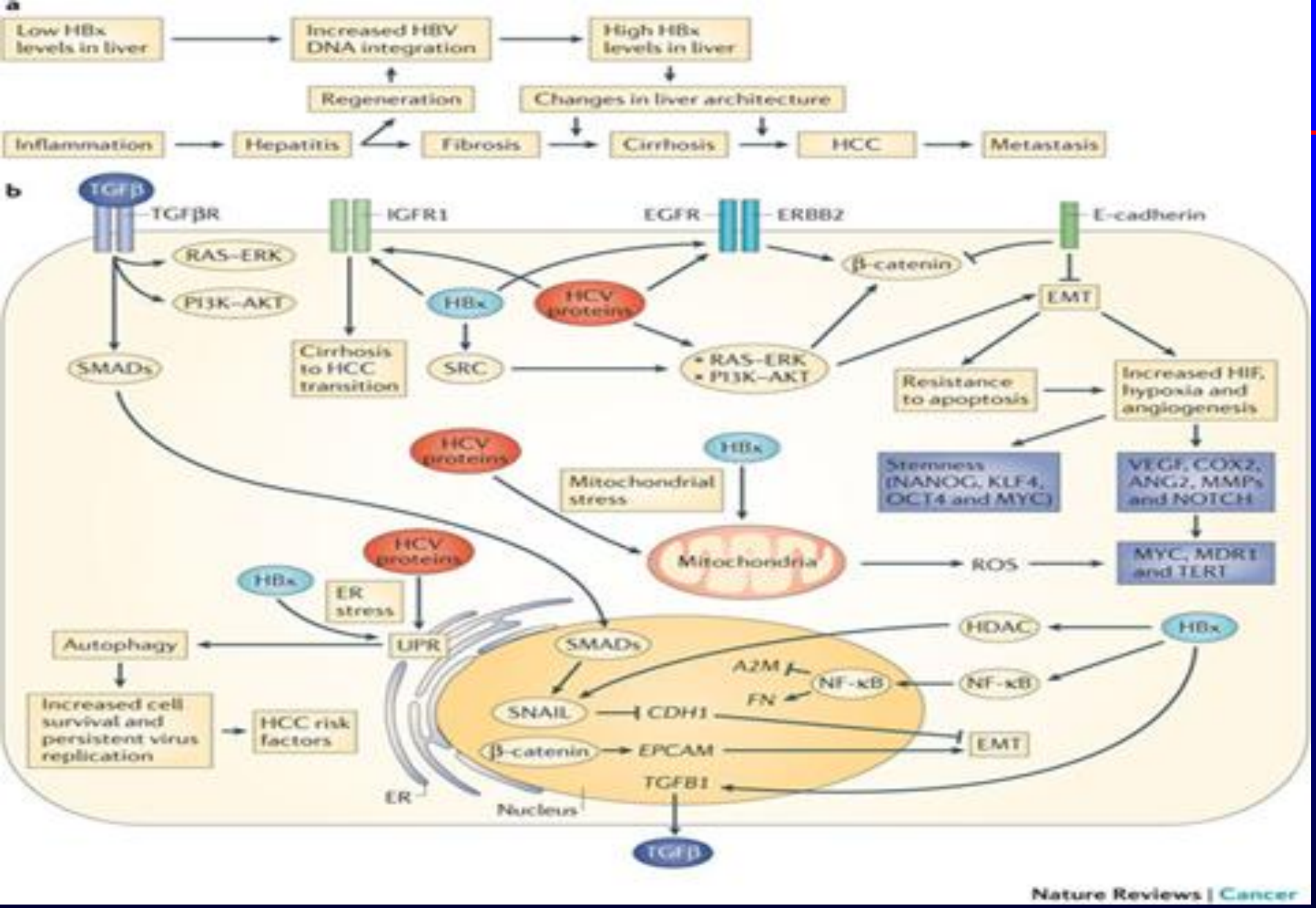

TRAIL
ECM
TRAIL Receptor
Cytosol
c-Flip
FADD
Pro
18
p43/41
10
Death Inducing
Signaling Complex
(DISC)
Initiator
Pro
18
10
Pro-caspase-8
processed
18
10
10
18
Processed
caspase-8
Cleaves downstream targets
HDAC7
Caspase 3, 7
BID
Intrinsic Pathway
activated
Apoptosis


extrinsic
Cell
intrinsic
Apo2L/TRAIL
DR4, DR5
DcR1
DcR2
FADD
FLIP
Caspase-8, 10
DNA damage
(radio- & chemo-therapy)
P53
Other
Bid
Bax/Bak
Bcl-2/Bcl-xL
Mitochondria
BH3I2'
Cytochrome C
Smac/Diablo
Apaf-1
Caspase-9
NF-κB
Caspase-3, 6, 7
IAP
NF-κB
Apoptosis

- **Angiogenesis-related Proteins**
- VEGF-C, Artemin, uPA, Vasohibin, Angiopoietin-2, VEGF-A, Endothelin-1, Thrombospondin-2, Amphiregulin, TGF-b1, CCL3, Persephin , PF-4 (PLATELET FACTOR-4), SerpinB5, Thrombospondin-1, Epidermal growth factor , FGF1 (acidic), FGF2 (basic), HBEGF, TYMP, SerpinF1
- sFlt-1 (VEGF RESEPTOR ,Vascular permeability factor/vascular endothelial cell growth factor (VPF/VEGF),
- TPFI







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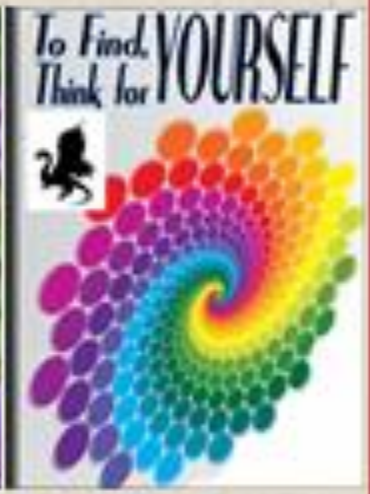
Thank you

Prof. Dr. Tse Wen CHANG, Ph.D. (Taiwan)
Prof. Dr. Saadet GUMUSLU, Ph.D.
Prof. Dr. Reginald M GORCZYNSKI, MD, PhD. (Canada)
Prof.Dr. Olcay YEGIN, MD.
Prof. Dr. Ludwig G. STRAUSS, MD (Germany)
Prof.Dr. Felix HERTH, MD, PhD. (Germany)
Prof. Dr. Aykut CILLI, MD.
Prof. Dr. Ramazan CETINKAYA, MD.
Gizem Esra PARLAK MSc.
Dr. Atil BISGIN, MD, PhD (Sweden)
Prof. Dr. Hasan Huseyin POLAT, MD.
Dr. Emel SAHIN, PhD.
Assoc. Prof. Dr. Sukran KOSE, MD.



Arzu Didem Yalcin ,MD adidyal@yahoo.com

Ignore those who say you do not suck. They said to me jerks.

I gave shred the hands of atoms

Special Theory of Relativity (1905), *Relativity* (1920 and 1950), *General Theory of Relativity* (1916), *Investigations on Theory of Brownian Movement* (1926), and *The Evolution of Physics* (1938). Among his non-scientific works, *About Zionism* (1930), *Why War?* (1933), *My Philosophy* (1934), and *Out of My Later Years* (1950).

If the bee disappeared off the surface of the globe then man would only have four years of life left. No more bees, no more pollination, no more plants, no more animals, no more man."