Hepatosellüler Karsinom: Moleküler Yolaklardan Patolojik Tanıya

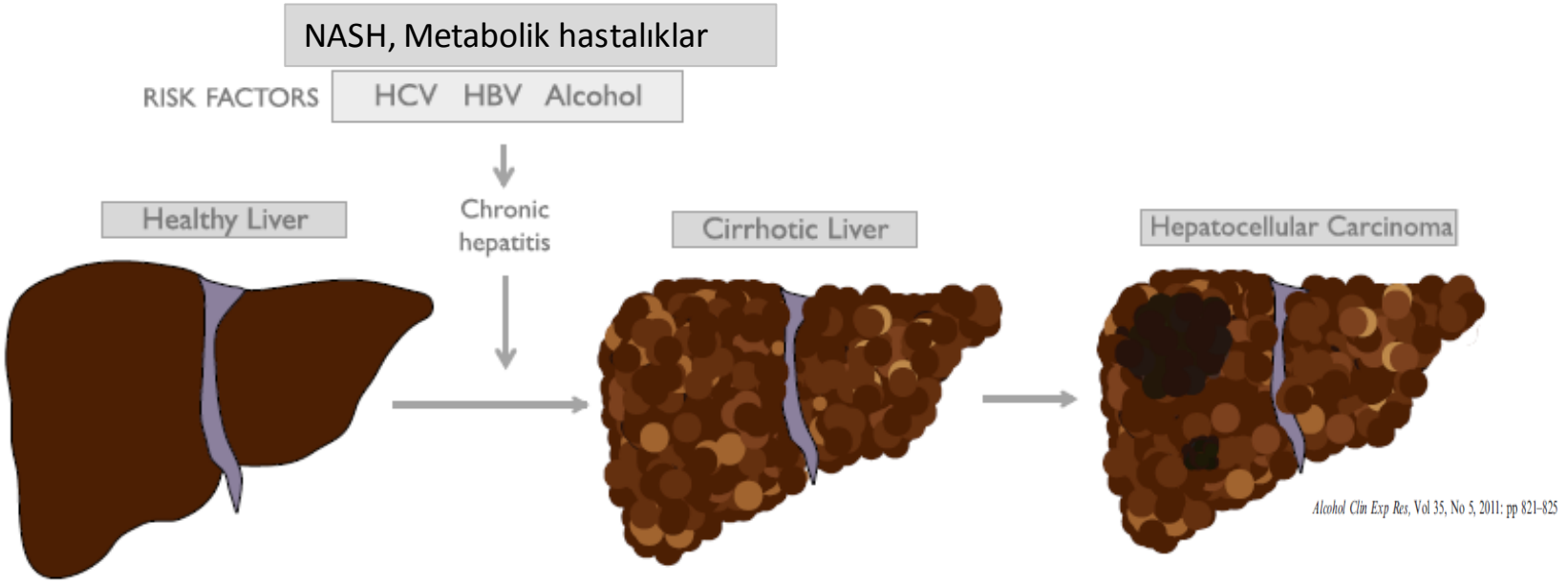
Prof. Dr. Funda Yılmaz
Ege Üniversitesi Tıp Fakültesi
Tıbbi Patoloji ABD

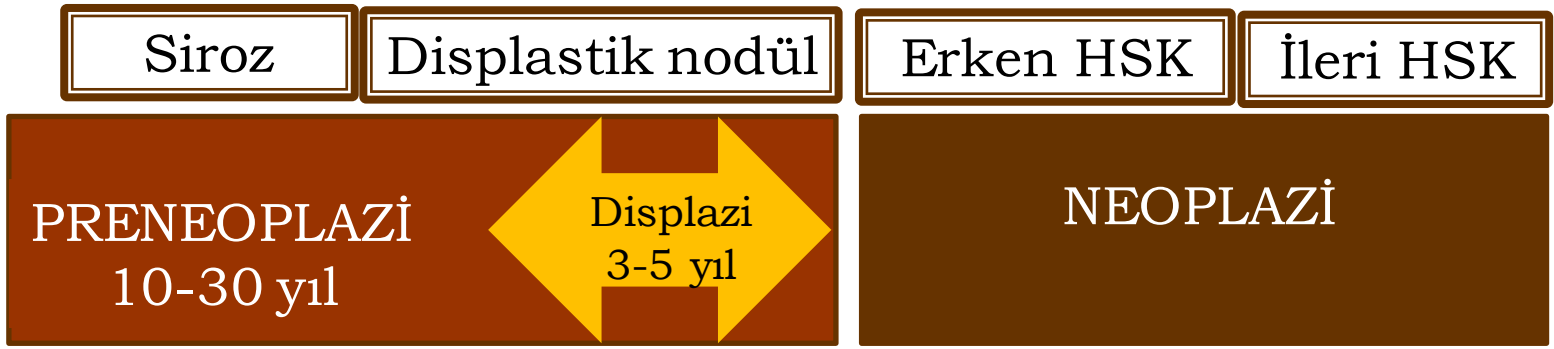
25. Ulusal Patoloji Kongresi
6. Sitopatoloji Kongresi
14 - 17 Ekim 2015 / Merinos AKKM - BURSA

Sunum Akışı

- Hepatokarsinogenez süreci
- Moleküler düzeyin hatırlanması
- Hepatosellüler karsinomun moleküler sınıflaması
- Moleküler sınıflamanın etiyoloji, tanı, prognoz ve tedavi ile ilişkileri

Hepatokarsinogenezin temel basamakları



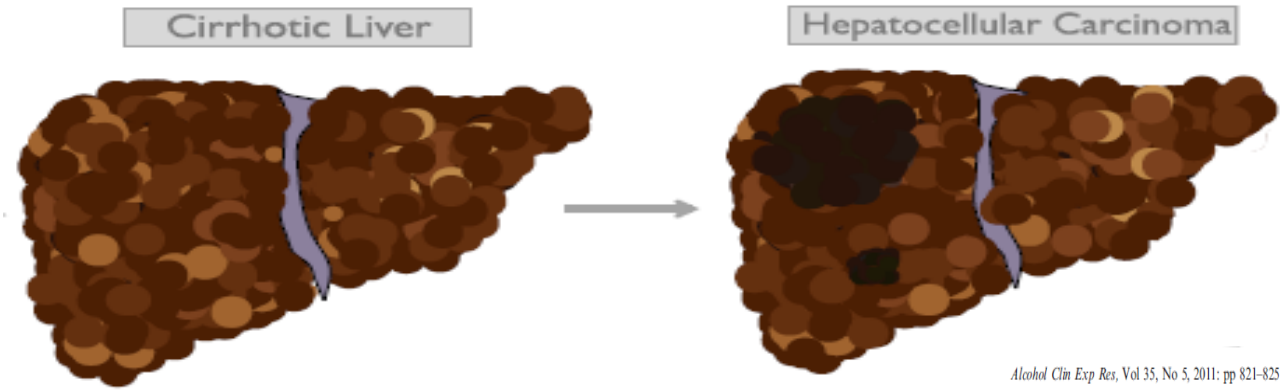


Hepatokarsinogenezin temel basamakları

KRONİK İNFLAMASYON

Sitokinler (TGF-β)

Reaktif oksijen ve nitrojen türevleri



Alcohol Clin Exp Res, Vol 35, No 5, 2011: pp 821–825

Hepatosit hasarı→ Hücre proliferasyonu + Biriken genom hasarı

Siroz | Displastik nodül | Erken- İleri HSK

Protoonkogenlerin aktivasyonu (Nras, cmyc, cfos)
Büyüme faktörleri aktivasyonu (IGF1,IGF2, TGFα, TGFβ)
Tümör baskılayıcı genlerin inaktivasyonu (p53, p16, RB, IGF2R)

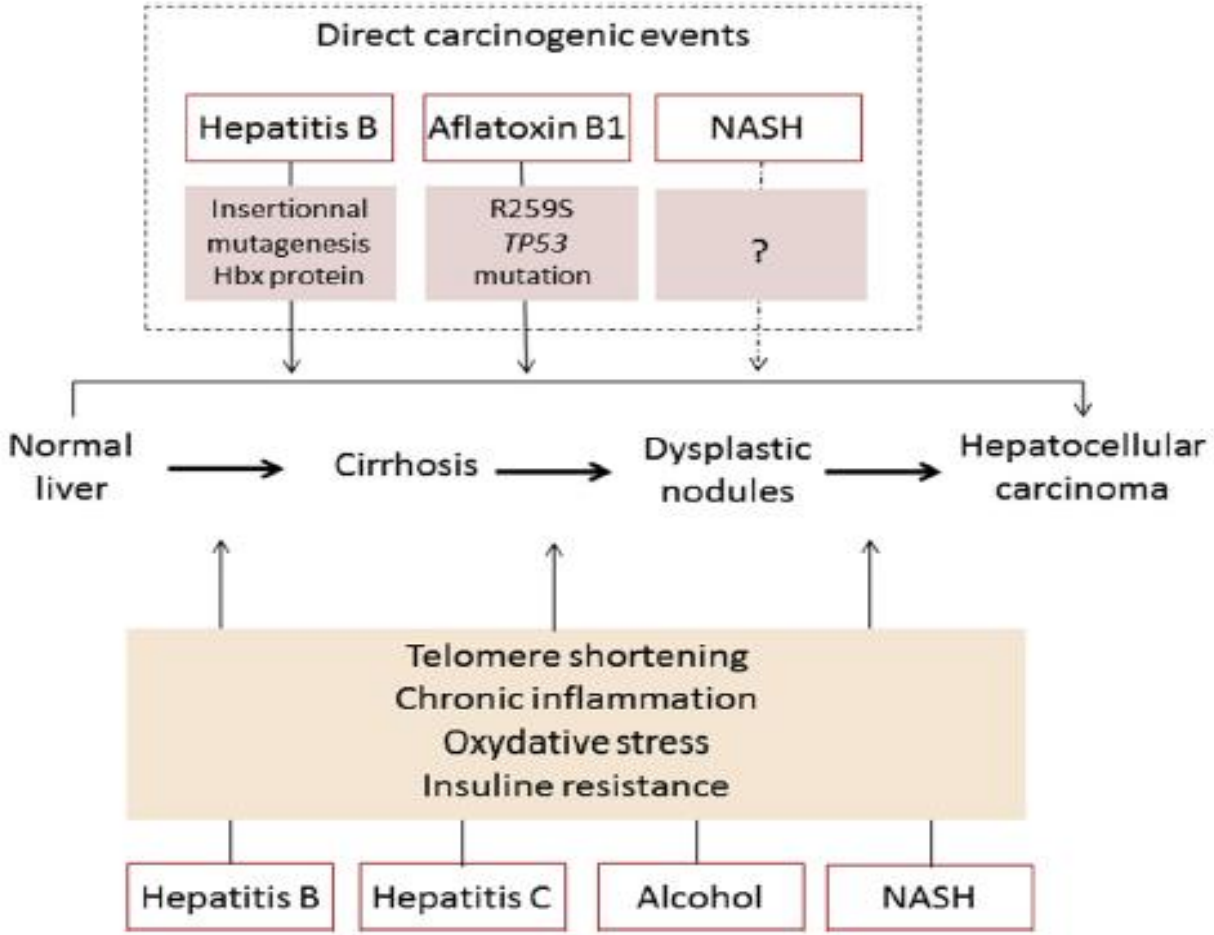


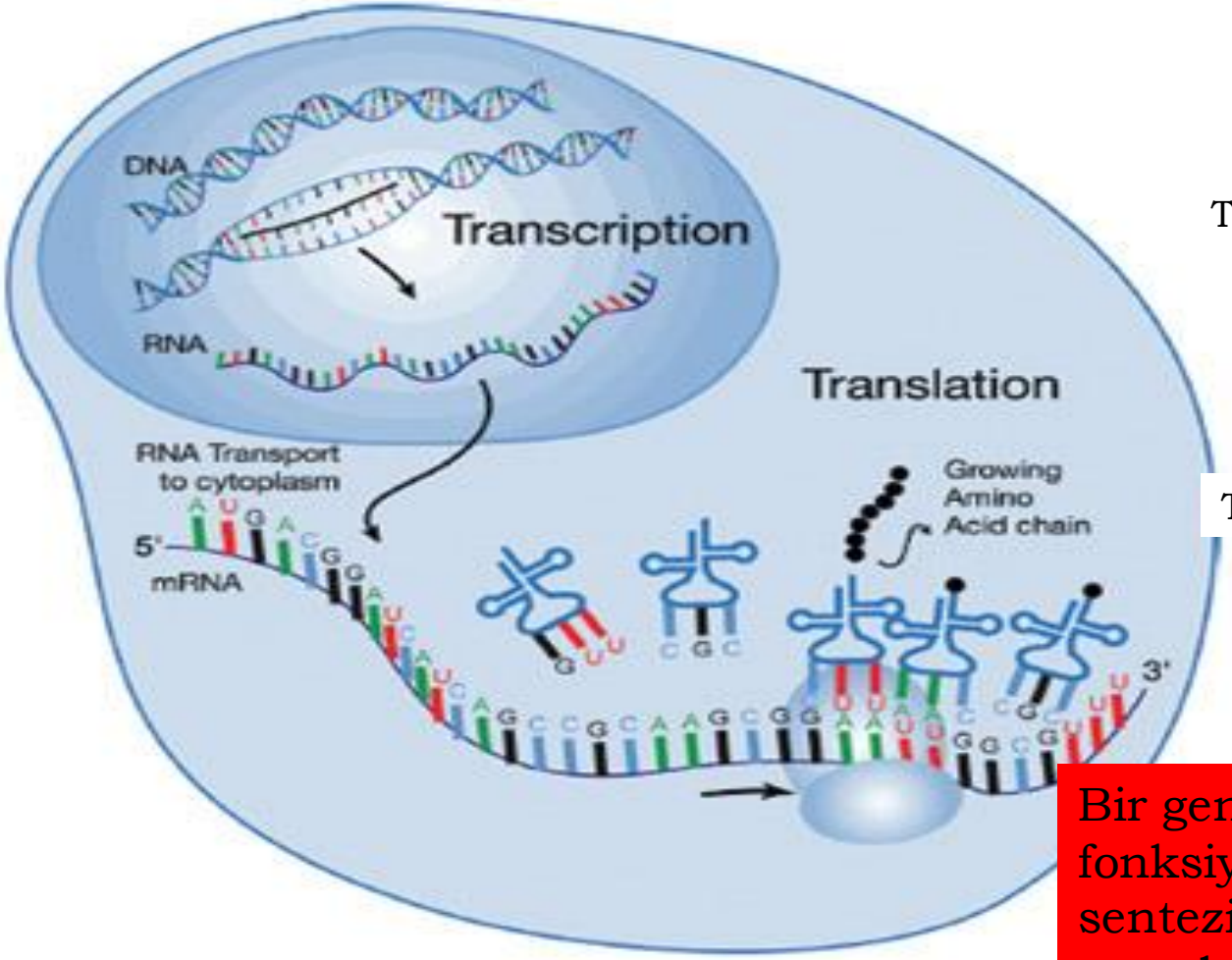
Fig. 1. The multistep process of liver carcinogenesis and the role of etiologies.

Moleküler düzeyi hatırlayalım

http://www.realmagick.com/molecular/

Moleküler Biyolojinin Santral Dogması

Biyolojik sistemlerde genetik bilginin akışı



DNA

Transkripsiyon= Kopyalama

↓

RNA

Translasyon= Proteine çeviri

↓

Protein

Bir genden gelen bilginin fonksiyonel bir gen ürününün sentezinde kullanıldığı süreç: gen ekspresyonu

http://www.tokresource.org/tok_classes/biobiobio/biomenu/transcription_translation/
http://cerch.org/research-programs/chamacos/chamacos-epigenetics/

Mikro RNA (Mi-RNA, MiR)

[Cancer Biology & Therapy 8:18, 1683-1690; 15 September 2009]; ©2009 Landes Bioscience

Review: Focus on the Liver

New kids on the block

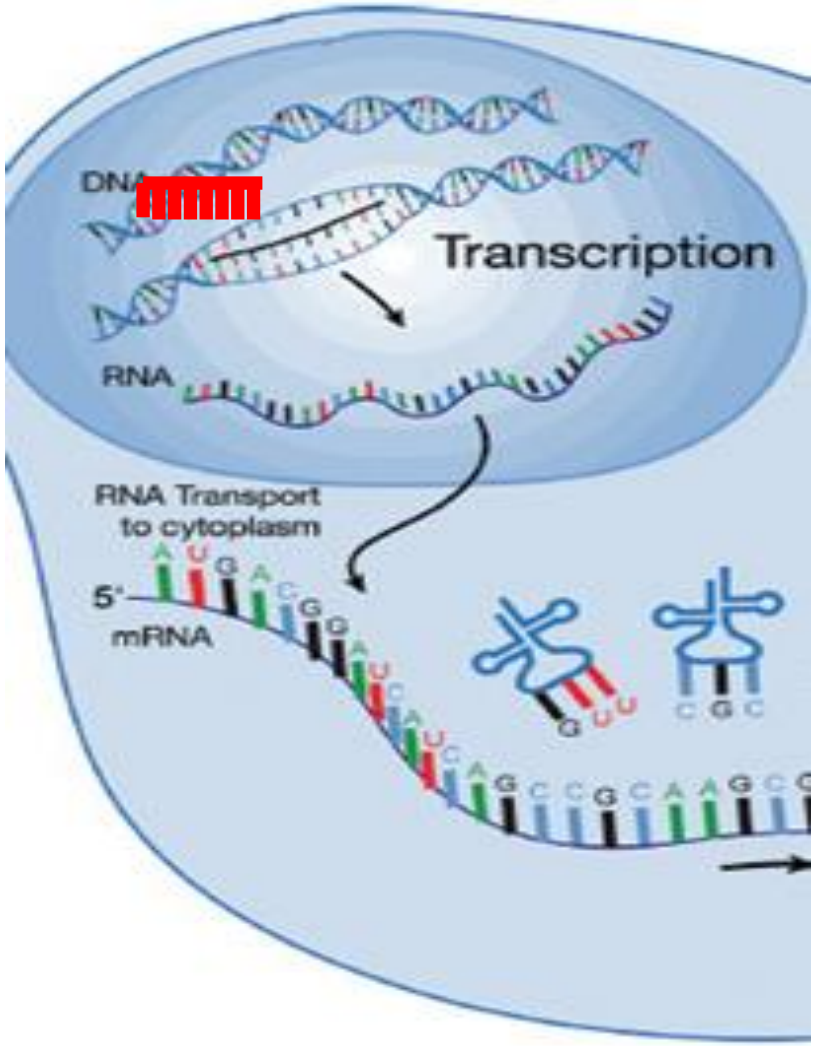
Diagnostic and prognostic microRNAs in hepatocellular carcinoma

Junfang Ji and Xin Wei Wang*

Liver Carcinogenesis Section; Laboratory of Human Carcinogenesis; Center for Cancer Research; National Cancer Institute; Bethesda, MD USA

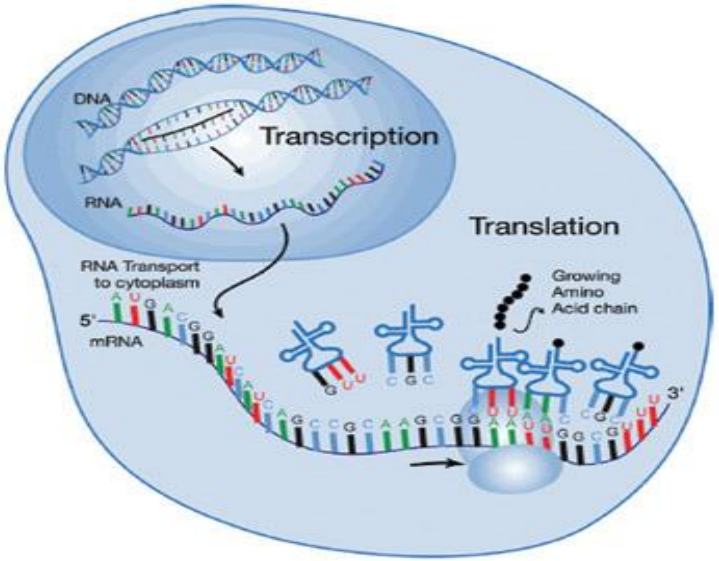
Mikro RNA (Mi-RNA, MiR)

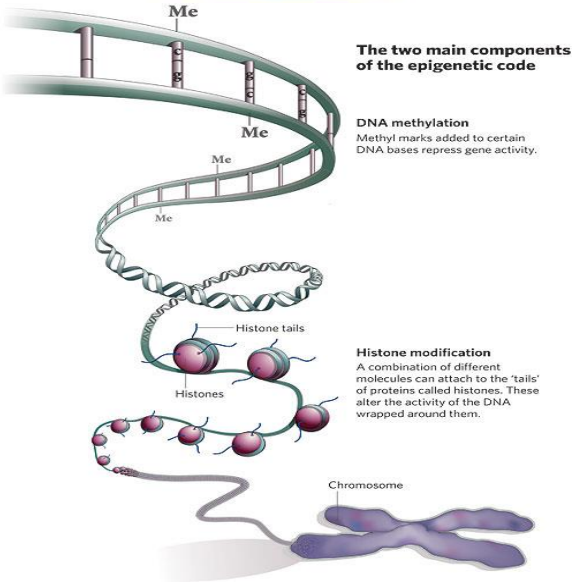
- Küçük, kodlama yapmayan RNA molekülü
- DNA tarafından kodlanır, mRNA'ya bağlanır
- Gen ifadesinin transkripsiyon sırasında ve sonrasında düzenlenmesinde görev alırlar (mRNA stabilitesi ve translasyonu kontrol ederler)
- SONUÇ: genin susturulması



Prolifere olan hücrelerde moleküler değişiklikler

- Genom düzeyinde
- Transkripsiyon düzeyinde

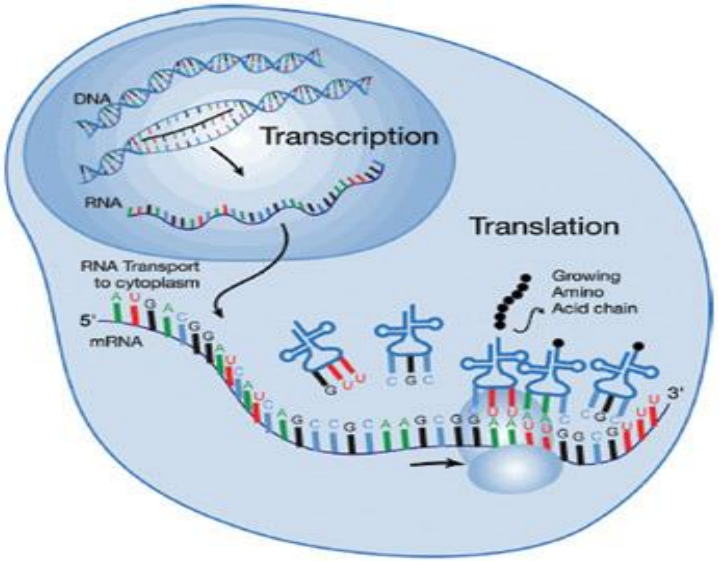


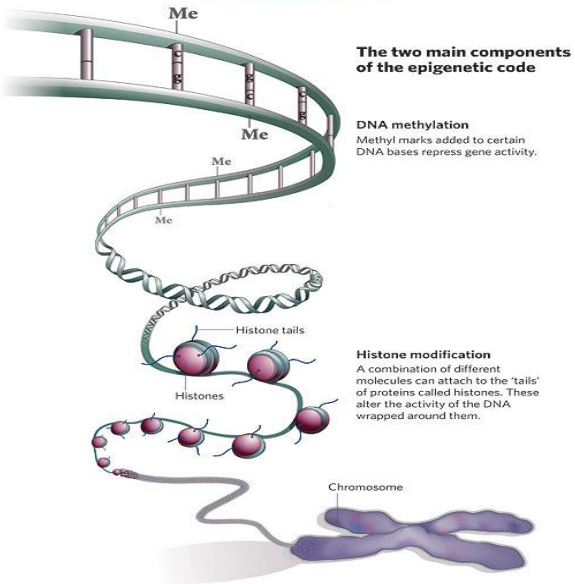


http://www.tokresource.org/tok_classes/biobiobio/biomenu/transcription_translation/
http://cerch.org/research-programs/chamacos/chamacos-epigenetics/

Prolifere olan hücrelerde moleküler değişiklikler

- **Genom düzeyinde**
  - **Kromozom instabilitesi**: Replikasyon, rekombinasyon, DNA tamiri, kromozom ayrılması sırasında veya hücre döngüsü kontrol noktalarında meydana gelen hatalara bağlı olarak kromozomların yeni hücrelerde eşit dağılmaması
  - **Mikrosatellit instabilitesi** : genom içinde dağılmış tekrar eden kısa DNA baz segmentleri olan mikrosatellitlerin delesyonu veya insersiyonu sonucunda segment uzunluğunun değişmesi
  - **MiRNA**

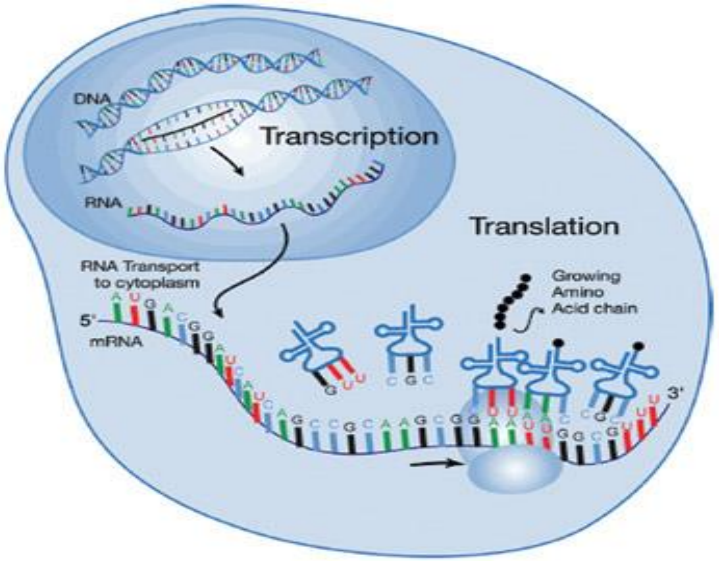


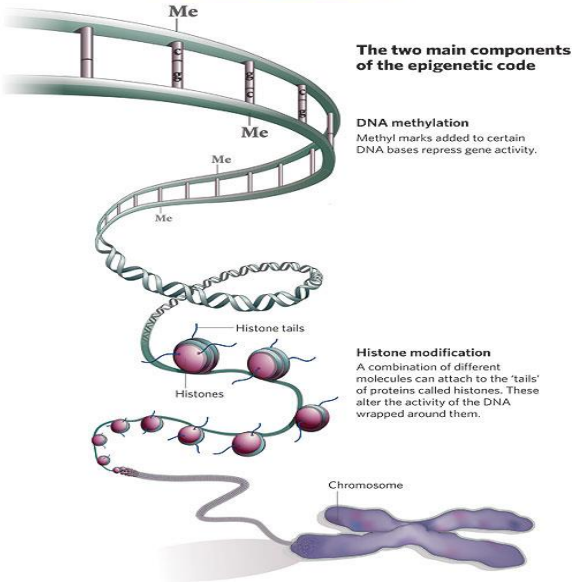


http://www.tokresource.org/tok_classes/biobiobio/biomenu/transcription_translation/
http://cerch.org/research-programs/chamacos/chamacos-epigenetics/

Prolifere olan hücrelerde moleküler değişiklikler

- **Transkripsiyon düzeyinde**
- Yapısal gen mutasyonları
- Epigenetik değişiklikler



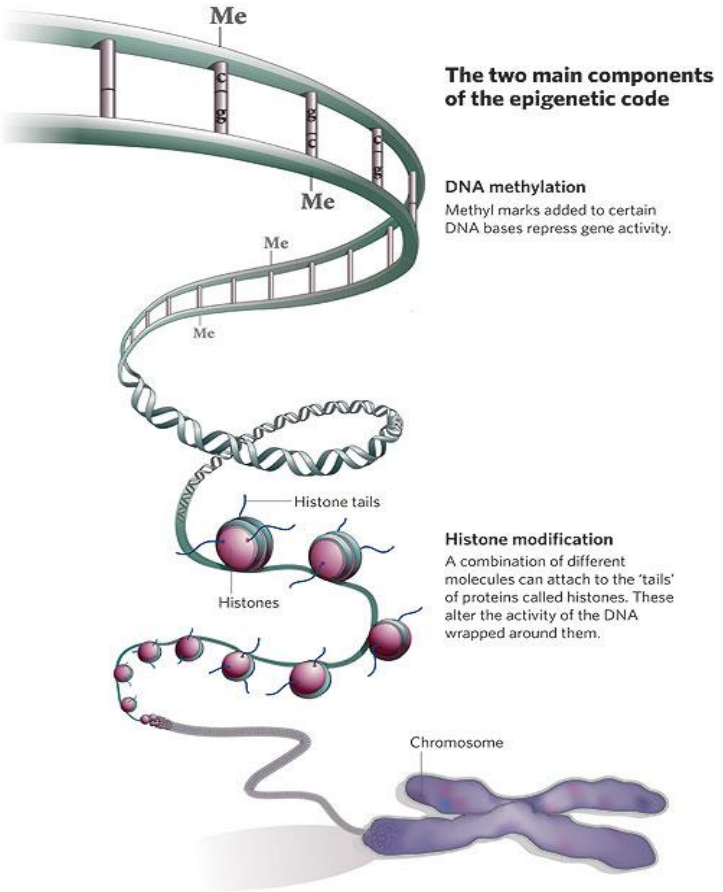


http://www.tokresource.org/tok_classes/biobiobio/biomenu/transcription_translation/
http://cerch.org/research-programs/chamacos/chamacos-epigenetics/

Epigenetik: «above» genetics, genetik dışı

- Genin DNA dizisinde değişiklik olmadan ekspresyonunda ortaya çıkan, miras bırakılabilen değişiklikler

- Genotipte değişiklik olmadan fenotipte değişiklik olması

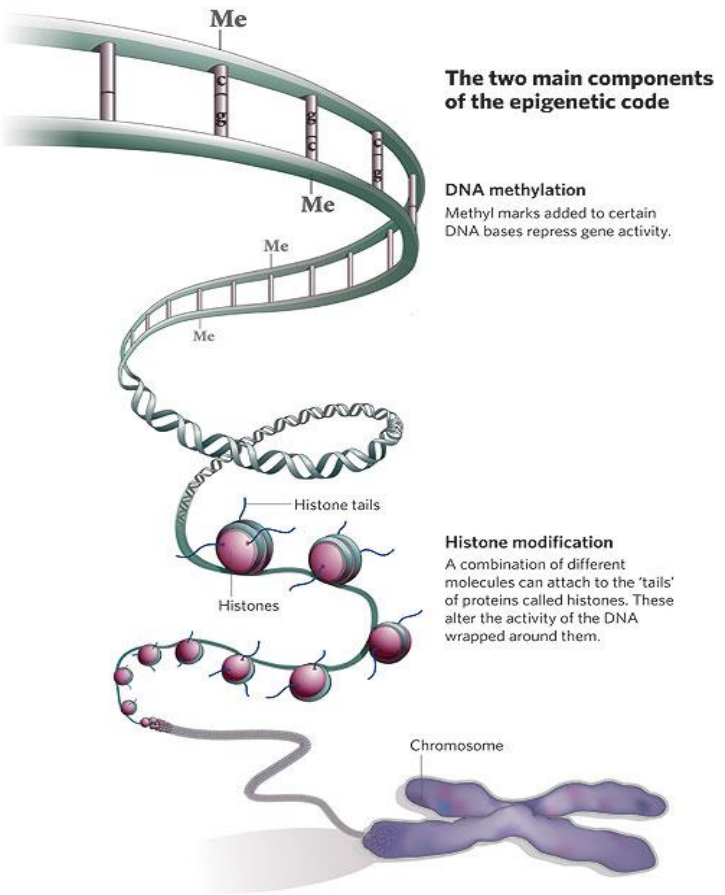


http://www.tokresource.org/tok_classes/biobiobio/biomenu/transcription_translation/
http://cerch.org/research-programs/chamacos/chamacos-epigenetics/

Epigenetik değişiklikler

- Düzenleyici modifikasyonlardan oluşur

- Bilinen en az üç sistem epigenetik değişiklik yapmaktadır:
- *DNA modifikasyonu*
  - DNA metilasyonu
- *Kromozom modifikasyonu*
  - histonların modifikasyonu
- *Kodlama yapmayan (non-coding) RNA (ncRNA) ile birlikte olan gen susturulması*

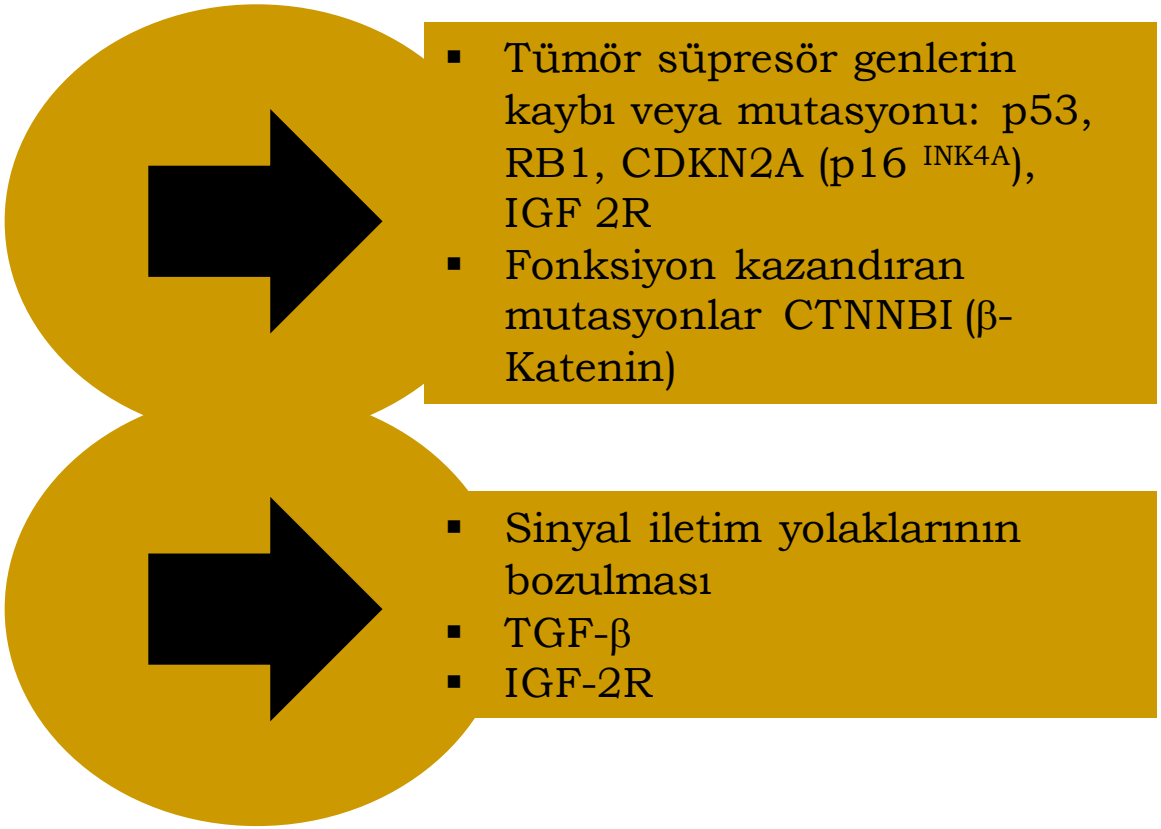


http://www.tokresource.org/tok_classes/biobiobio/biomenu/transcription_translation/
http://cerch.org/research-programs/chamacos/chamacos-epigenetics/

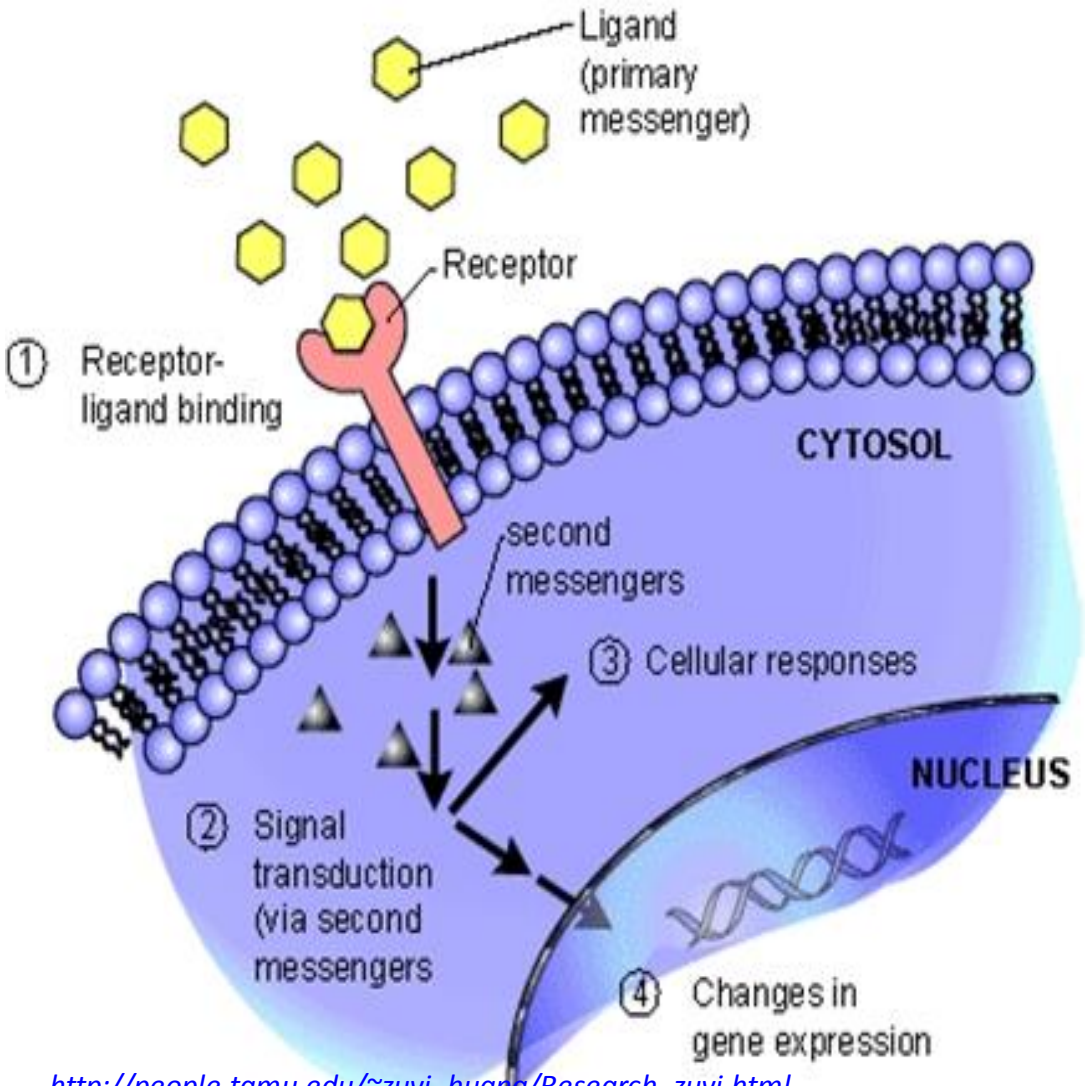
Hepatokarsinogenezde hücrelerde biriken genetik değişiklikler

- **Genom düzeyinde**
  - Kromozom instabilitesi
  - Delesyon
  - Kazanım
  - Mikrosatellit instabilitesi

- **Transkripsiyon düzeyinde**
  - Yapısal gen mutasyonları
  - Epigenetik değişiklikler



Sinyal iletimi yolağı

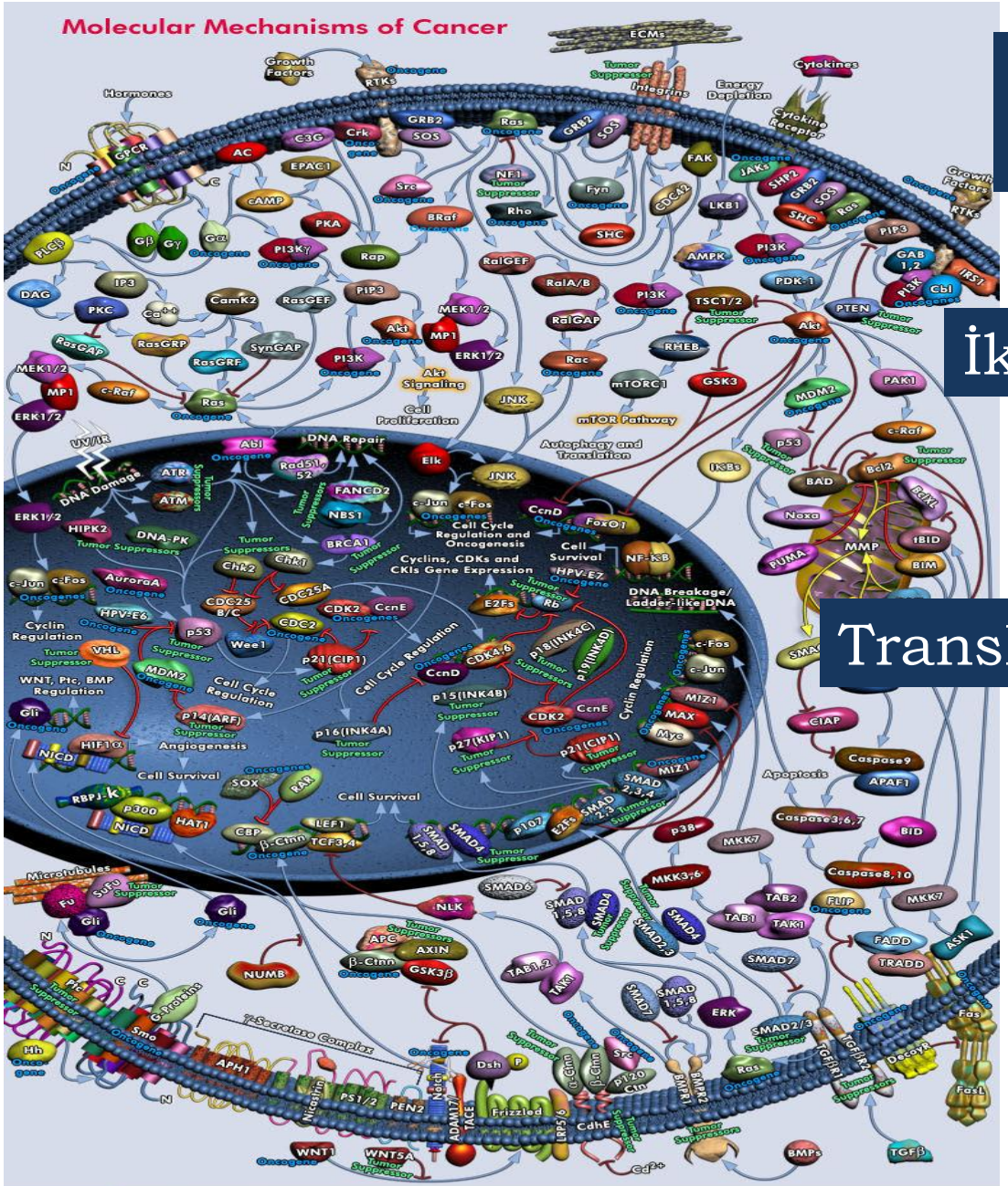


http://people.tamu.edu/~zuyi_huang/Research_zuyi.html

Birinci mesajcı ve Membran reseptörleri

İkincil mesajcılar

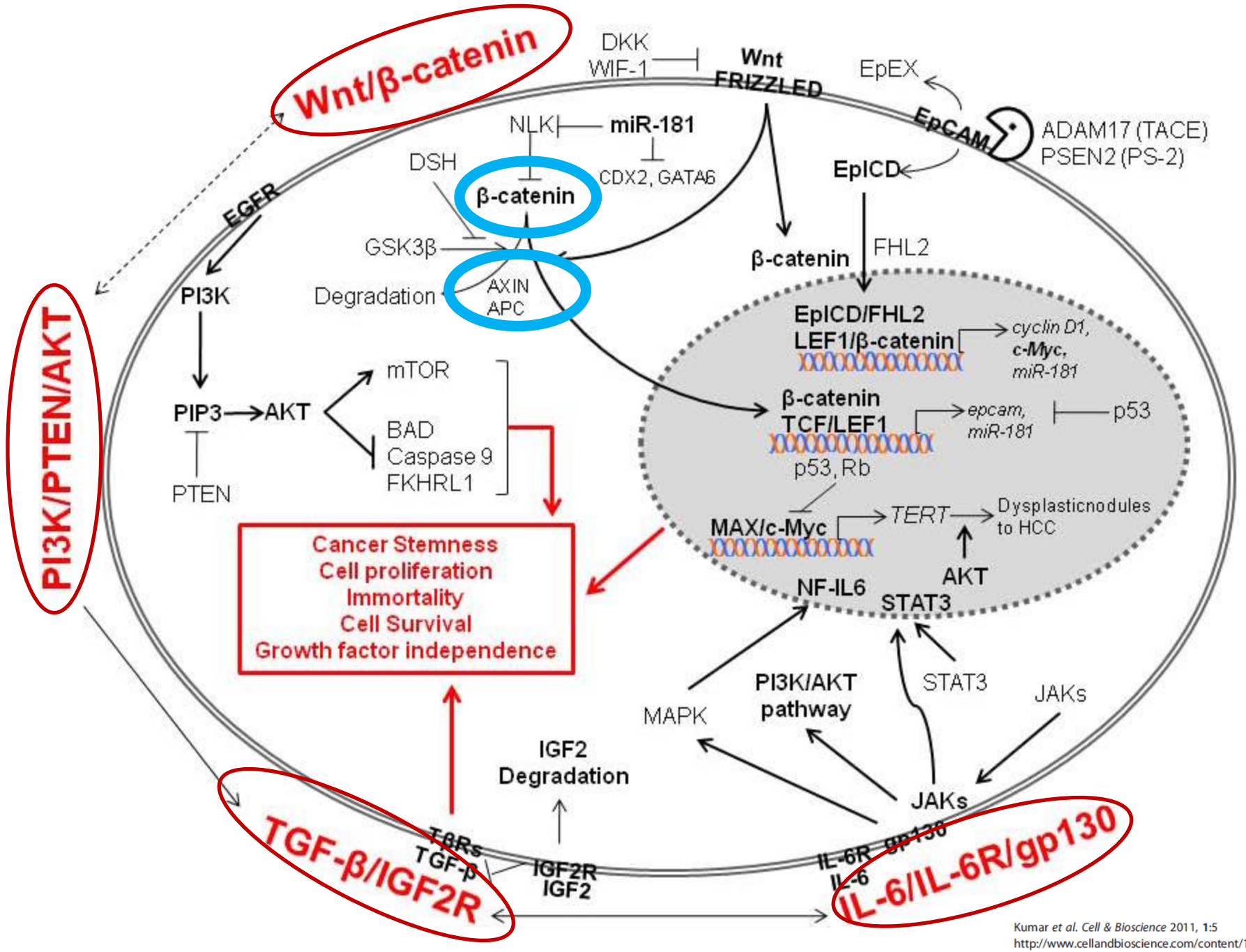
Transkripsiyon faktörleri



Birinci mesajcı ve Membran reseptörleri

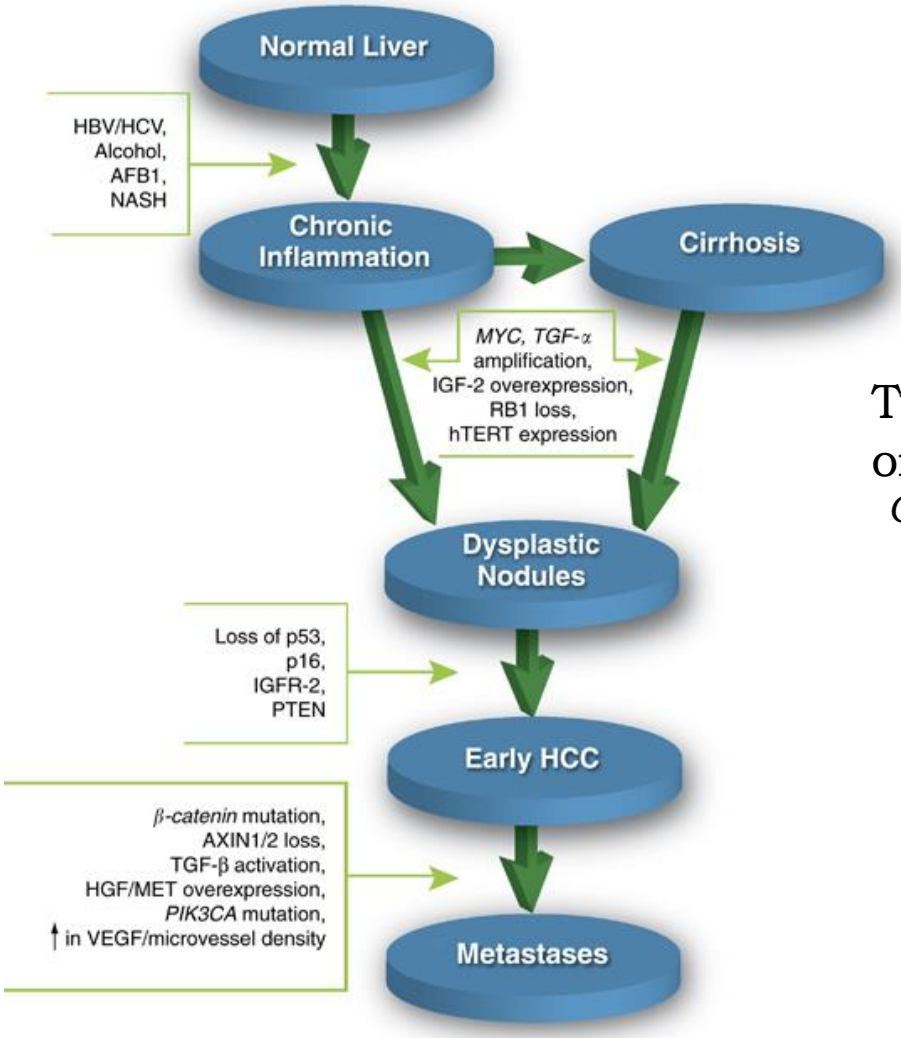
İkincil mesajcılar

Transkripsiyon faktörleri



Kumar *et al. Cell & Bioscience* 2011, **1**:5
http://www.cellandbioscience.com/content/1/1/5

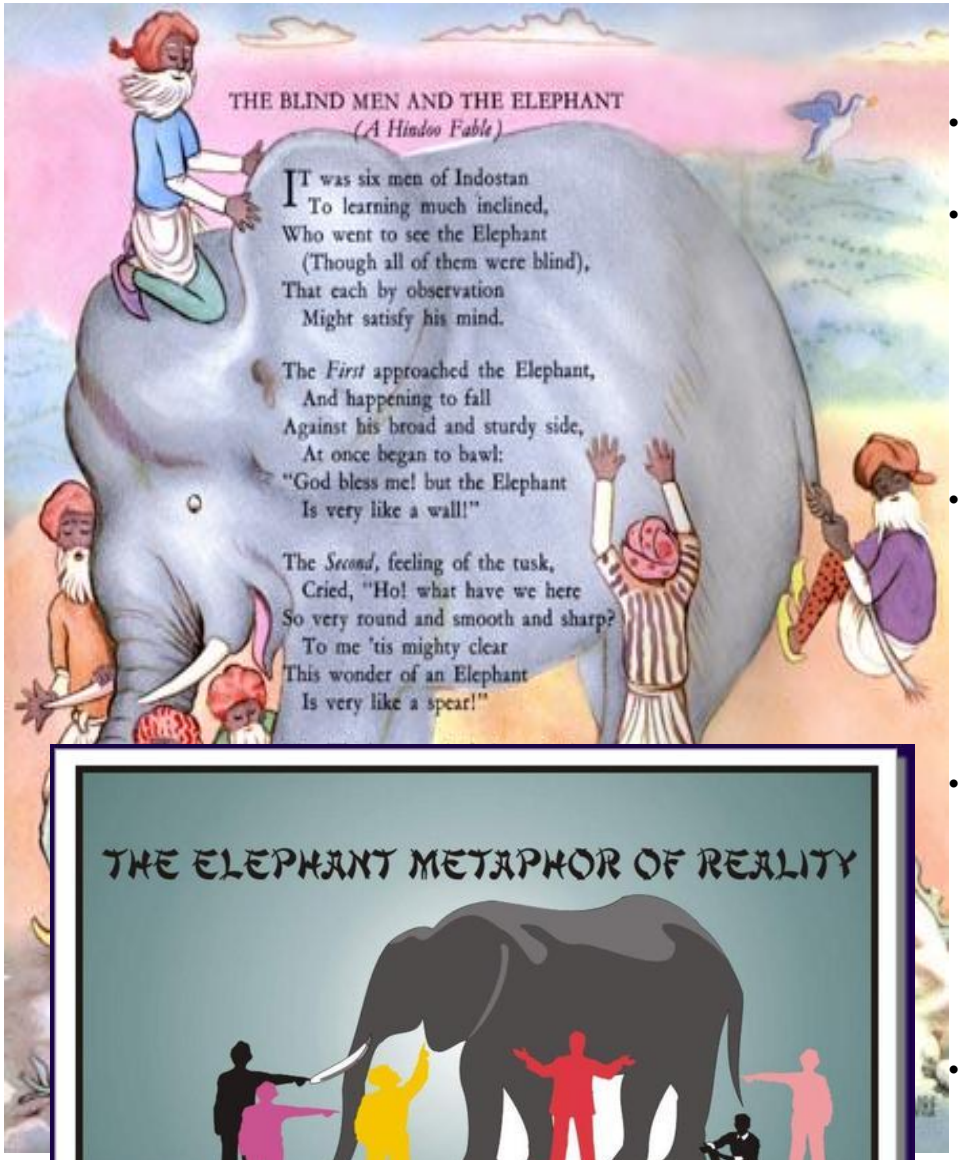
Hepatokarsinogenezde ana yolaklar



Tümör başına ortalama 66 mutasyon

Clearly SP, Hepatology 2013

Whittaker s, ve ark., Oncogene (2010) 29, 4989–5005



- **The Blind Men and the Elephant**

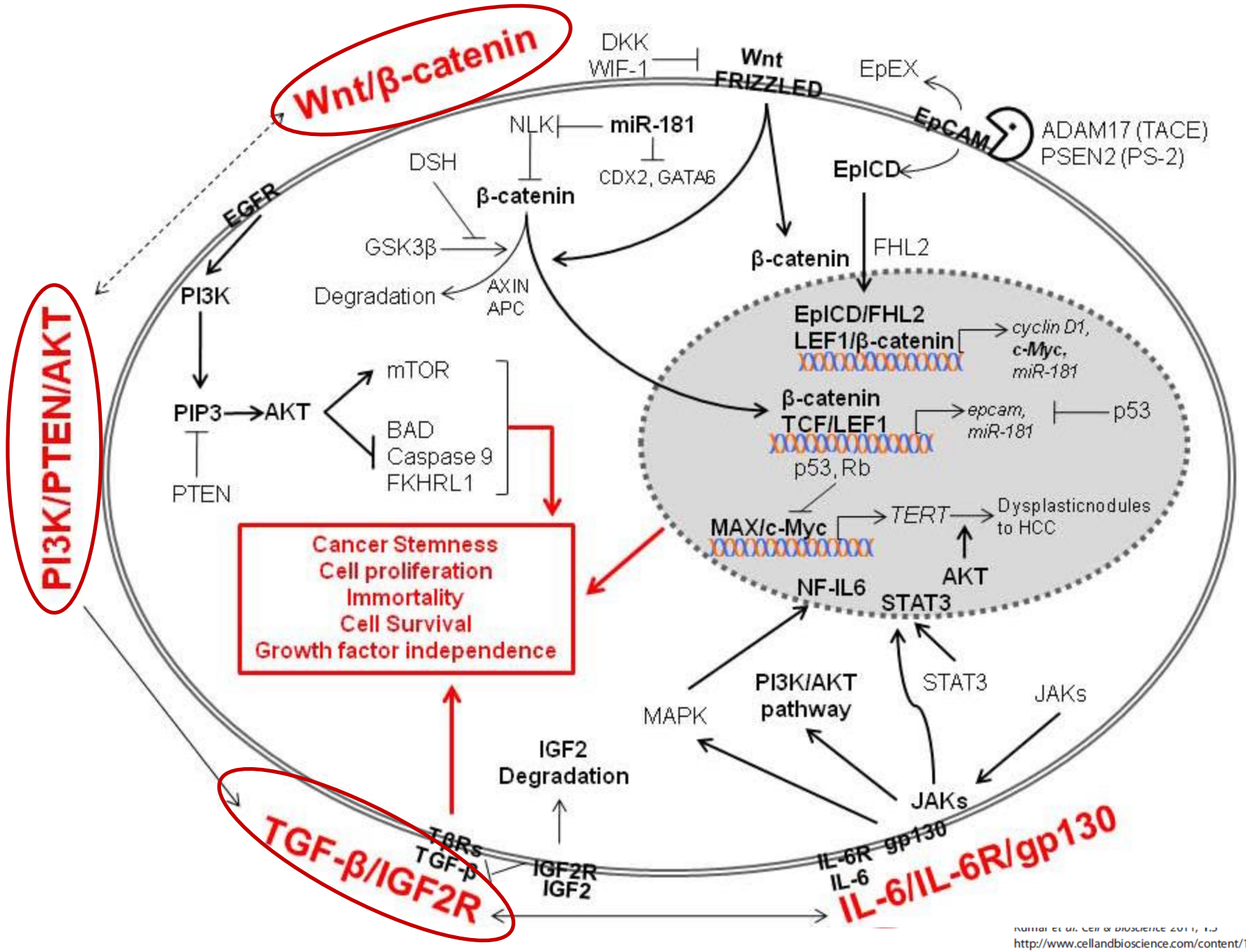
- It was six men of Hindustan
  To learning much inclined,
  Who went to see the Elephant
  (Though all of them were blind),
  That each by observation
  Might satisfy his mind

- The *First* approached the Elephant,
  And happening to fall
  Against his broad and sturdy side,
  At once began to bawl:
  "God bless me! but the Elephant
  Is very like a wall!«

- The *Second*, feeling of the tusk,
  Cried: "Ho!-what have we here
  So very round and smooth and sharp?
  To me't is mighty clear
  This wonder of an Elephant
  Is very like a spear!«

- The *Third* approached the animal,
  And happening to take
  The squirming trunk within his hands,
  Thus boldly up and spake:
  "I see," quoth he, "the Elephant
  Is very like a snake!«.....

John Godfrey Saxe (1816–1887).


Wnt/β-catenin
DKK
WIF-1
Wnt
FRIZZLED
EpEX
EpCAM
ADAM17 (TACE)
PSEN2 (PS-2)
EpICD
NLK
miR-181
CDX2, GATA6
DSH
β-catenin
EGFR
GSK3β
Degradation
AXIN
APC
β-catenin
FHL2
PI3K
PI3K/PTEN/AKT
EpICD/FHL2
LEF1/β-catenin
cyclin D1,
c-Myc,
miR-181
PIP3
AKT
mTOR
BAD
Caspase 9
FKHRL1
PTEN
β-catenin
TCF/LEF1
epcam,
miR-181
p53
p53, Rb
MAX/c-Myc
TERT
Dysplasticnodules
to HCC
AKT
NF-IL6
STAT3
Cancer Stemness
Cell proliferation
Immortality
Cell Survival
Growth factor independence
MAPK
PI3K/AKT
pathway
STAT3
JAKs
IGF2
Degradation
JAKs
TGF-β/IGF2R
TβRs
TGF-β
IGF2R
IGF2
IL-6R
gp130
IL-6
IL-6/IL-6R/gp130

Hepatosellüler karsinomun moleküler sınıflaması

Neden moleküler sınıflama?

- Histolojik olarak uniform, moleküler düzeyde heterojen bir tümör
- Histolojik tiplendirme ve derecelendirme yeterince bilgi vermiyor
- Moleküler sınıflama farklı HSK alt tiplerini ortaya çıkartmıştır

Transcriptome Classification of HCC Is Related to Gene Alterations and to New Therapeutic Targets

Sandrine Boyault,[1,2*] David S. Rickman,[3*] Aurélien de Reyniès,[3*] Charles Balabaud,[4,5] Sandra Rebouissou,[1,2] Emmanuelle Jeannot,[1,2] Aurélie Hérault,[1,2] Jean Saric, [6], Jacques Belghiti, [7,8] Dominique Franco, [8,9] Paulette Bioulac-Sage, [4,9] Pierre Laurent-Puig,[10] and Jessica Zucman-Rossi[1,2]

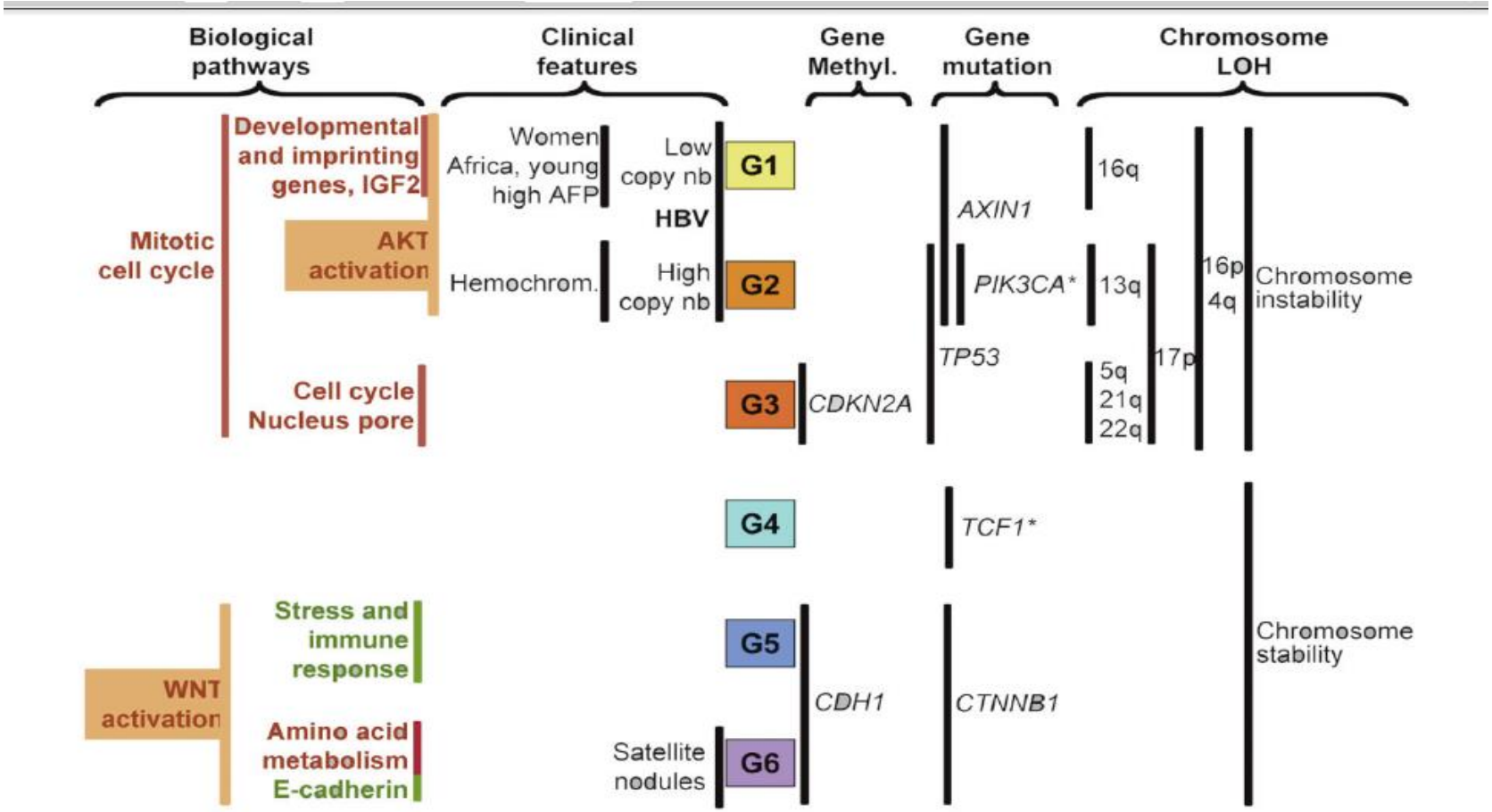
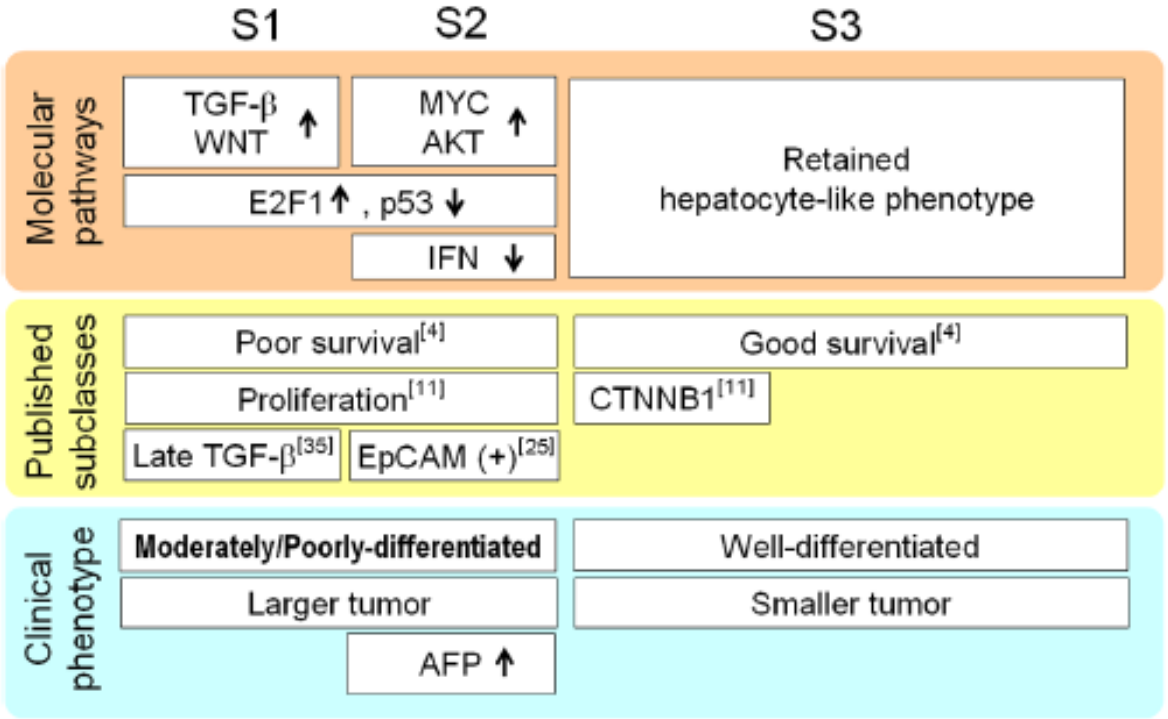


Fig. 6. Schematization of the different HCC subgroups defined by transcriptome analysis with their related clinical and genetic pathways. G1 to G6 are the subgroups of HCCs defined by transcriptome analysis. Vertical lines indicate significantly associated features (see Table 1, Fig. 3, and supplementary Table 5). Red and green primarily indicate over- and underexpressed genes, respectively, in that particular functional category. LOH, loss of heterozygosity; Hemochrom, hemochromatosis; AFP, alpha-fetoprotein; HBV, hepatitis B virus; *rare feature.

Published in final edited form as:
Cancer Res. 2009 September 15; 69(18): 7385–7392. doi:10.1158/0008-5472.CAN-09-1089.

Integrative Transcriptome Analysis Reveals Common Molecular Subclasses of Human Hepatocellular Carcinoma

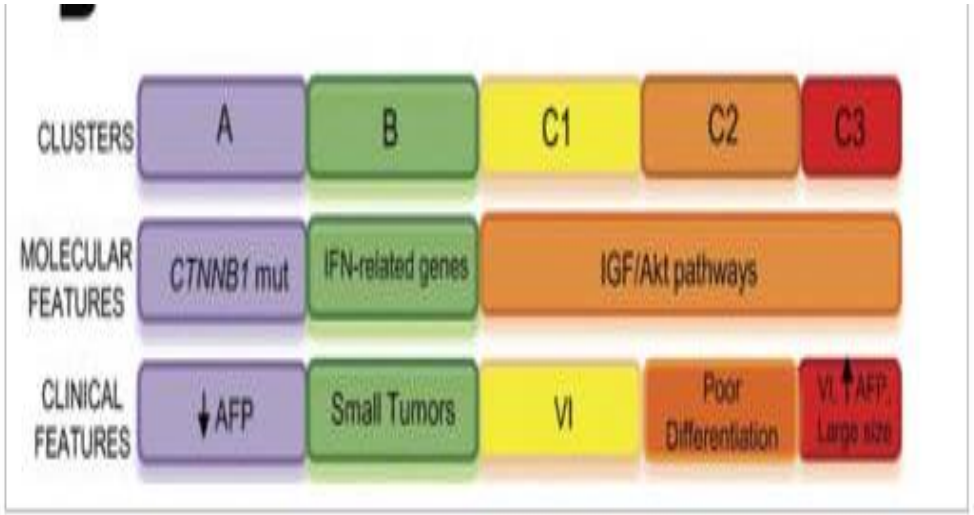
Yujin Hoshida[1,2], **Sebastian M.B. Nijman**[1,3], **Masahiro Kobayashi**[4], **Jennifer A. Chan**[1,5], **Jean-Philippe Brunet**[1], **Derek Y. Chiang**[1], **Augusto Villanueva**[6], **Philippa Newell**[7], **Kenji Ikeda**[4], **Masaji Hashimoto**[4], **Goro Watanabe**[4], **Stacey Gabriel**[1], **Scott L. Friedman**[7], **Hiromitsu Kumada**[4], **Josep M. Llovet**[6,7,8], and **Todd R. Golub**[1,2,9,10]



MicroRNA-Based Classification of Hepatocellular Carcinoma and Oncogenic Role of miR-517a

Sara Toffanin, ‡, Yujin Hoshida§, Anja Lachenmayer, ‖, Augusto Villanueva¶, Laia Cabellos, Beatriz Minguez, Radoslav Savic, Stephen C. Ward, Swan Thung, Derek Y. Chiang#, Clara Alsinet¶, Victoria Tovar¶, Sasan Roayaie, Myron Schwartz, Jordi Bruix¶, Samuel Waxman, Scott L. Friedman, Todd Golub§, , Vincenzo Mazzaferro‡, Josep M. Llovet, ¶, ‡‡, .

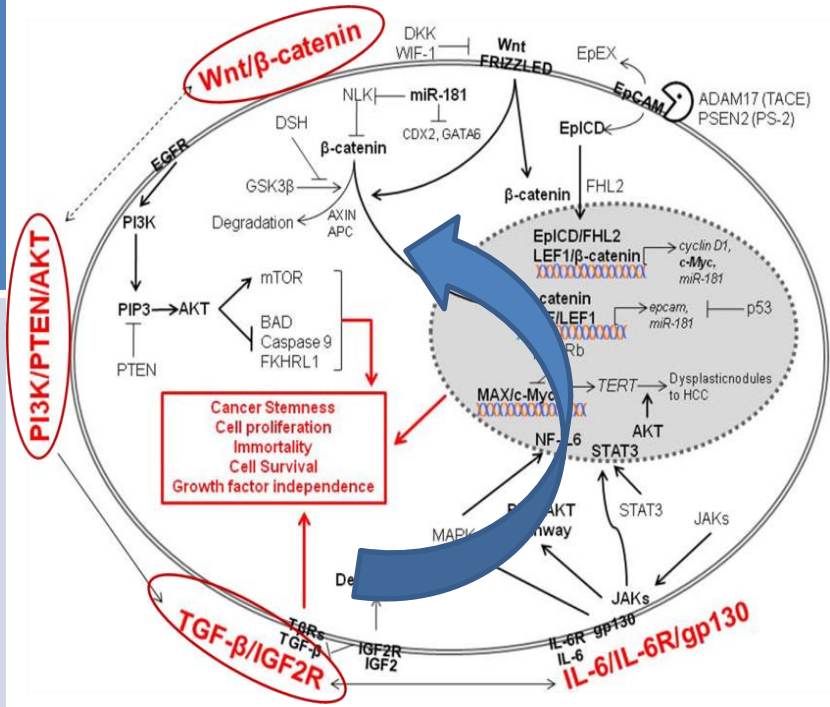
- We identified 3 main clusters of HCCs: the wingless-type MMTV integration site (32 of 89; 36%), interferon-related (29 of 89; 33%), and proliferation (28 of 89; 31%) subclasses. A subset of patients with tumors in the proliferation subclass (8 of 89; 9%) overexpressed a family of poorly characterized miRNAs from chr19q13.



Moleküler Grup 1 (S1)

Wnt/ β-katenin hedeflerinde aktivasyon
B-katenin mutasyonu yok
Aktivasyon TGF-β üzerinden

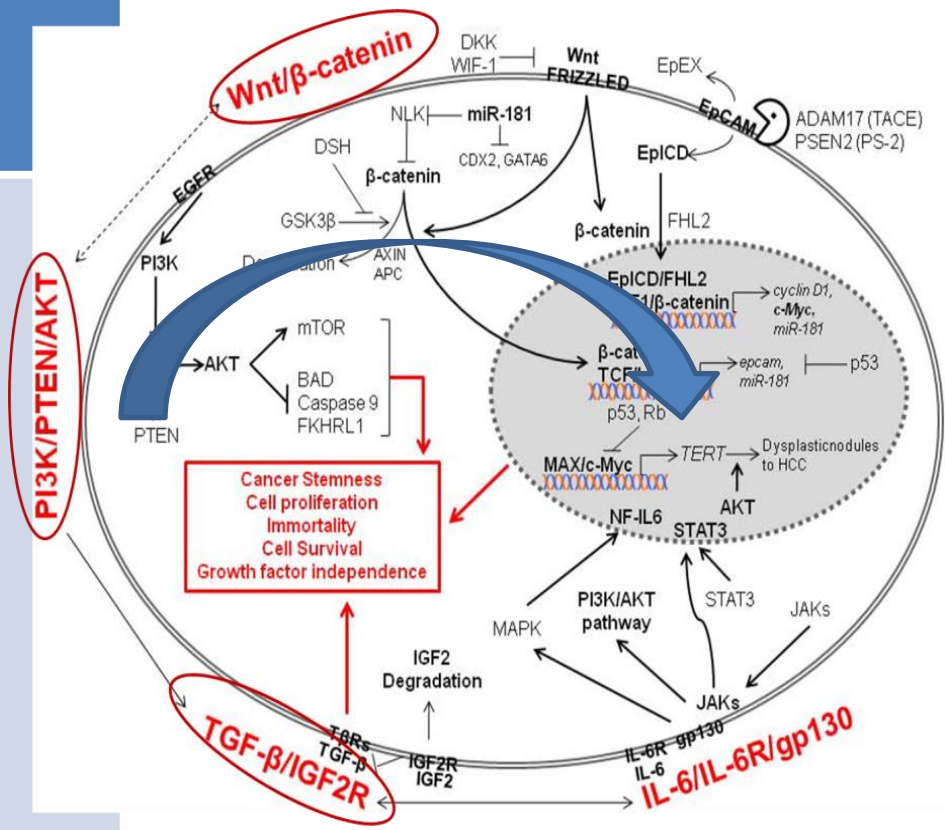
- Erken rekürrens
- Daha invaziv fenotip (vasküler invazyon, satellit)
- Nükleer p53 pozitifliği yüksek
- B-katenin sitoplazmada pozitif, KRT 19 (+)
- TGF-β ekspresyonu



Moleküler Grup 2 (S2)

PI3K /PTEN/Akt
Myc aktivasyonu

- IFN yolağı genlerinin baskılanması
- Kök hücre fenotipinin ortaya çıkışı (Tümörde EpCAM+)

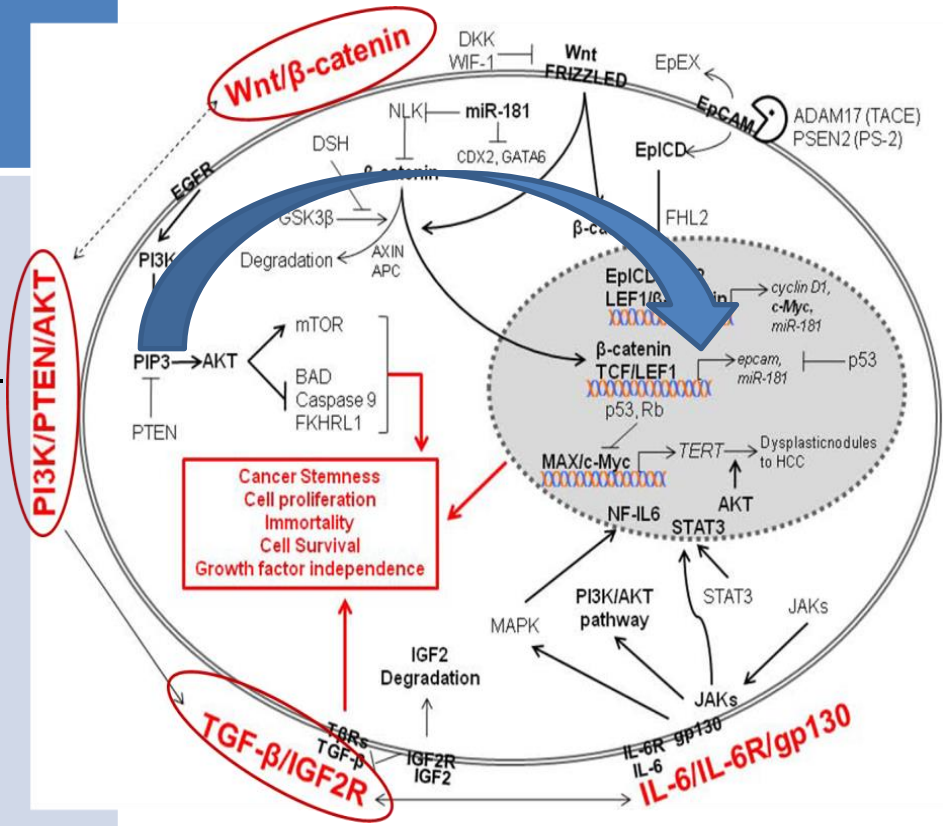


PI3K: Phosphoinositide 3-kinase
PTEN: Phosphatase and tensin homolog

Moleküler Grup 2 (S2)

PI3K /PTEN/Akt Myc aktivasyonu

- HCC'lerin %30-50'sinde aktif
- Myc/AKT aktivasyonu, p-AKT (+)
- Yüksek serum AFP
- Dokuda AFP ve GLY-3 ekspresyonu

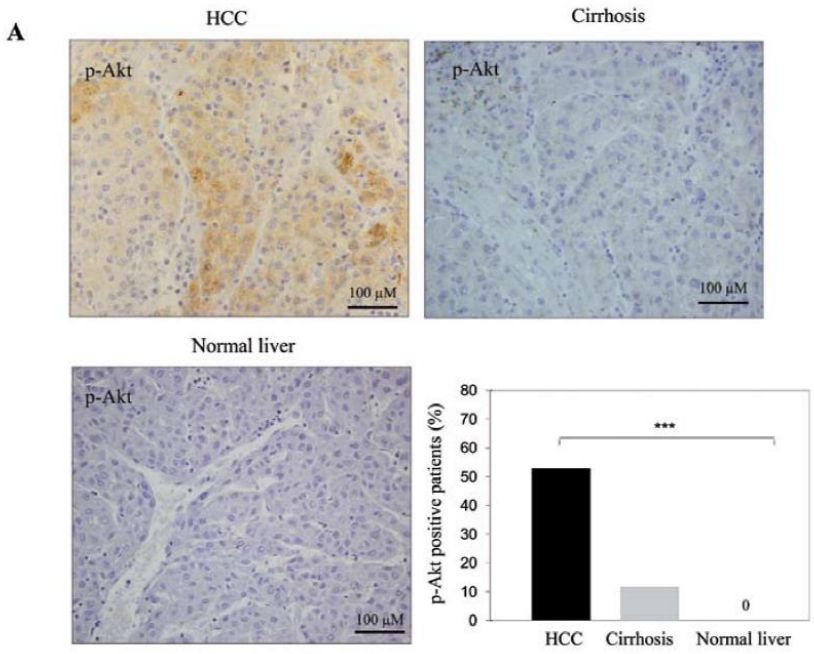


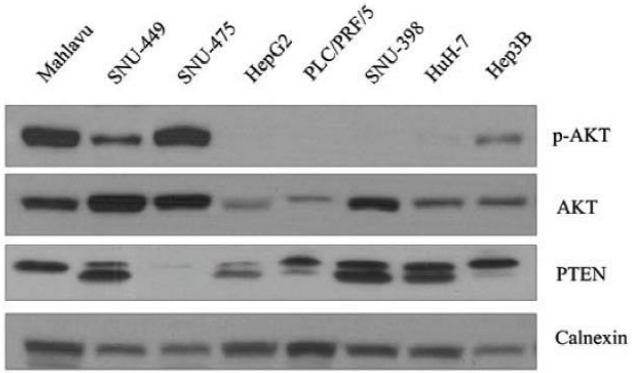
PI3K: Phosphoinositide 3-kinase
PTEN: Phosphatase and tensin homolog

Active form of AKT controls cell proliferation and response to apoptosis in hepatocellular carcinoma

IMGE KUNTER[1*], ESRA ERDAL[1*], DENIZ NART[2], FUNDA YILMAZ[2], SEDAT KARADEMIR[3], OZGUL SAGOL[4] and NESE ATABEY[1]

ONCOLOGY REPORTS 31: 573-580, 2014

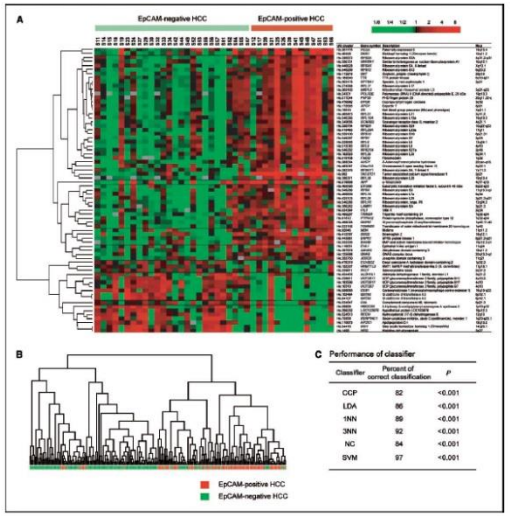




EpCAM and α-Fetoprotein Expression Defines Novel Prognostic Subtypes of Hepatocellular Carcinoma

Taro Yamashita,[1] Marshonna Forgues,[1] Wei Wang,[1] Jin Woo Kim,[1] Qinghai Ye,[4] Huliang Jia,[4] Anuradha Budhu,[1] Krista A. Zanetti,[1,3] Yidong Chen,[2] Lun-Xiu Qin,[4] Zhao-You Tang,[4] and Xin Wei Wang[1]

[1]Liver Carcinogenesis Section, Laboratory of Human Carcinogenesis, [2]Genetics Branch, Center for Cancer Research, and [3]Cancer Prevention Fellowship Program, Division of Cancer Prevention, National Cancer Institute, Bethesda, Maryland; and [4]Liver Cancer Institute and Zhongshan Hospital, Fudan University, Shanghai, China



- EpCAM (Epithelial cell Adhesion Molecule)
- Serum AFP
- İki farklı HSK alt tipi tanımlıyor

EpCAM (+)
Hepatik kök/progenitör hücre özellikleri

- AFP (+) → ▪İyi prognoz
- AFP (-) → ▪Kötü prognoz

EpCAM (-)
Matür hepatosit gen ekspresyon özellikleri

- AFP (+) → ▪Kötü prognoz
- AFP (-) → ▪Orta prognoz

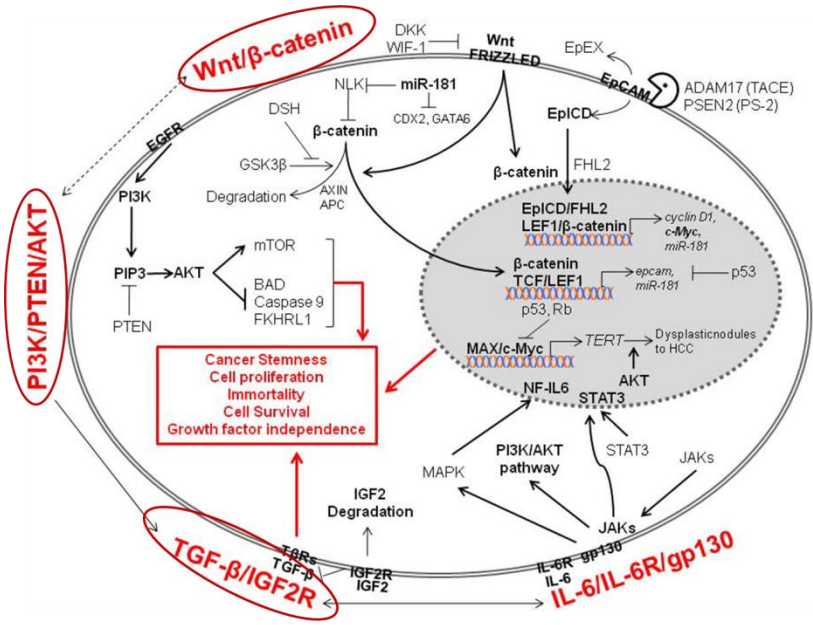
▪EpCAM (+) HSK:
- ▪Artmış Wnt yolağı aktivasyonu
- ▪Progenitör hücre belirleyicileri: CK19 (+), Ckit (+)

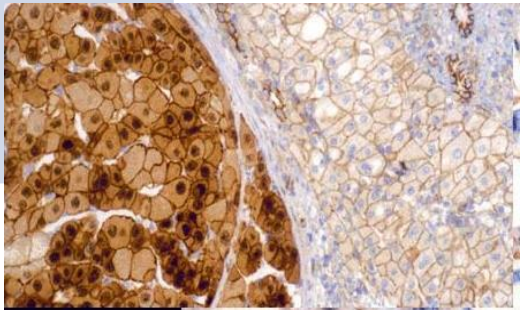
Cancer Res 2008; 68: (5). March 1, 2008

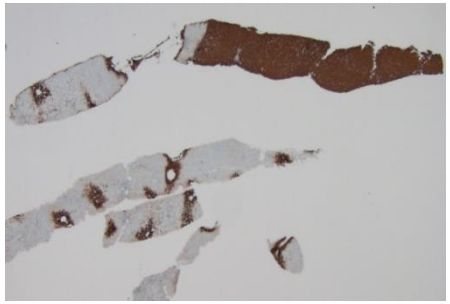
Moleküler Grup 3 (S2)

B-katenin mutasyonu
Matür hepatosit profili

- Daha iyi diferansiye ve daha küçük tümörler
- Prognoz iyi
- Nükleer p53 pozitifliği az
- B-katenin nükleer pozitif
- Glutamin sentetaz dağılımı diffüz (S1 tümörde (-)



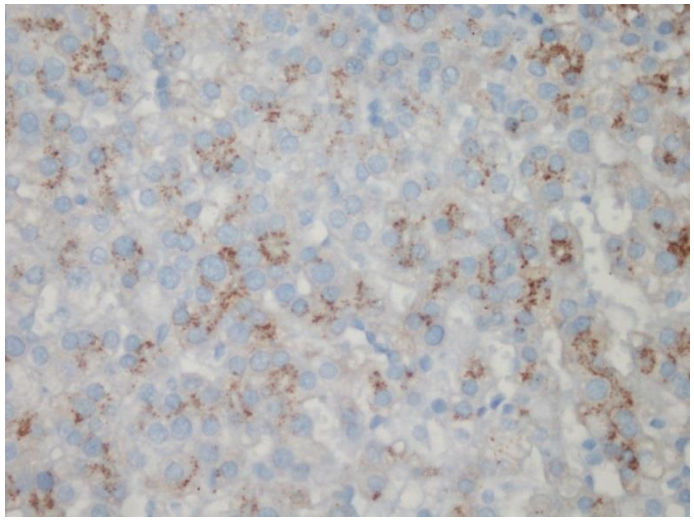




Moleküler çalışmaların Hepatosellüler karsinom tanısına katkıları

Moleküler çalışmaların Hepatosellüler karsinom tanısına katkıları

Yeni immünohistokimyasal belirleyicilerin tanımlanması



GLİPİKAN-3 (GYP-3)

- Hücre yüzeyi bağlantılı heparan sülfat proteoglikanların bir üyesi
- Onkofetal protein: fetal KC ve plasenta (+), erişkin KC (-)
- Hücre büyümesi, diferansiasyon ve migrasyonda rol alır

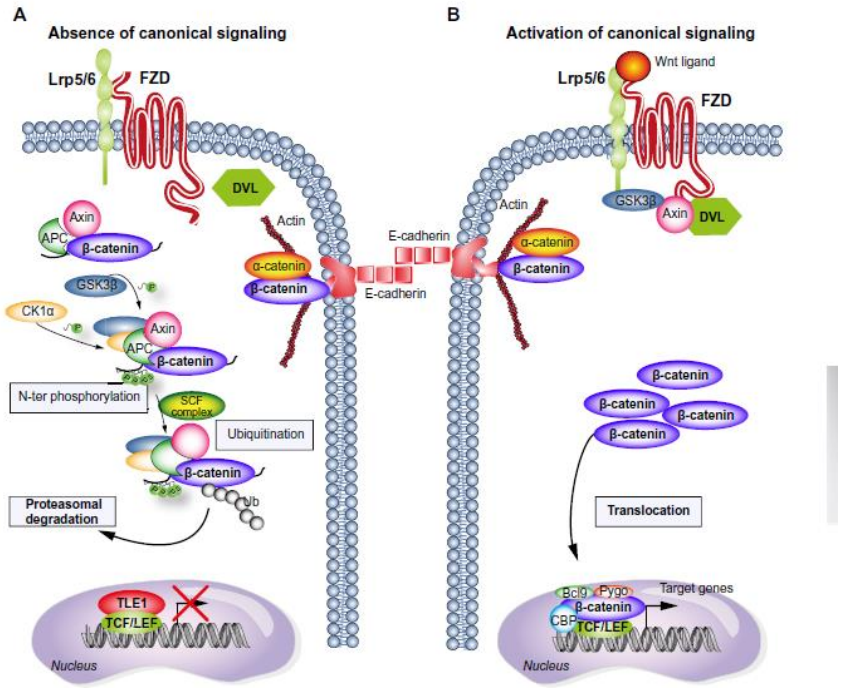
İyi Diferansiye	Orta Diferansiye	Kötü diferansiye
%50-62	%83	%86

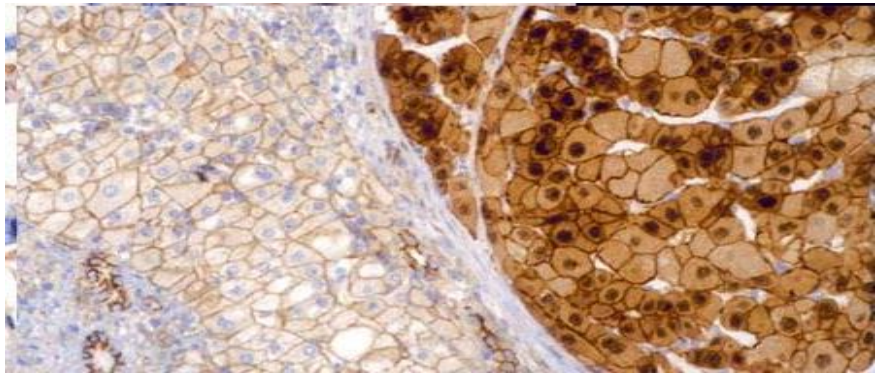
GLİPİKAN-3 (GYP-3)

- Nihon Rinsho. 2012 Dec;70(12):2136-41.
- **[The cancer specific antigen, glypican-3 (GPC3)-targeted immunotherapy].**
- [Article in Japanese]
- Sawada Y, Nakatsura T.
- **Source**
- Division of Cancer Immunotherapy, Research Center for Innovative Oncology, National Cancer Center Hospital East.
- **Abstract**
- The carcinoembryonic antigen glypican-3 (GPC3) is an ideal target of tumor antigen-specific immunotherapy against hepatocellular carcinoma (HCC), because it is overexpressed specifically in HCC. We have reported that a GPC3-derived peptide vaccination was well-tolerated, and immune responses and antitumor efficacy were noted in a phase I trial for HCC patients. We have begun a phase II study of the GPC3-derived peptide vaccine as an adjuvant therapy for HCC patients, and a pilot study of liver biopsies performed before and after GPC3 peptide vaccination for advanced HCC to determine whether tumor-infiltrating lymphocytes are indeed GPC3 peptide-specific CTLs. Furthermore, we are initiating clinical trials of a GPC3-derived peptide vaccine for patients with hepatoblastoma or ovarian clear cell carcinoma

Beta Katenin

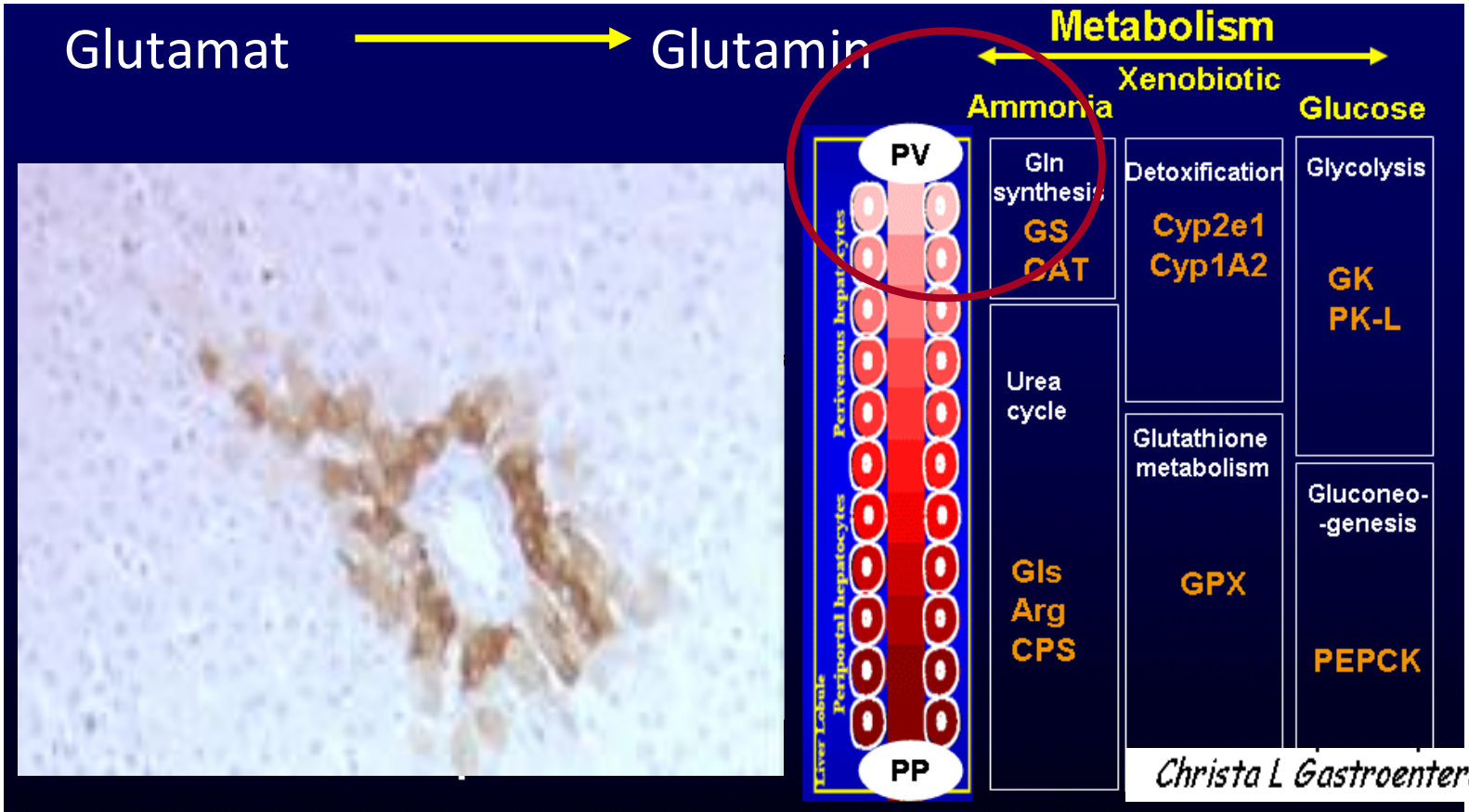
- Kodlayan gen: CTNNB1 geni
- Standard Wnt sinyal yolağında hücre içi sinyal ileticisi



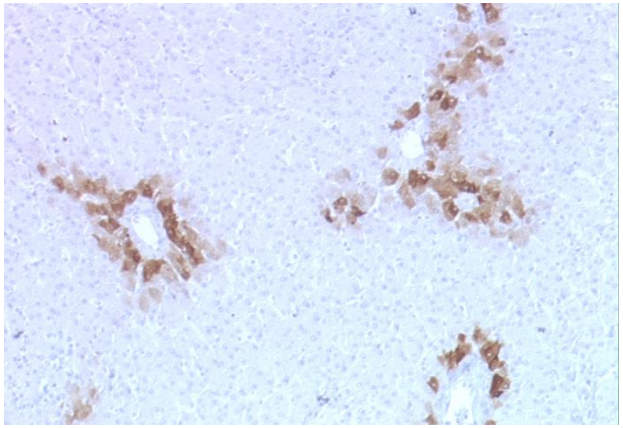


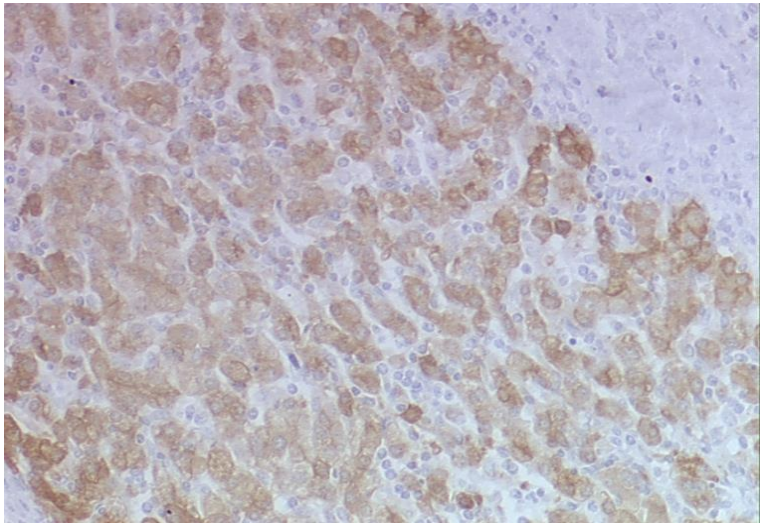
GLUTAMİN SENTETAZ (GS)

- Beta Katenin'in kodladığı genlerden biri
- KC'de glutamat ve amonyaktan glutamini dönüştürerek nitrojen metabolizmasında anahtar rol oynayan bir enzimdir
- N KC'de santral ven çevresindeki 2-3 hepatosit kalınlığındaki perivenüler bölgede eksprese olur.



GLUTAMİN SENTETAZ (GS)

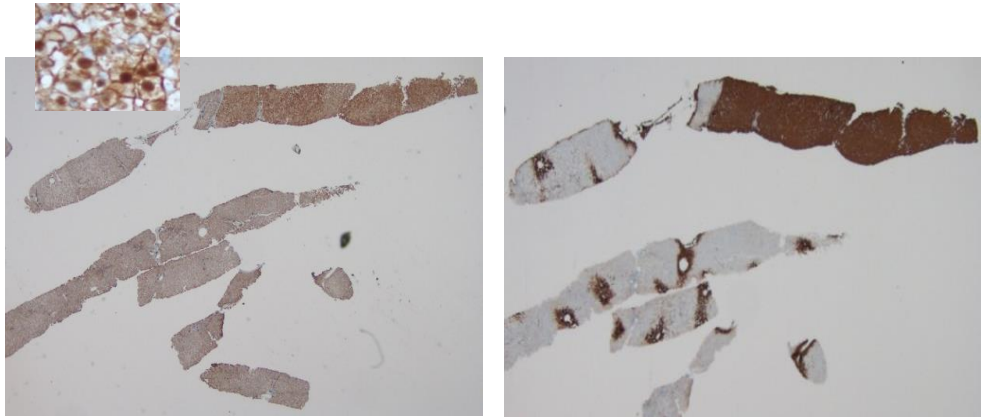




YDDN	eHCC	İyi Diferansiye	Orta Diferansiye	Kötü diferansiye
%10-15 (fokal)	%13-70 (fokal)	%56 Diffüz	%66 Diffüz	%66 Diffüz

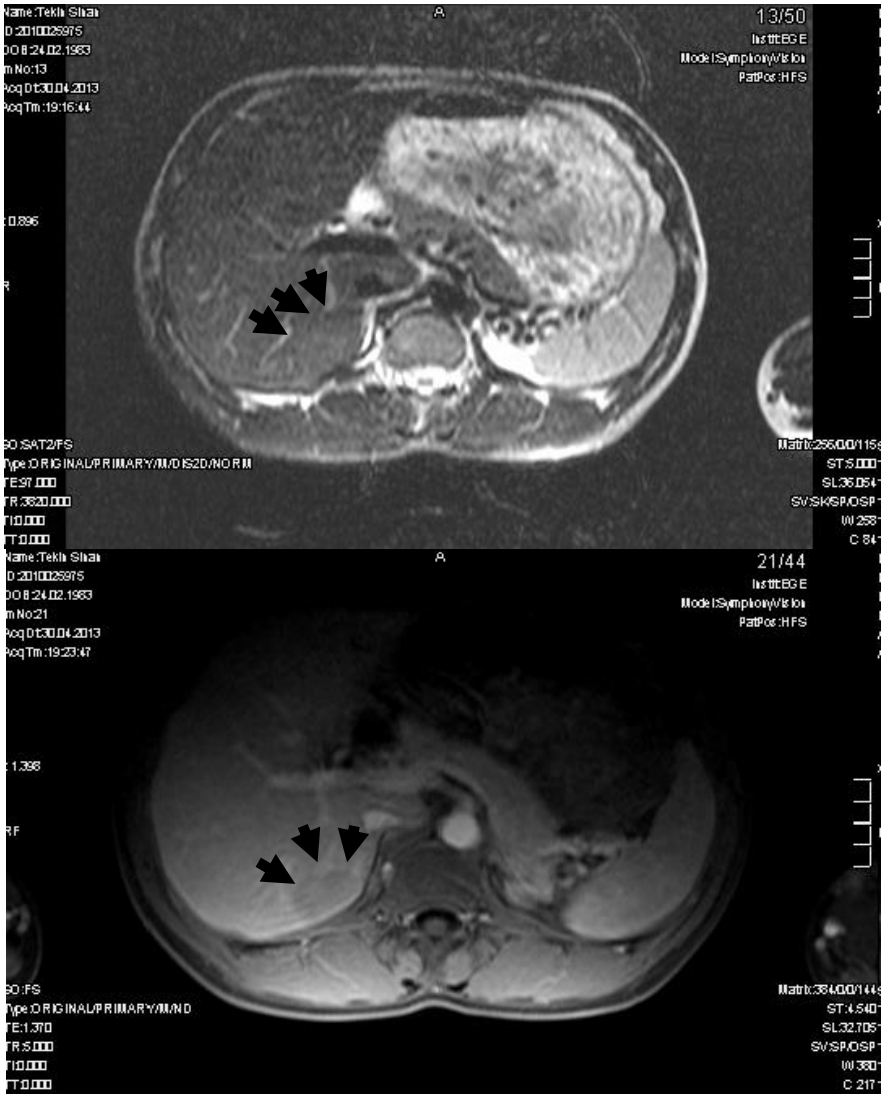
Beta Katenin / Glutamin Sentetaz

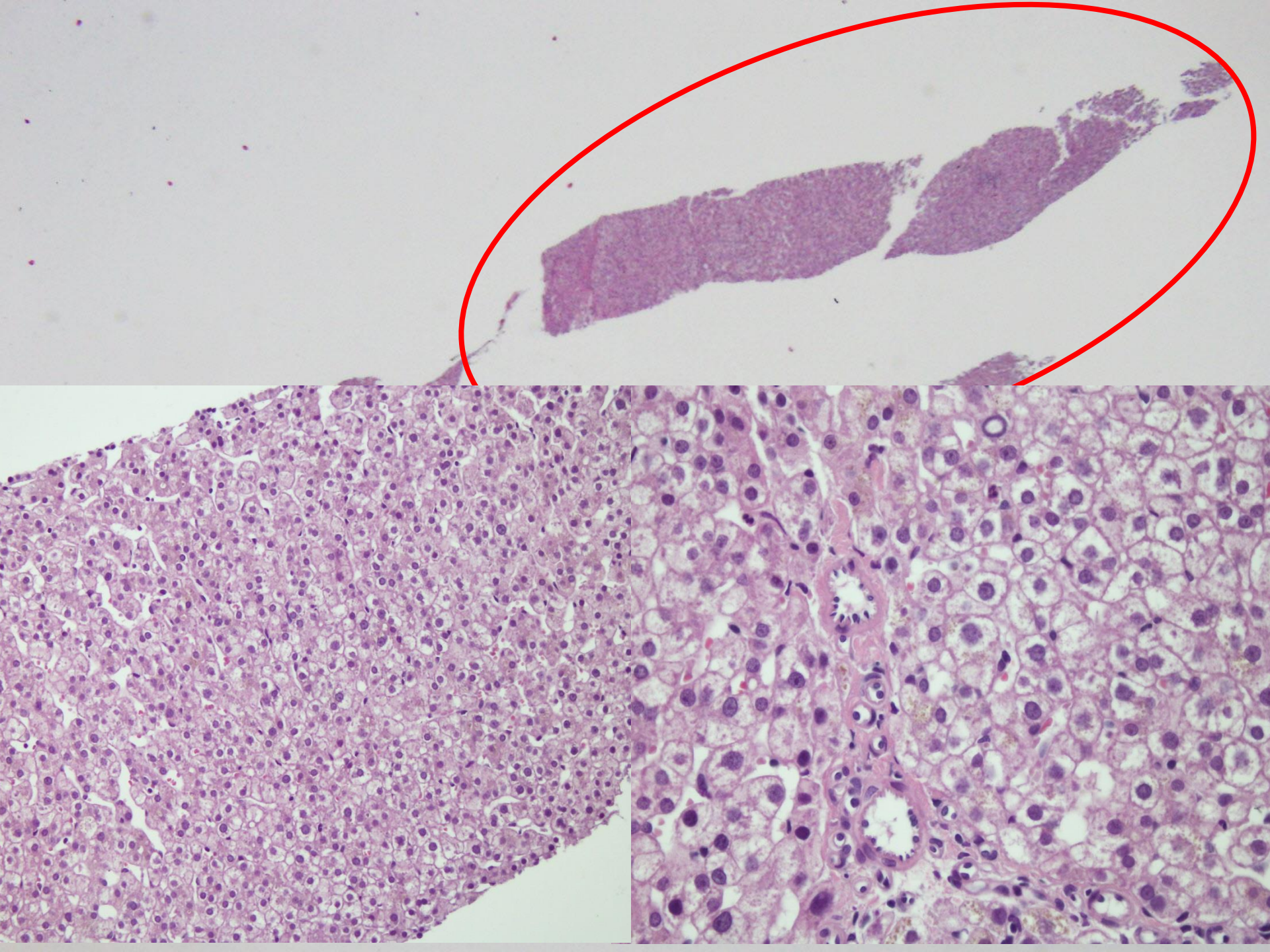
- Hepatosellüler adenom ve iyi diferansiye HSK: Beta katenin nükleer ve sitoplazmik (+), Glutamin Sentetaz diffüz (+)
- Kötü diferansiye HSK Beta katenin sitoplazmik, GS negatif
- Beta katenin aktivasyonu farklı mekanizma ile

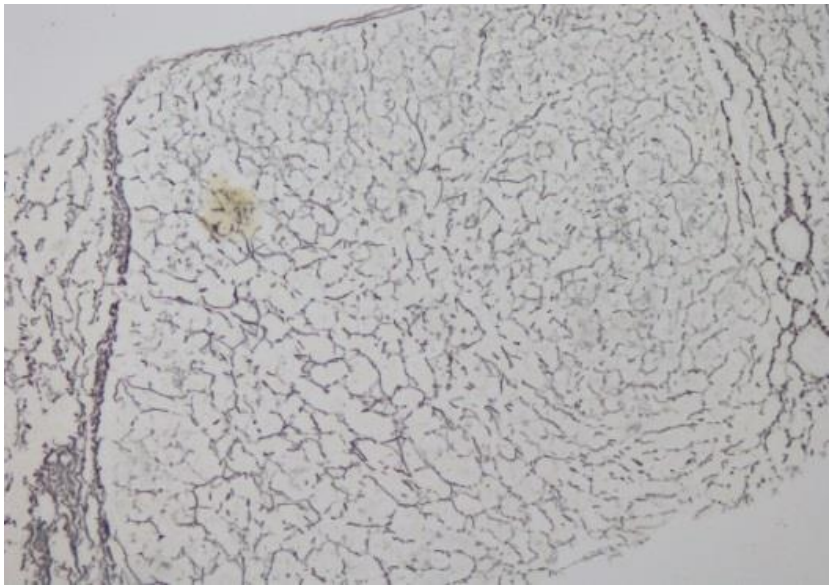


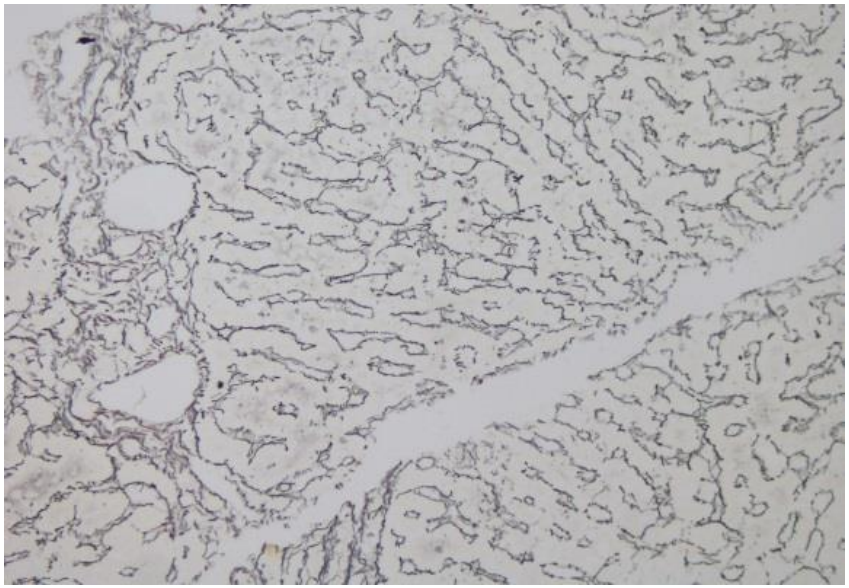
OLGU SUNUMU

- Böbrek nakilli hasta
- Kontrollerde KC'de kitle
- KC enzim tesleri: normal
- AFP: 2,1 ng/ml
- CEA:2,3 ng/ml
- CA19-9: 1,7 U/ml
- CA15-3 7,2 U/ml
- CA 125: 6,7 U/ml
- Görüntüleme yöntemleri ile kuşkulu



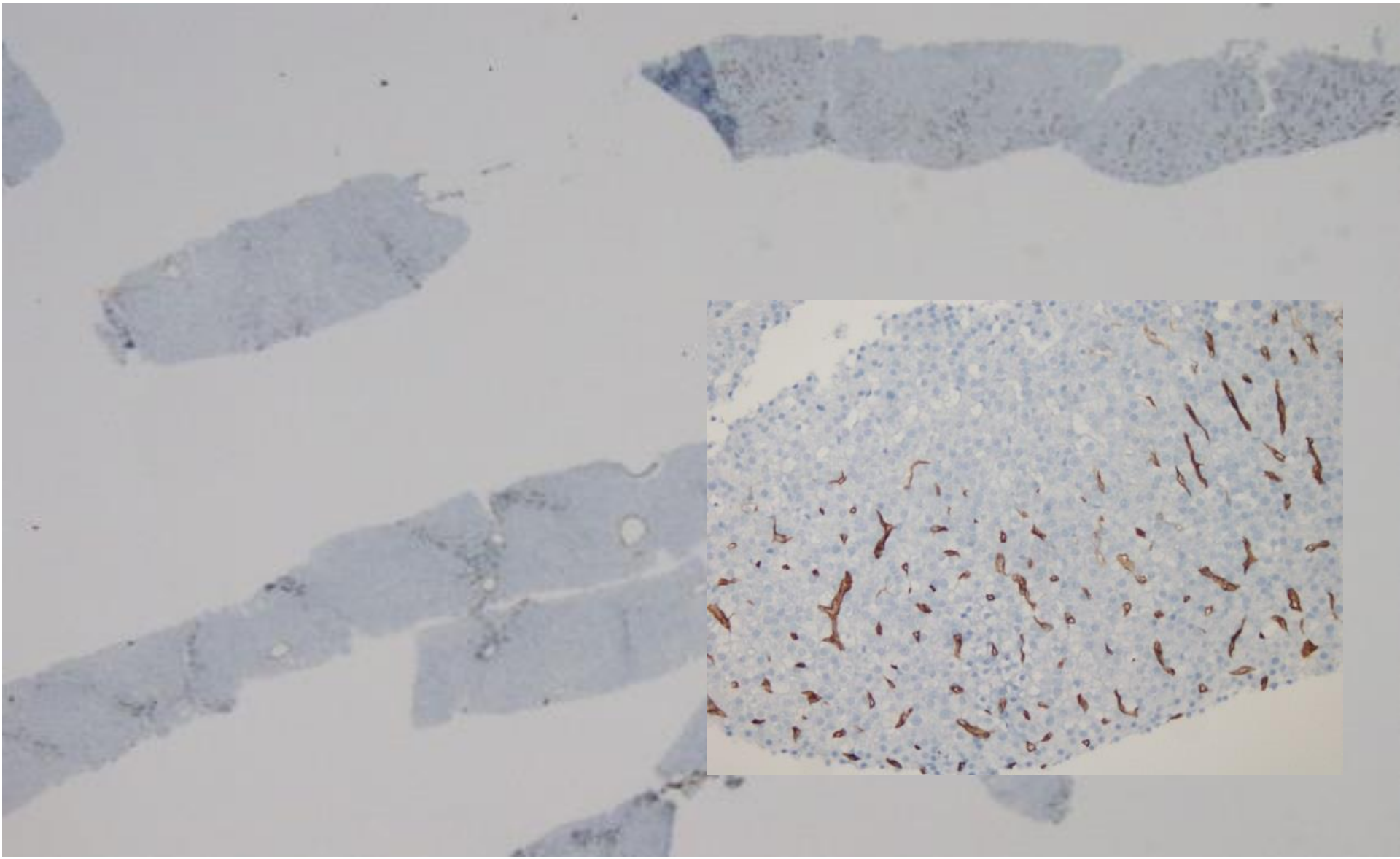




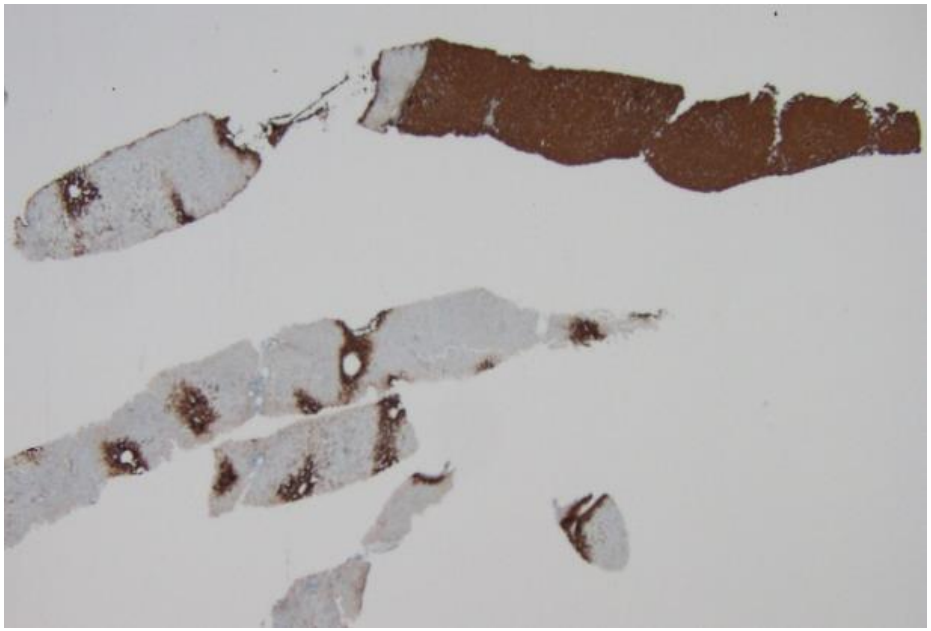


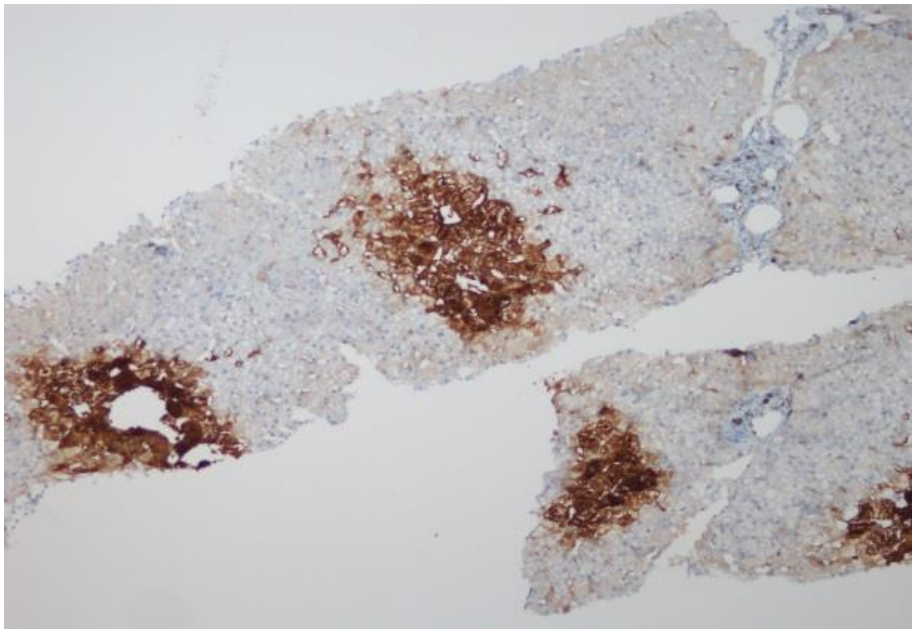
Retikulum çatısı

CD 34- neoanjiyogenez

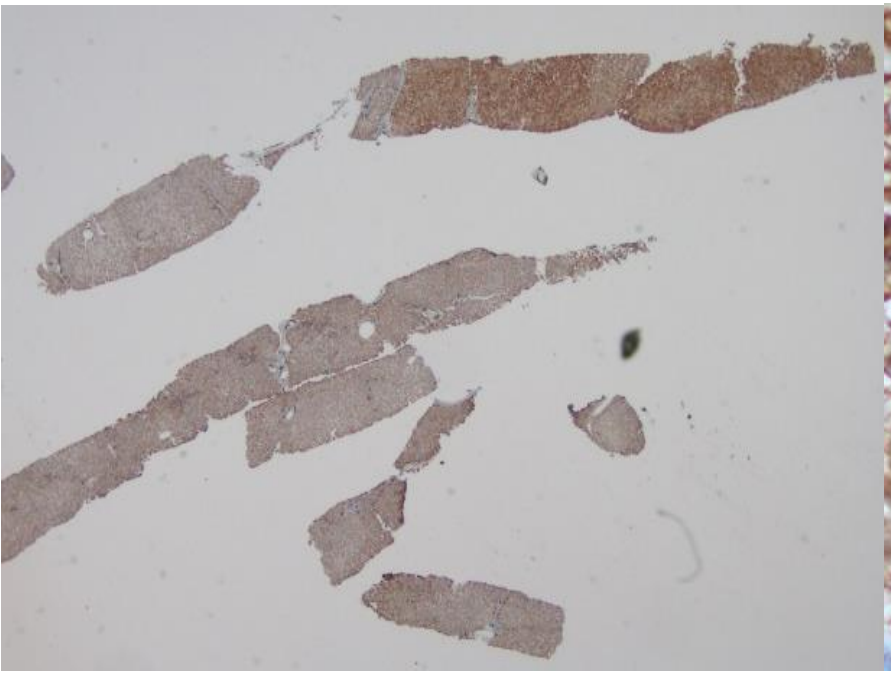


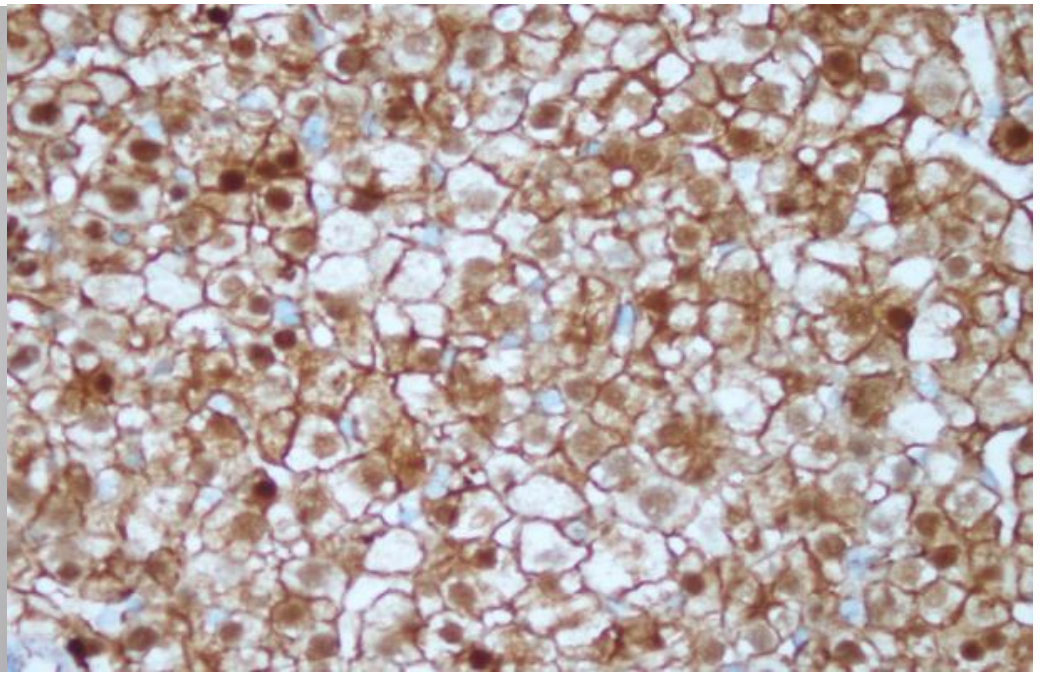
Glutamin Sentetaz





Beta-catenin





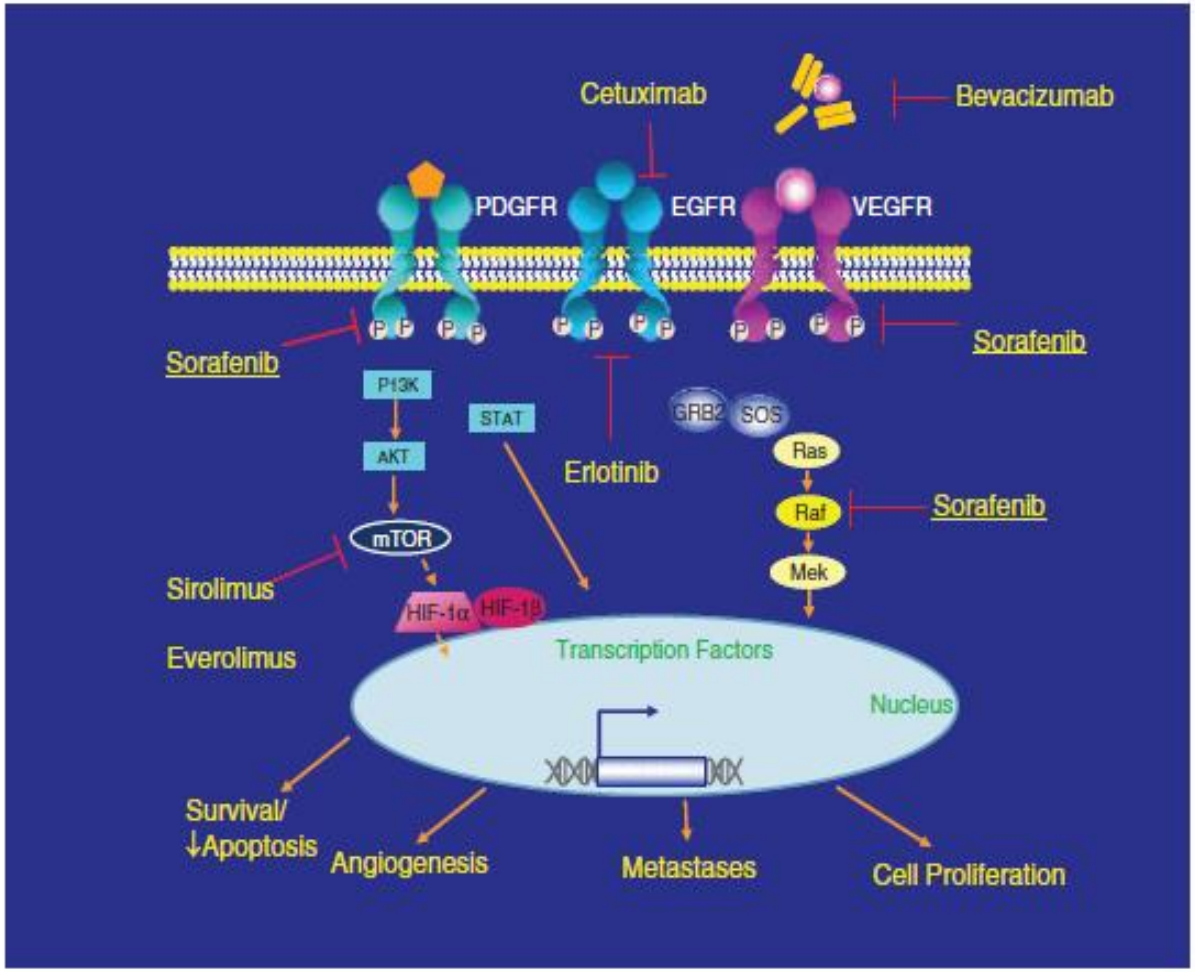


Figure 1. Molecularly targeted therapy in hepatocellular carcinoma (HCC). Reprinted with permission of John Wiley & Sons, Inc. [Zhu, 2008].

Ther Adv Gastroenterol
(2010) 3(1) 55–66
DOI: 10.1177/
1756283X09346669

Mikro RNA (Mi-RNA, MiR)

[Cancer Biology & Therapy 8:18, 1683-1690; 15 September 2009]; ©2009 Landes Bioscience

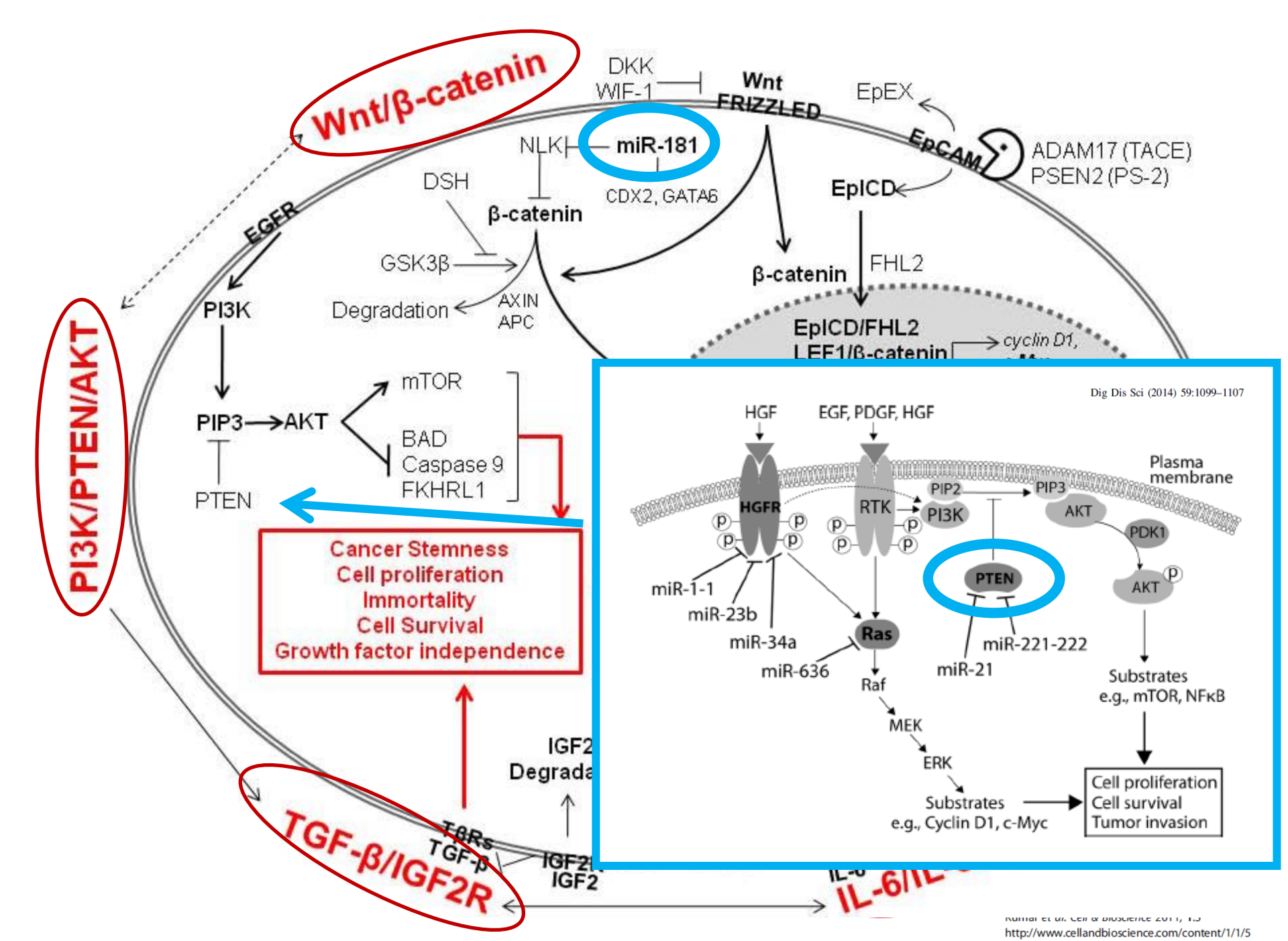
Review: Focus on the Liver

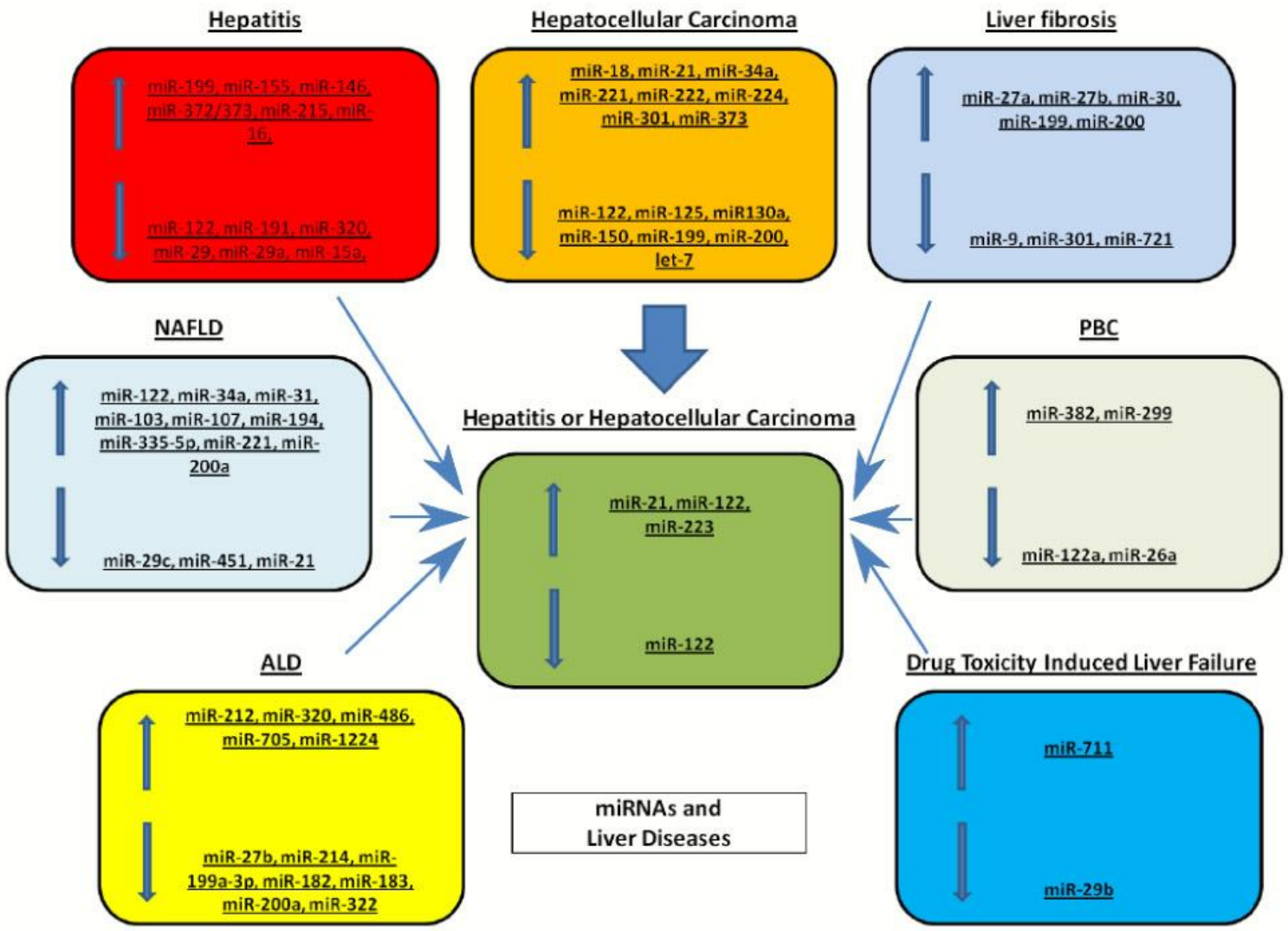
New kids on the block

Diagnostic and prognostic microRNAs in hepatocellular carcinoma

Junfang Ji and Xin Wei Wang*

Liver Carcinogenesis Section; Laboratory of Human Carcinogenesis; Center for Cancer Research; National Cancer Institute; Bethesda, MD USA


Wnt/β-catenin
DKK
WIF-1
Wnt
FRIZZLED
EpEX
EpCAM
ADAM17 (TACE)
PSEN2 (PS-2)
NLK
miR-181
CDX2, GATA6
DSH
β-catenin
EpICD
EGFR
GSK3β
Degradation
AXIN
APC
β-catenin
FHL2
PI3K
EpICD/FHL2
LEF1/β-catenin
cyclin D1,
PI3K/PTEN/AKT
PIP3
AKT
mTOR
BAD
Caspase 9
FKHRL1
PTEN
Cancer Stemness
Cell proliferation
Immortality
Cell Survival
Growth factor independence
IGF2
Degrada
TGF-β/IGF2R
TβRs
TGF-β
IGF2R
IGF2
IL-6/IL
Dig Dis Sci (2014) 59:1099–1107
HGF
EGF, PDGF, HGF
Plasma membrane
HGFR
RTK
PIP2
PIP3
PI3K
AKT
PDK1
PTEN
miR-1-1
miR-23b
miR-34a
miR-636
Ras
miR-21
miR-221-222
Raf
MEK
ERK
Substrates
e.g., Cyclin D1, c-Myc
Substrates
e.g., mTOR, NFκB
Cell proliferation
Cell survival
Tumor invasion



Swiss Med Wkly. 2011;141:w13287

Table 1 Unique miRNA signatures as candidate diagnostic biomarkers for HCC

miRNA signatures	Clinical implications	References
let-7f, miR-25 and miR-375 (up)	HCC	[52]
miR-23a, miR-23b, miR-342-3p, miR-375, and miR-423 (up)	HBV–HCC	[52]
miR-10a, miR-100 and miR-122 (up) + miR-145 and miR-198 (down)	HCV–HCC	[54]
miR-126 (down)	Alcohol-HCC	[55]
miR-21, miR-192 and miR-801 (up); miR-26a, miR-27a, miR-122 and miR-223 (down)	Differentiate HCC from chronic HBV or cirrhosis group	[53]
a 20-miRNA signature containing miR-181	$EpCAM^{+}$ AFP^{+} HCC	[56]

Up upregulated, *down* downregulated

Table 2 Unique miRNA signatures as candidate prognostic biomarkers for HCC

miRNA signatures	Clinical implications	References
31-miRNAs	HCC staging	[62]
20-miRNAs including let-7g and miR122a(down)	HCC metastasis	[63]
miR-26 (down)	Sensitive to IFN-α therapy	[68]
miR-146a (up)	Resistant to IFN-α therapy	[70]
miR-21 (up)	Resistant to combined therapy with IFN-α and 5-FU	[69]

Up upregulated, *down* downregulated

Mikro RNA ve Hepatosellüler Karsinom

- **Prognostik Mi-RNA'lar**
  - Metastaz: Venöz metastaz ile ilişkili 20-MiRNA içeren profil

    (Budhu A, Hepatology 2008)
  - Rekürrens: MiRNA 15b artışı

    (Chung GE, Oncol Rep 2013)
  - Sağ kalım

    (Ji J, J Hepatol 2010) (Ji J, N Engl J Med 2009)(Budhu A, Hepatology 2008)

Mikro RNA ve Hepatosellüler Karsinom

- **Terapötik potansiyeli var**
- **Anti-MiR181**: farede tümör gelişimini azaltıyor, 5FU'ya dirençli hücrelerde (kök hücre özellikli)
- **MiR-26**: tümör baskılayıcı, Düşük MiR26 ekspresyonu → kötü prognoz
- **MiR-26a, MiR- 26 b**→ Sağ kalım ve adjuvan IFN tedavisine yanıt ile ilişkili
- Hepatositlere gen tedavisi ile MiR 26 verilmesi Myc'e bağlı HSK bloke ediyor

(Ji J, N Engl J Med 2009) (Kota J, Cell 2009)

-

SONUÇ- HCC

- Genom/transkriptom/MiRNA düzeyindeki moleküler klasifikasyonlar klinik ve histolojik korelasyon göstermiştir
- Histolojik değerlendirmede saptanan β-katenin, Glutamin sentetaz, EpCAM, p53, Glipikan, TGF-β, p-AKT pozitifliği prognostik bilgi verebilir, tedavi seçimini belirleyebilir
- Mi-RNA'lar prognostik ve terapötik öneme sahiptir.