Kanser Genetiği

D3M2

Kanser gelişim sürecinde rol oynayan ve tedavi hedefi olan yolaklar ve moleküller

Çoklu uyaranların neden olduğu ortak yanıtlar

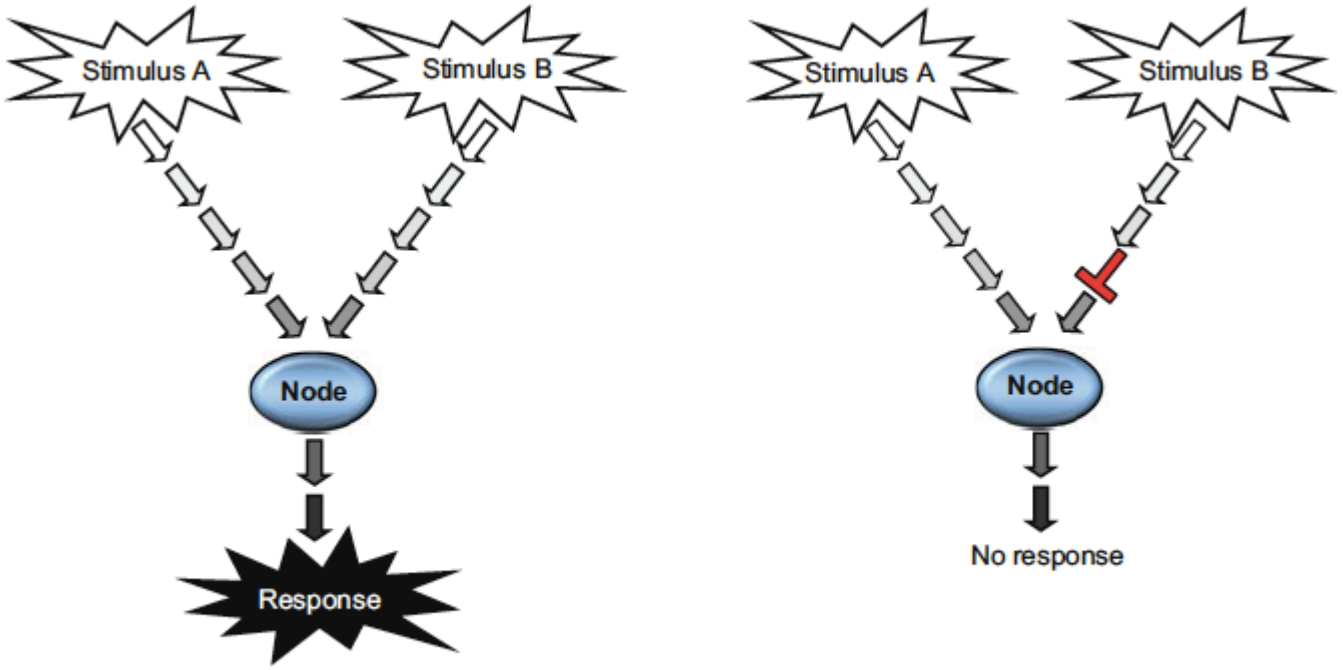


Fig. 6.4 Convergent pathways. Distinct upstream signals can lead to a common response. On the left, two pathways, triggered by stimulus A and stimulus B, converge at a single point and join a

Paralel yolaklarda çapraz etkileşim

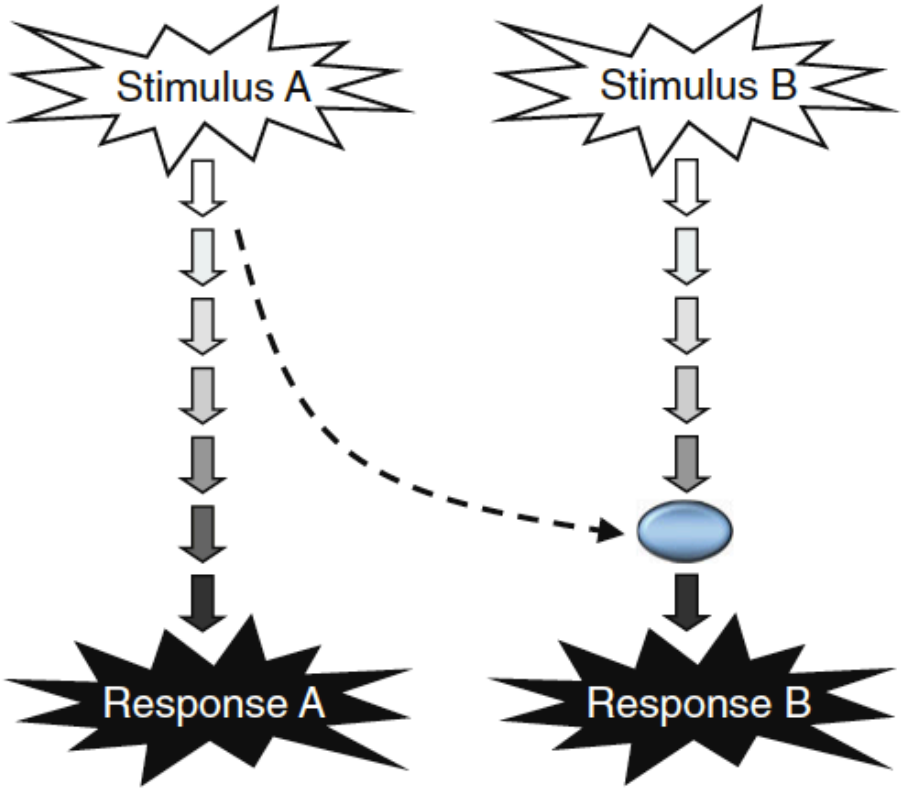


Fig. 6.5 Crosstalk between parallel pathways. In this example, Stimulus A leads primarily to Response A, Stimulus B leads to Response B via a distinct pathway. The "A" pathway is intercon-

Çapraz etkileşimli – çoklu uyaran ve çoklu yanıtlı yolaklar

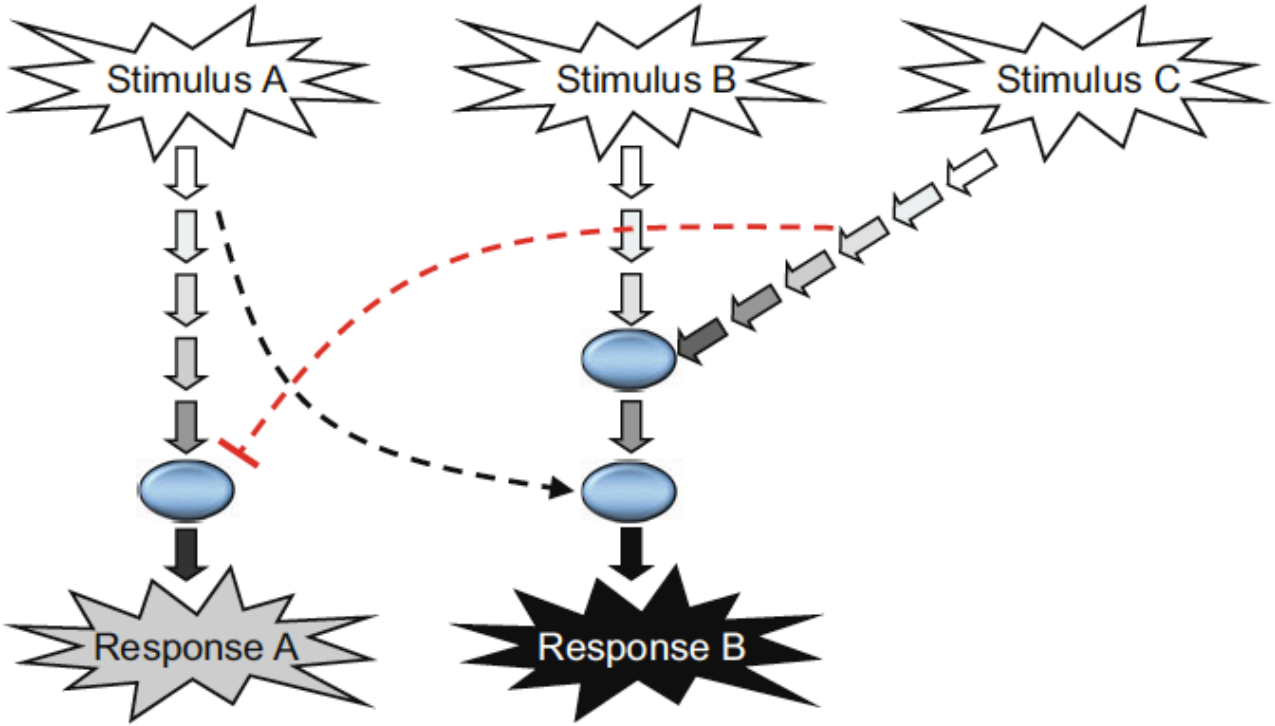


Fig. 6.6 Interconnected pathways form signaling networks. Multiple upstream signals affect multiple downstream responses. The activation of pathways that are influenced by crosstalk pro-

RTK gen mutasyonları kanserlerde sıklıkla etkilidir

Proto-oncogene	Ligand	Oncogenic alteration	Cancers
EGFR (ERBB1)	Epidermal growth factor (EGF), Transforming growth factor β (TGFβ)	Point mutation, deletion	Lung, Colorectal, and Breast Carcinoma
		Amplification	Glioblastoma
ERBB2 (HER2/ neu)	None	Amplification	Breast, ovarian, gastric, cervical, and lung carcinoma
		Point mutation	Neuroblastoma
FLT3	FLT3L (cytokine)	Tandem duplication	Acute myelogenous leukemia (AML)
MET	Hepatocyte growth factor	Amplification	Medulloblastoma, Esophageal and Gastric carcinoma
		Point mutation	Hereditary papillary renal cell carcinoma
RET	Glial-derived neurotropic factor	Complex rearrangement	Thyroid carcinoma
		Point mutation	Multiple Endocrine Neoplasia syndromes 2A & 2B
KIT	Stem cell factor	Point mutation	Acute myeloid leukemia, germ cell tumors
		Amplification	Glioblastoma
FGFR1	Fibroblast growth factor	Point mutation	Glioblastoma
		Translocation	Acute myelogenous leukemia, lymphoma

Reseptör tirozin kinaz aktivasyonu ile yolak altı olayların gelişimi

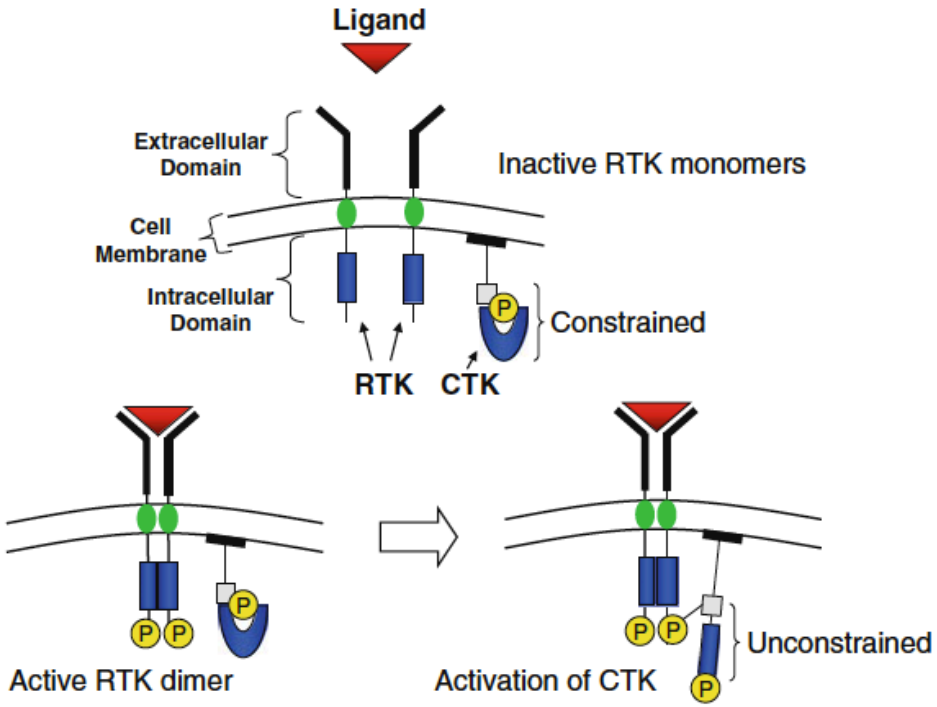
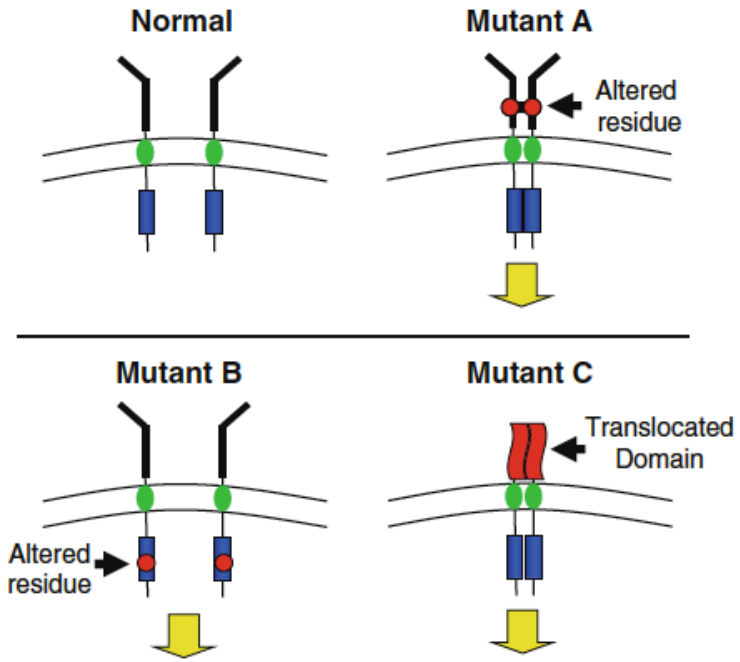


Fig. 6.8 Activation of a protein tyrosine kinase by an extracellular ligand. A generic receptor protein tyrosine kinase (RTK) is composed of an extracellular domain (*black*) that directly interacts with ligands (*red*), a transmembrane domain (*green*) and an intracellular domain that contains a conserved catalytic region (*blue*). A membrane-associated cytoplasmic tyrosine kinase (CTK), is maintained in inactive form by intramolecular constraints that inhibit its catalytic domain. Upon ligand binding, the RTK molecules form dimers, and activate their catalytic domains by autophosphorylation. The intramolecular constraints that keep the CTK inactive are relieved when the SRC-homology domain (*gray*) preferentially associates with the phosphorylated form of the RTK dimer. Thus activated, RTK and CTK can turn on downstream pathways

RTK sinyal iletim sisteminin nokta mutasyonları ile bozulması



BCR-ABL

Fig. 6.9 Point mutations can result in RTK dysregulation. Mutant A contains an amino acid substitution (shown in red) in the extracellular domain that causes RTK molecules to have an increased affinity for one another and to dimerize. Mutations in the transmembrane domain can have a similar effect (not shown). Mutant B carries an amino acid substitution mutation in the activation loop of the catalytic domain, increasing the basal kinase activity of RTK monomers. Mutant C is a fusion protein in which the extracellular domain derived from an unrelated protein that is normally 'sticky' and therefore participates in protein-protein interactions. In each case, signaling is ligand-independent

RTK gen amplifikasyonu ile normal RTK lerin ligand duyarlılığının artması

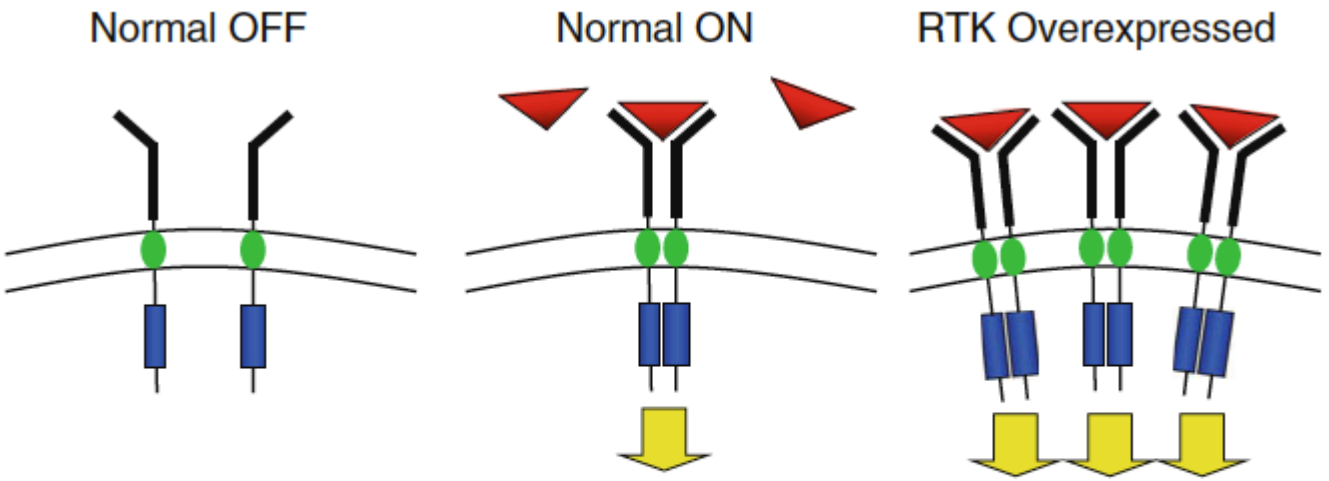


Fig. 6.10 Amplification of RTK genes can cause cells to become hypersensitive to ligand. RTK proteins encoded by wild type genes normally trigger downstream responses (*yellow arrow*) that depend upon the presence of ligand (*red*). Amplification of RTK genes leads to overexpression of RTK receptors, and their increased numbers at the cell surface. Although each receptor is normal in structure and function, cells are hypersensitive to ligand

Membran ilişkili GTPaz lar

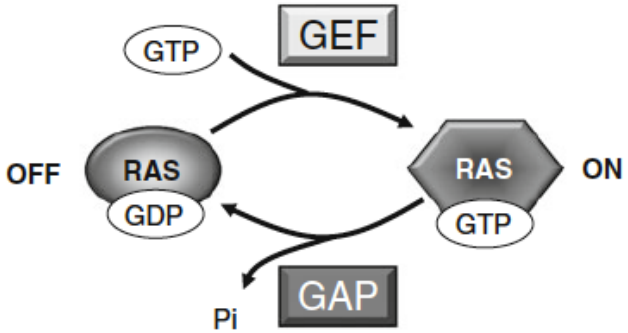


Fig. 6.11 Regulation of RAS-mediated GTP binding and hydrolysis. RAS proteins have low

RAS proteinleri RTK'ler tarafından aktive olurlar

RAS aracılı GTP bağlanması ve hidrolizi

RAS sinyalleri RTK ile kinaz kaskatını ilişkilendirerek gen ifadesi ve protein sentezini değiştirir

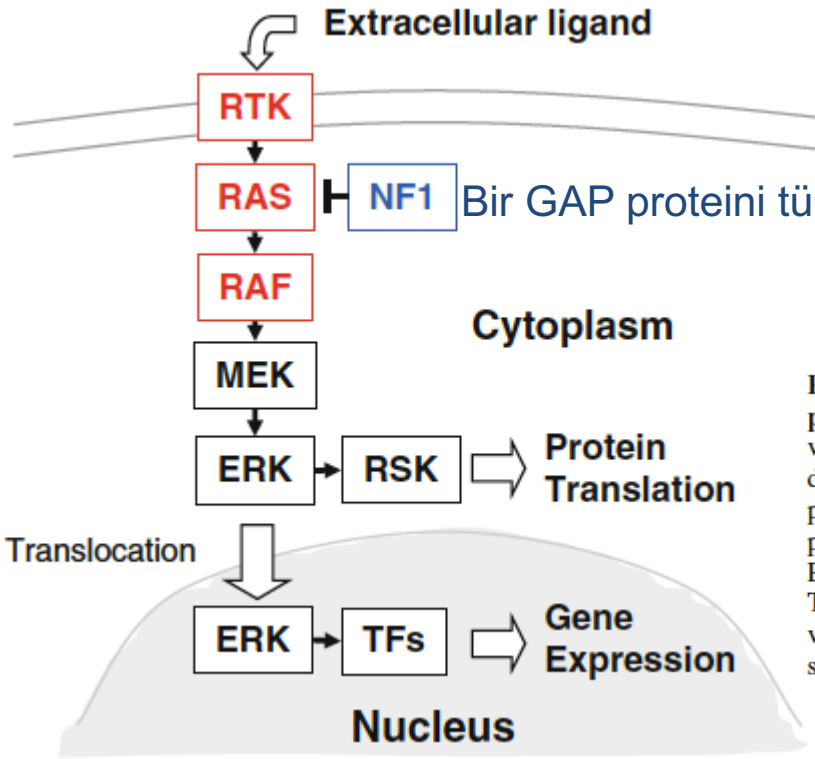


Fig. 6.13 RAS signaling connects RTKs with kinase cascades that alter gene expression and protein translation. RAS represents a node at which upstream and downstream pathways converge. In response to RTK signaling, RAS proteins activate RAF family members. RAS can be deactivated by the GAP proteins, which include the product of the *NF1* gene. RAF proteins phosphorylate and activate the MEKs, which in turn phosphorylate and activate the ERKs. The ERK proteins can activate the ribosome-associated RSK proteins, thereby affecting protein synthesis. ERKs can also translocate into the nucleus and regulate numerous transcription factors (TFs). Thus, RAS signals are transmitted throughout the cell. Proteins that can be constitutively activated via oncogenic mutations are shown in *red*. NF1 is the product of a tumor suppressor gene and is shown in *blue*

RTK gen mutasyonları kanserlerde sıklıkla etkilidir

Proto-oncogene	Ligand	Oncogenic alteration	Cancers
EGFR (ERBB1)	Epidermal growth factor (EGF), Transforming growth factor β (TGFβ)	Point mutation, deletion	Lung, Colorectal, and Breast Carcinoma
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		Translocation	Acute myelogenous leukemia, lymphoma

Membran ilişkili lipid fosforilasyonu: PI3K/AKT yolağı

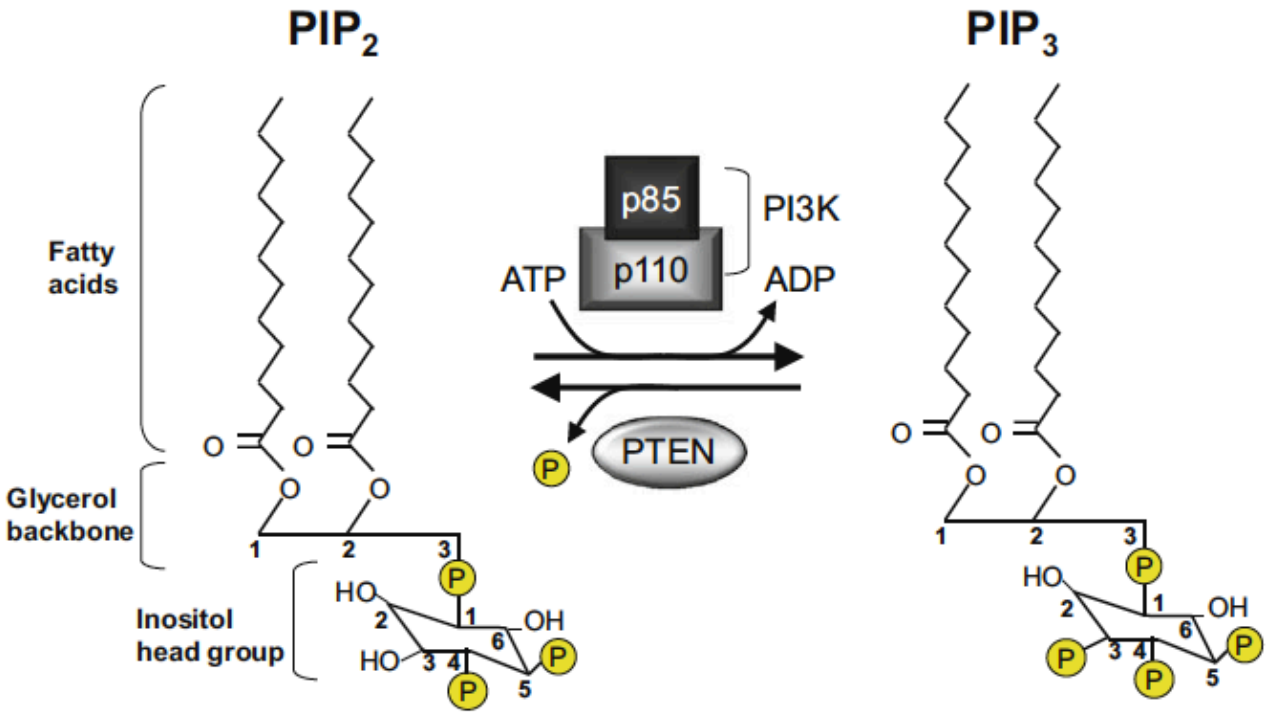
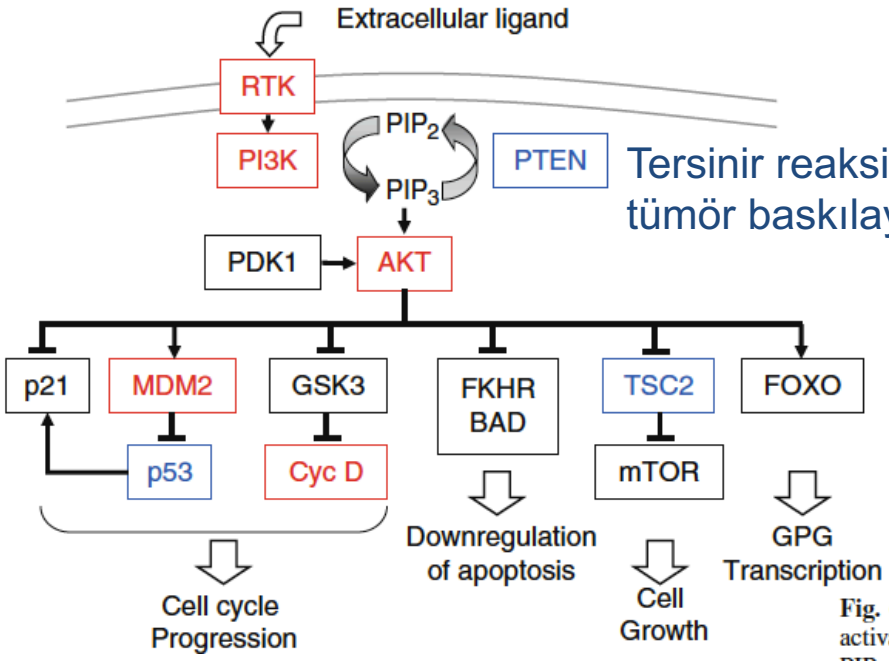


Fig. 6.14 Regulation of the PIP_2-PIP_3 cycle by PI-3 K and PTEN. The heterodimeric PI3K complex catalyzes the ATP-dependent phosphorylation of phosphatidylinositol (4,5)-bisphosphate (PIP_2) at the D3 position of the inositol moiety to generate phosphatidylinositol (3,4,5)-triphosphate (PIP_3). The reverse reaction is catalyzed by the lipid phosphatase encoded by the *PTEN* tumor suppressor gene. Relevant phosphate groups are shown in *yellow*

AKT hücre siklus engelleyicilerini baskılar



Tersinir reaksiyonu katalizleyan bir defosforilaz: tümör baskılayıcıdır (fosfataz tensin homolog)

Fig. 6.15 The PI3K/AKT pathway. Ligand-dependent activation of RTK signaling causes the activation of PI3K, and the generation of PIP_3. Via its pleckstrin homology domain, AKT binds PIP_3 and is thus recruited to the inner surface of the cell membrane. AKT is activated by a dual regulatory mechanism that requires translocation and subsequent phosphorylation by PDK1. Active AKT phosphorylates numerous downstream substrates; several representative regulators are shown. Cell cycle progression is stimulated by the AKT-dependent phosphorylation of the cyclin-dependent kinase inhibitor p21. Expression of p21 is also inhibited by the MDM2-dependent inhibition of p53. The activity of cyclin D is increased by the AKT dependent inhibition of glycogen synthetase kinase 3B (GSK3). Apoptosis is downregulated by inhibitory signaling to several proapoptotic proteins, including BAD. AKT inhibits the mTOR pathway via inhibition of TSC2, and thereby promotes protein biosynthesis. The expression of growth-promoting genes (GPG) is increased by the activation of the FOXO family of transcription factors

Hücre çoğalmasının besin ve enerji koşulları ile ilişkilendirilmesi mTOR kompleksleri ile sağlanır.

TSC1/2 mTOR negatif regülatörü olarak çalışır

Hücre canlılığını sağlamaya çalışan sistemlerdir.
PIK3/AKT ve mTOR yolağındaki değişiklikler ile etkilenirler

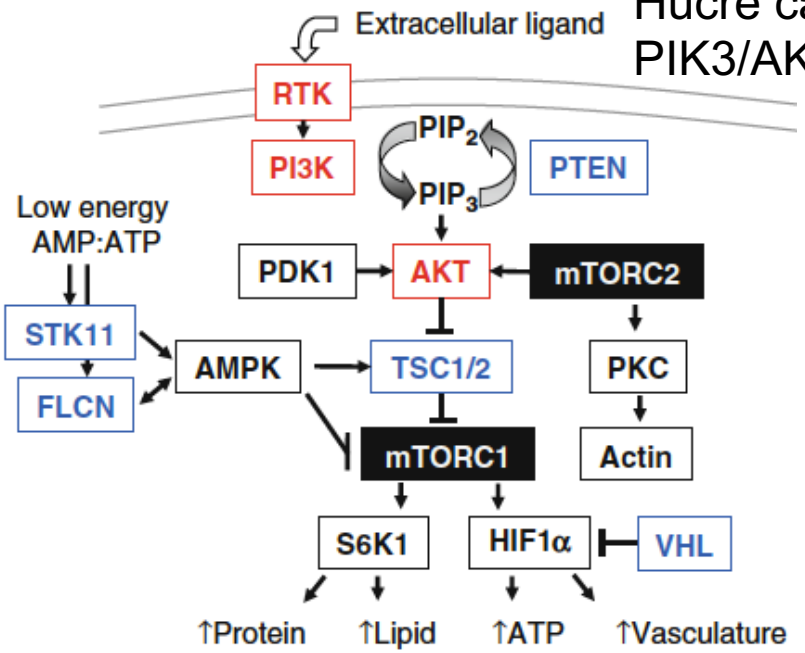


Fig. 6.16 The control of biosynthetic and energetic pathways by mTOR complexes. mTOR activity is controlled by multiple regulatory proteins. AKT promotes activation of the mTORC1 complex via the inactivation of the TSC1/2 heterodimer. A second complex, mTORC2, promotes the activity of AKT. mTORC2 also interacts with the cytoskeleton by a promoting an interaction between protein kinase C (PKC) and actin. The TSC1/2 complex is activated in response to the 5′-adenosine monophosphate-activated protein kinase (AMPK), an evolutionarily conserved metabolic master switch that senses fluctuations in the AMP:ATP ratio via signals from the STK11 kinase. A complex of proteins containing foliculin (FLCN) also appears to be involved in energy and nutrient sensing by AMPK. Downstream targets of mTORC1 include S6K1, which promotes the biosynthesis of proteins and lipids, and HIF1α, which promotes ATP generation by glucose metabolism. HIF1α is negatively regulated by the tumor suppressor VHL. Proteins encoded by proto-oncogenes are shown in *red*; tumor suppressor gene products are shown in *blue*

HIF1a ve VHL ilişkisi ve yeni damar oluşumunun kontrolu

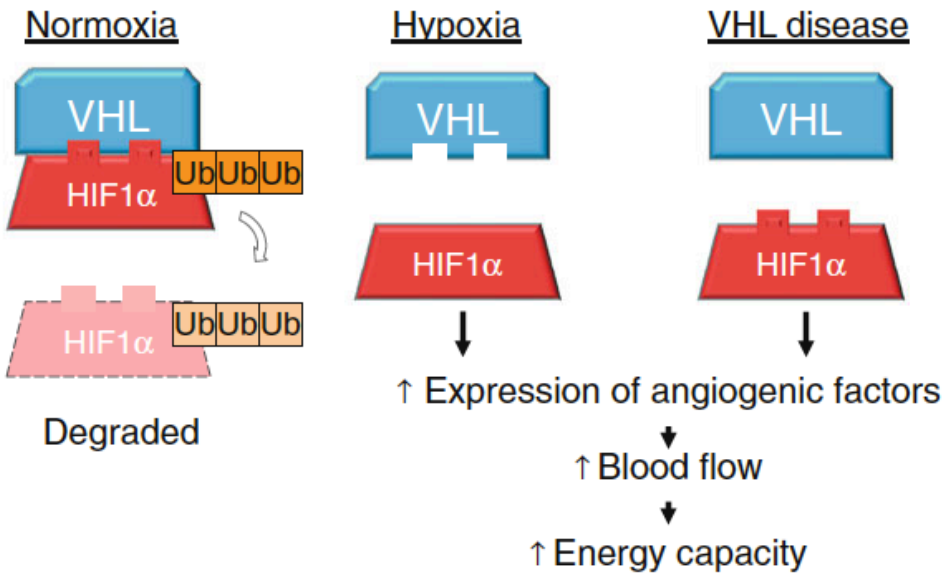
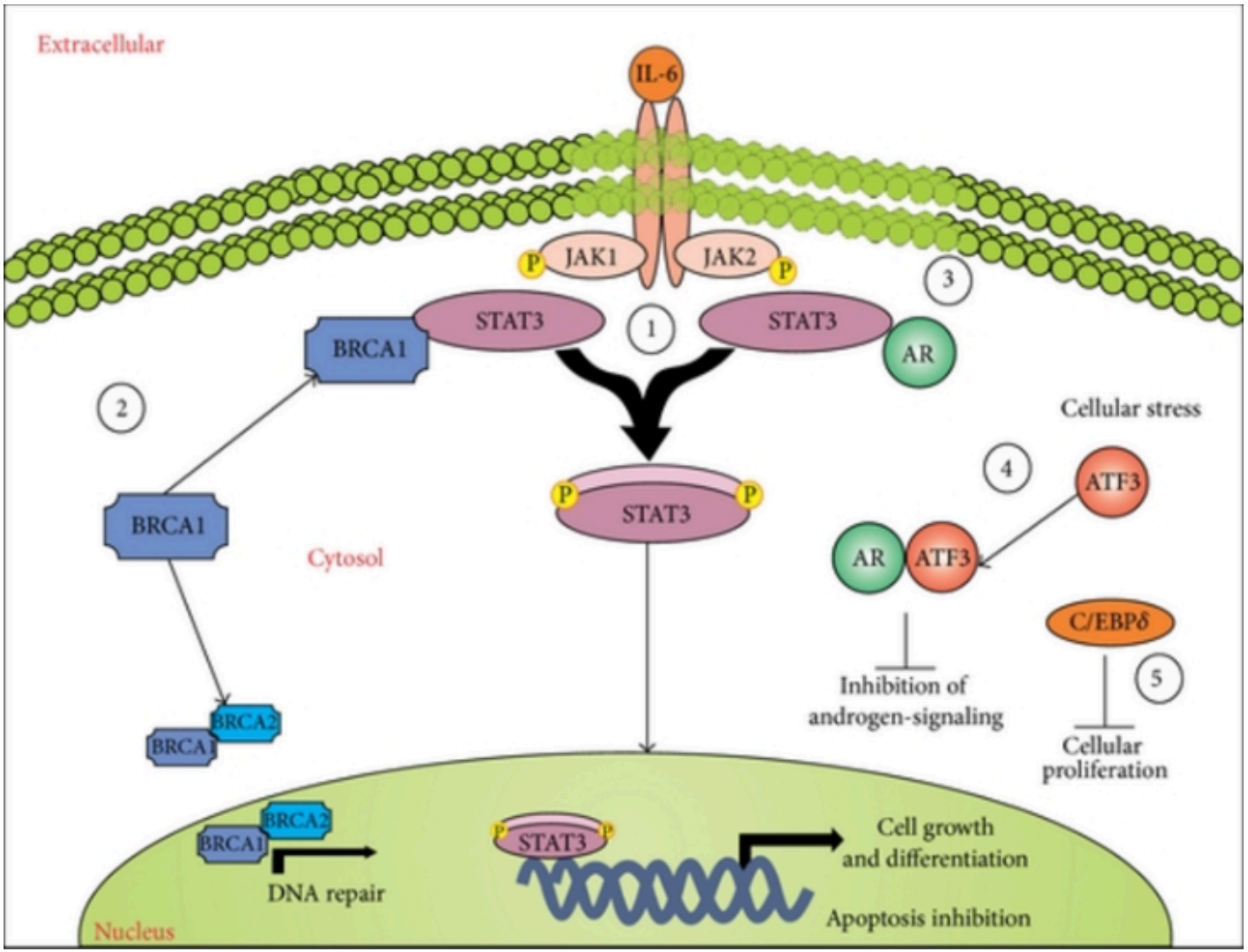


Fig. 6.18 The regulation of HIF1α by VHL. HIF1α is a transcription factor that is highly responsive to the microenvironmental oxygen concentration. At normal oxygen levels (normoxia), two proline residues on HIF1α are covalently modified and facilitate its interaction with a specific site on VHL. This interaction results in the poly-ubiquitination of HIF1α, and its subsequent degradation by the proteasome. Under conditions of hypoxia, which are frequently encountered in growing tumors, the specific proline residues on HIF1α are unmodified and VHL is therefore not bound. The mutations that cause VHL disease commonly alter the HIF1α binding site. In the stable VHL-unbound state, HIF1α induces the expression of genes, including VEGFA, that promote angiogenesis and increase local blood flow

JAK/STAT yolağı: Sitokin sinyallerinin çekirdeğe iletilmesini sağlar (hücre içi tirozin kinaz / sinyal iletimi, transkripsiyon aktivatörü)



Morfogenez ve Kanser: WNT/APC yolağı

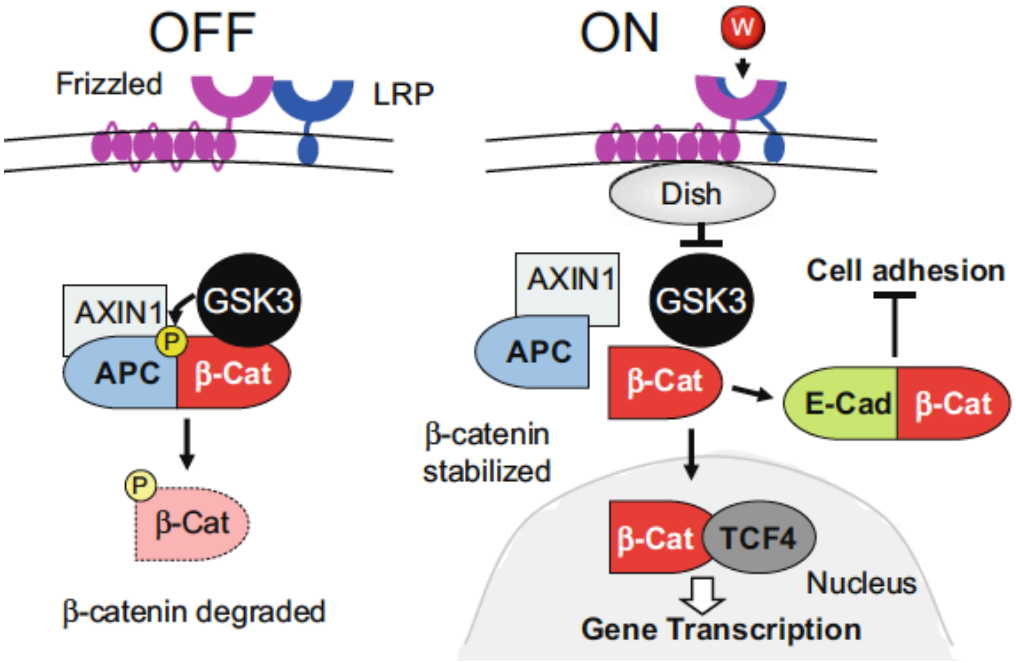


Fig. 6.19 The canonical WNT signaling pathway. In the absence of WNT ligand (OFF; *left panel*), phosphorylation of β-catenin by the GSK3 kinase favors the formation of a complex composed of APC and AXIN. β-catenin is targeted for degradation when the WNT pathway is OFF. When the pathway is turned on by ligand, Frizzed and LRP cooperatively activate Disheveled at the cell membrane, which functions to inactivate GSK3. In the absence of GSK3-mediated phosphorylation, the degradation complex is dissociated and β-catenin is stabilized, translocates to the nucleus and, in cooperation with the TCF family of transcription factors, activates the expression of growth promoting genes. Cytoplasmic β-catenin can also associate with E-cadherin, which mediates cell adhesion

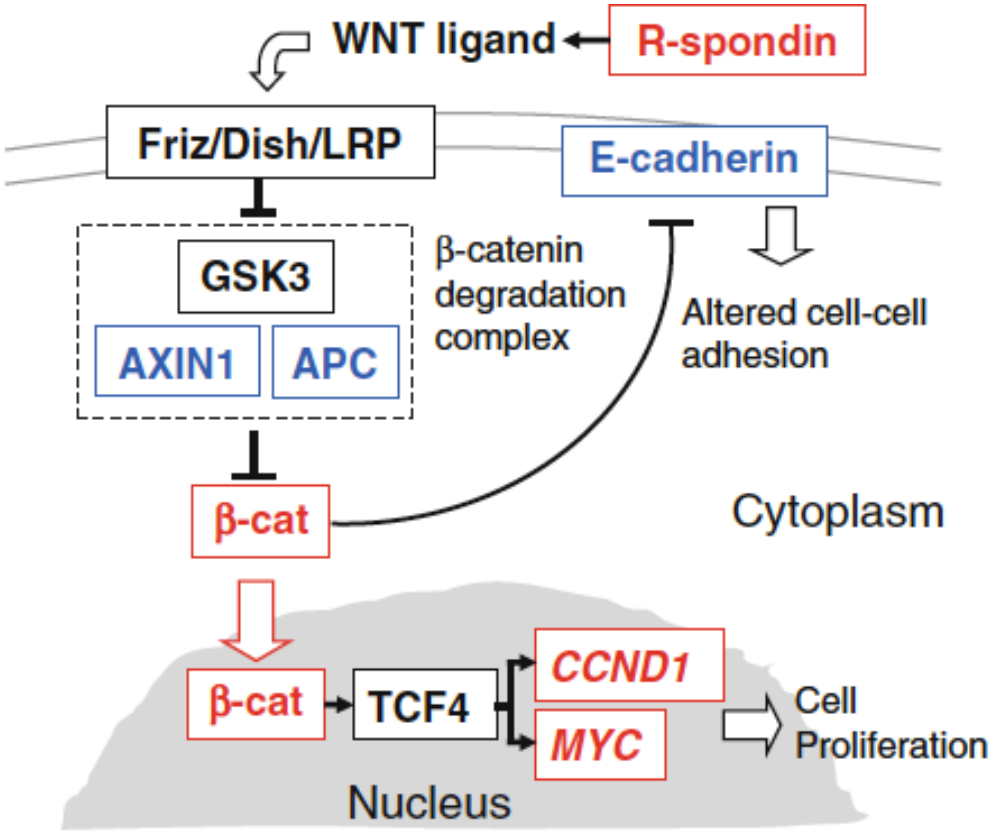


Fig. 6.20 Constitutive WNT signaling in cancer. Several types of mutations can mimic or enhance the effects of activated WNT signaling. The secreted R-spondin proteins appear to interact with WNT ligands on the cell surface and promote upstream pathway activation. Mutations in *APC* in colorectal cancers very frequently disrupt the β-catenin degradation complex, leading to WNT ligand-independent stabilization of β-catenin. Oncogenic mutations that affect the APC binding site of β-catenin have the same effect. Inactivating mutations in AXIN-encoding genes can also disrupt the β-catenin degradation complex. Stabilized β-catenin alters cell adhesion via interactions with cytoplasmic E-cadherin, and also promotes transcriptional transactivation by TCFs. Among the targets of β-catenin/TCF transcription are the proto-oncogenes *CCND1*, which encodes the cell cycle regulator cyclin D, and *MYC*. Proteins and genes affected by oncogenic mutations are shown in *red*, tumor suppressors are shown in *blue*

YAŞLARA GÖRE KANSER İNSİDANSI

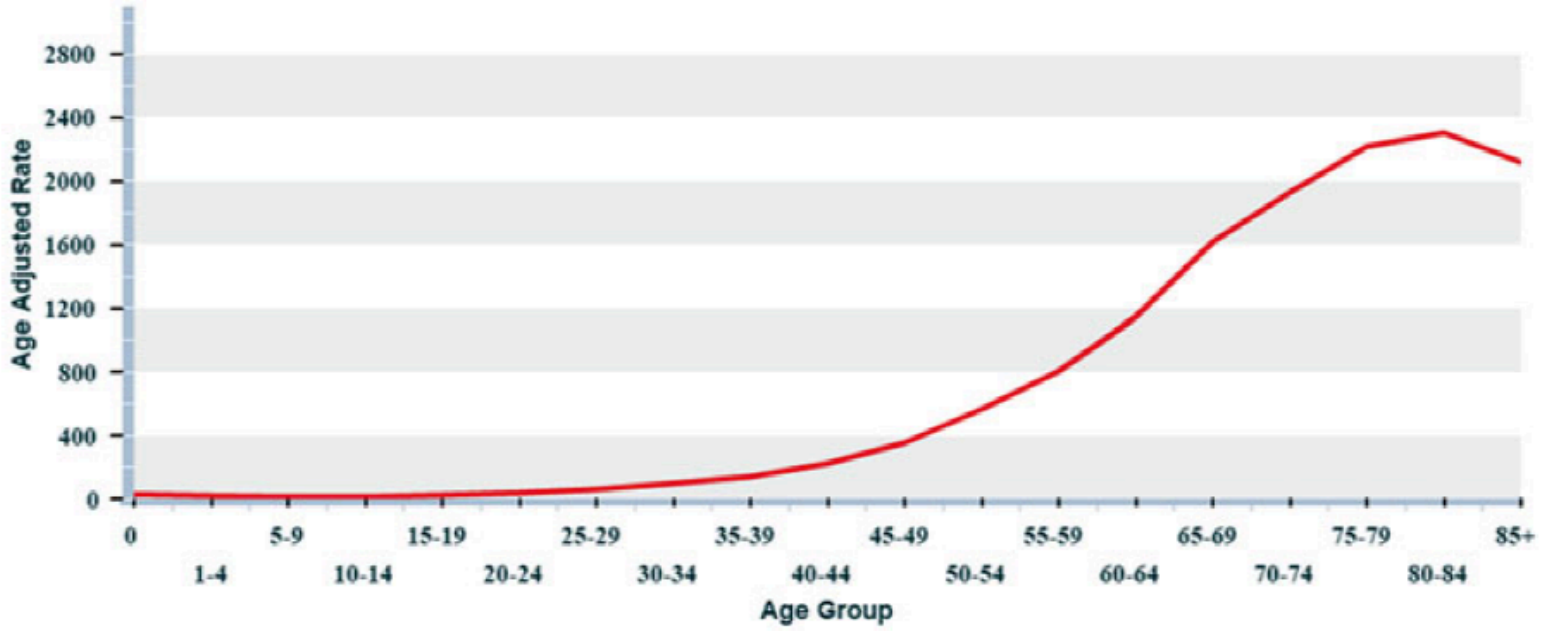


Fig. 5.2 Cancer incidence, by age group. The overall incidence of cancer at all sites rises with increasing age and peaks around age 80. Incidence rates include both sexes and all races, are per 100,000 and are from surveys dating from 1975 to 2012, age-adjusted to the 2000 US population. Primary data are from the Surveillance, Epidemiology and End results program (SEER), of the National Cancer Institute

Zigottan başlayarak somatik hücrelerde kanser gelişim süreci

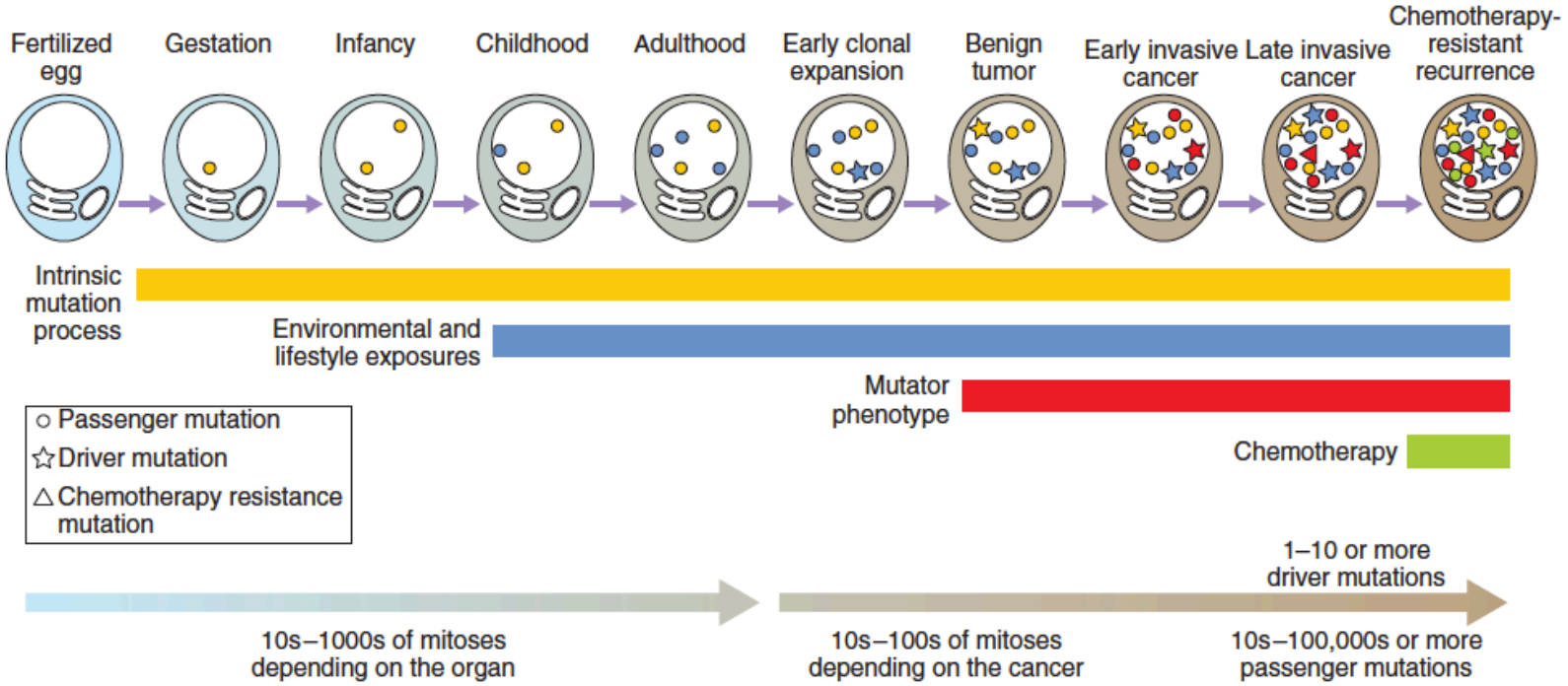


FIGURE 14.1 The lineage of mitotic cell divisions from the fertilized egg to a single cell within a cancer showing the timing of the somatic mutations acquired by the cancer cell and the processes that contribute to them. Mutations may be acquired through both intrinsic cell division processes and as a result of mutagens. DNA repair defects may contribute, but driver mutations will cause clonal expansion, with passenger mutations having little overall effect. Relapse following chemotherapy may be due to resistant mutations predating treatment. *(Reproduced with permission from Stratton MR, Campbell PJ, Futreal PA 2009 The cancer genome. Nature 458:719–24.)*

Kanser genomlarında en sık gözlenen mutasyonların saptanması

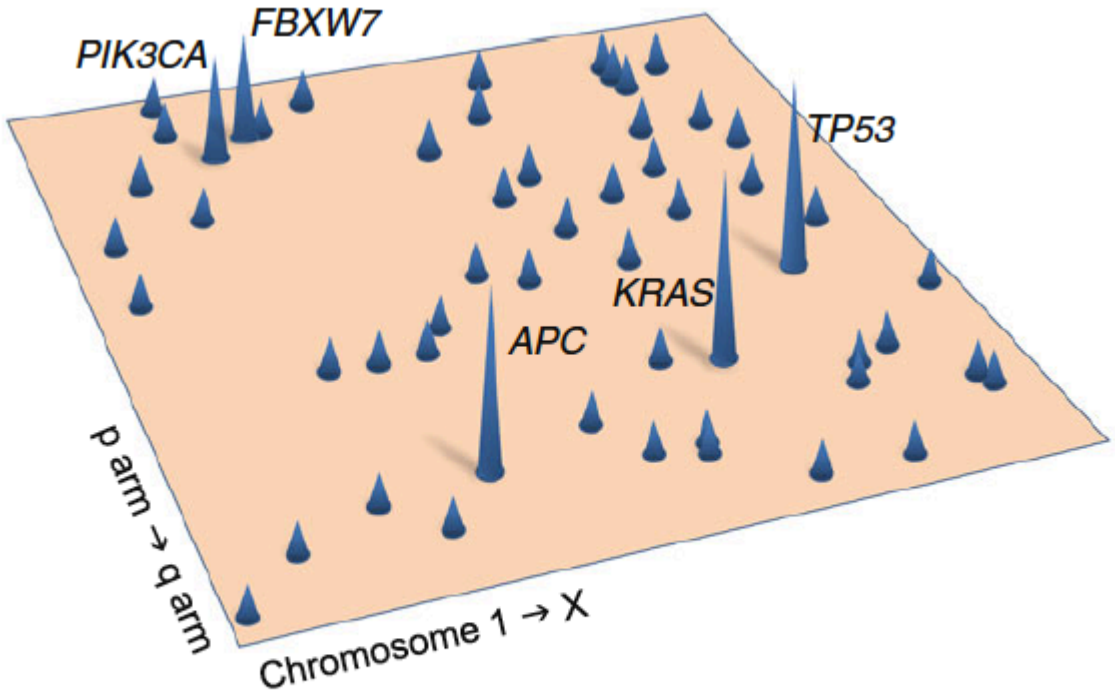
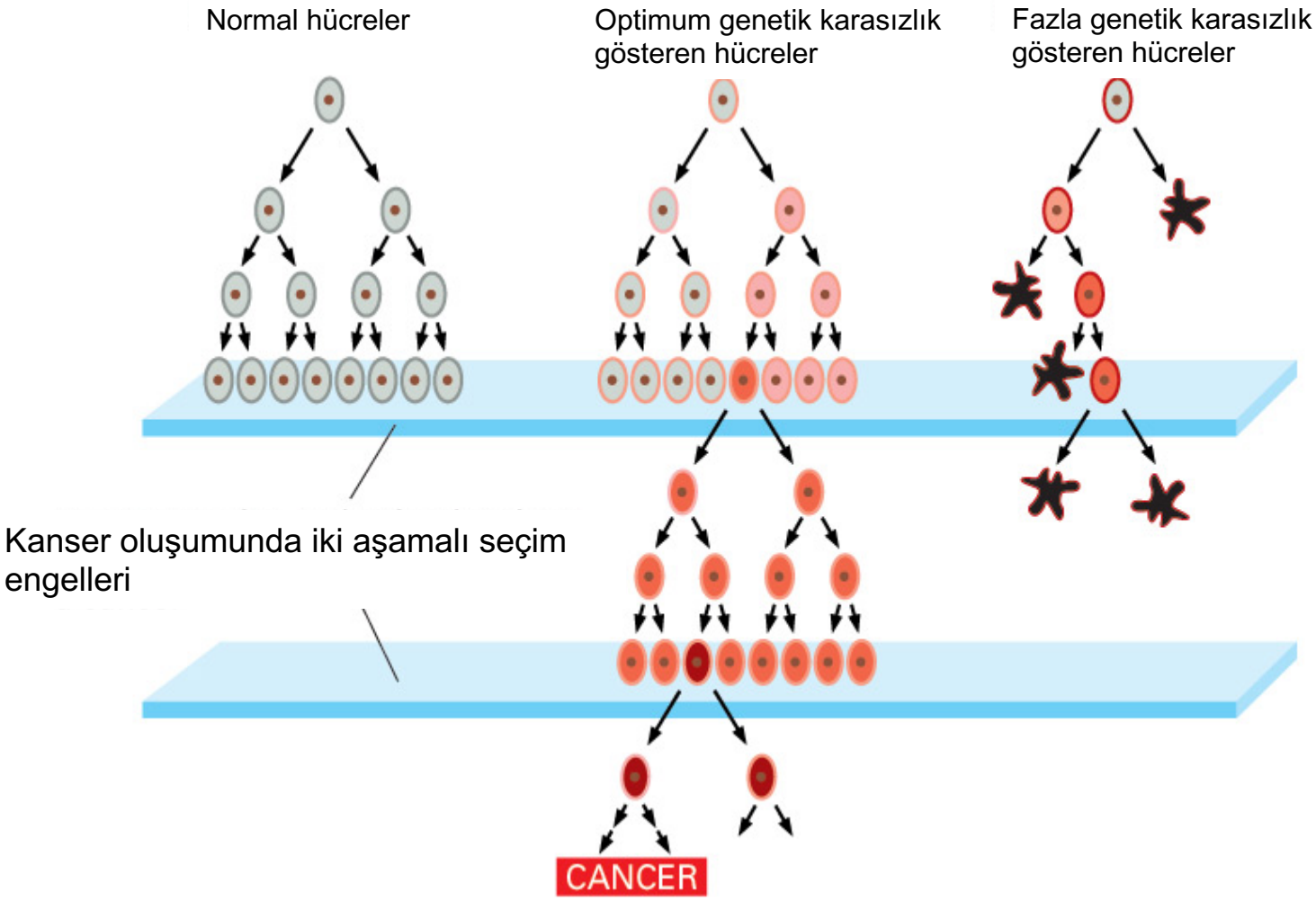
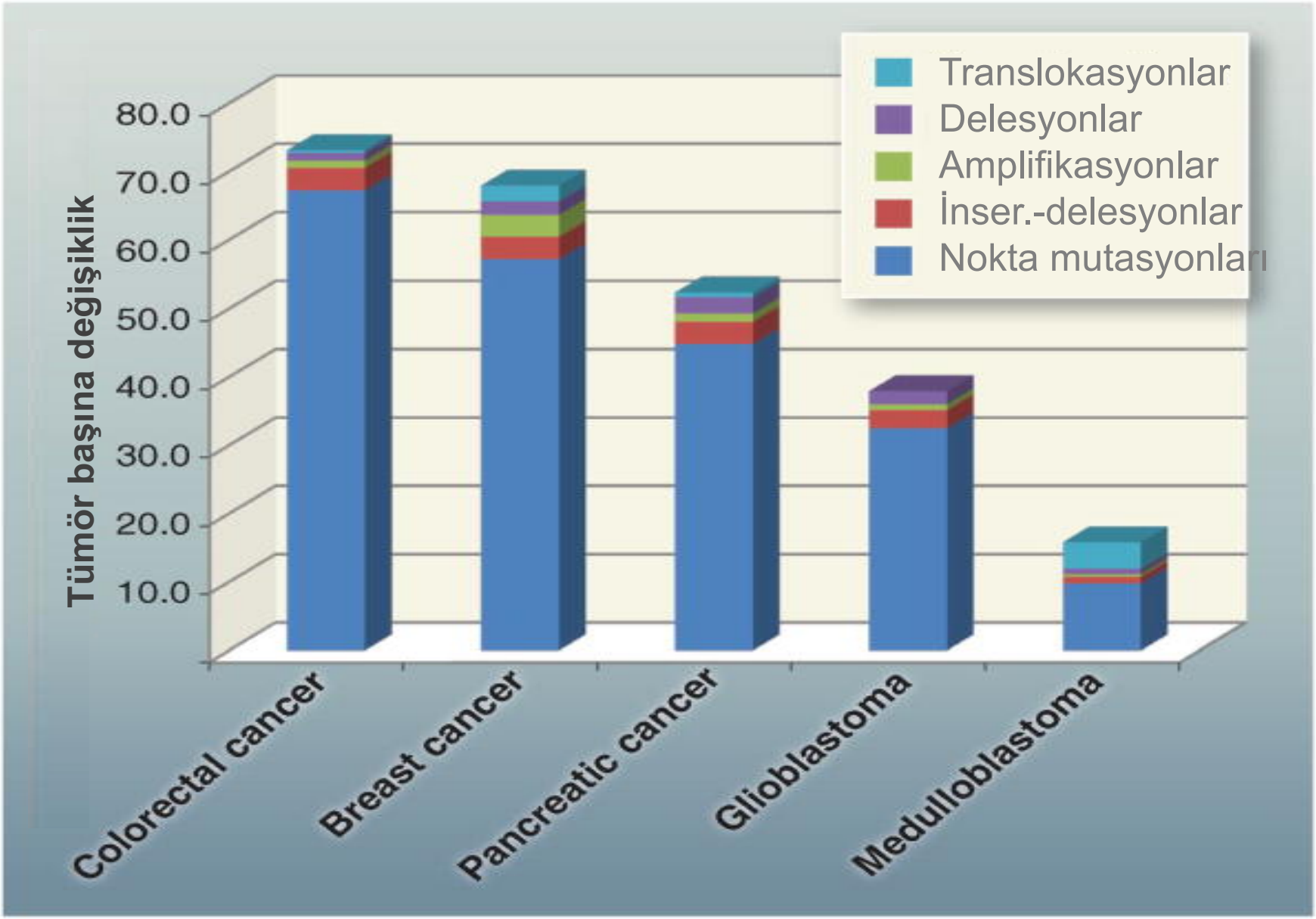


Fig. 5.3 The landscape of the cancer genome: mountains, hills and flatlands. A two-dimensional map of the colorectal cancer genome landscape shows the cancer genes positioned according to their chromosomal locations. Five gene 'mountains' are mutated in a large proportion of tumors, the remaining 'hills' represent genes that are mutated less frequently. This map indi-

Genetik kararsızlık düzeyi en uygun hücreler tümör gelişiminde en başarılı olanlardır.



Bazı tümör örneklerinde protein kodlayan genleri etkileyen değişiklikler



Kanserde
tedavi hedefleri

Geleneksel Kanser Tedavisi:

Hücre çoğalmasını baskılayan iki temel mekanizma üzerinden çalışır

DNA hasarı oluşturma
DNA sentezini engelleme

Modern kanser tedavisi

Moleküler yolaklarda özgün hedefler üzerinden çalışır

Uyaran reseptör ilişkisini bozma
Sinyal iletimini engellemek

Tedavi Hedefleri

Monoklonal antikorlar (-mab)	**Reseptör tirozin kinaz**	ERBB *HER1/EGFR* (Cetuximab, Panitumumab) *HER2/neu* (Trastuzumab)
	Diğer (Solid tümörler)	*EpCAM* *VEGF-A* (Bevacizumab)
	Diğer (lösemi/lenfoma)	Lenfoid *CD20* (Ibritumomab, Ofatumumab, Rituximab, Tositumomab), *CD52* (Alemtuzumab) Myeloid *CD33* (Gemtuzumab)
Tirozin kinaz inhibitörleri (-nib)	**Reseptör tirozin kinaz**	ERBB *HER1/EGFR* (Erlotinib, Gefitinib, Vandetanib) *HER1 ve HER2* (BIBW 2992, Lapatinib, Neratinib) RTK clasIII *CKIT ve PGFR* (Axitinib, Pazopanib, Sunitinib, Sorafenib, Toceranib) *FLT3* (Lestaurtinib) *VEGFR* (Axitinib,Cediranib,Pazopanib,Regorafenib,Semaxanib,Sorafenib,Sunitin Toceranib, Vandetanib)
	Reseptör olmayan tirozin kinaz	*BCR/ABL* (Dasatinib, Imatinib, Nilotinib) *SRC* (Bosutinib) *JAK2* (Lestaurtinib)
Diğer	**füzyon protein**	*VEGF* **F** (Aflibercept)
	ekzotoksin	*IL2* (Denileukin diftitox)

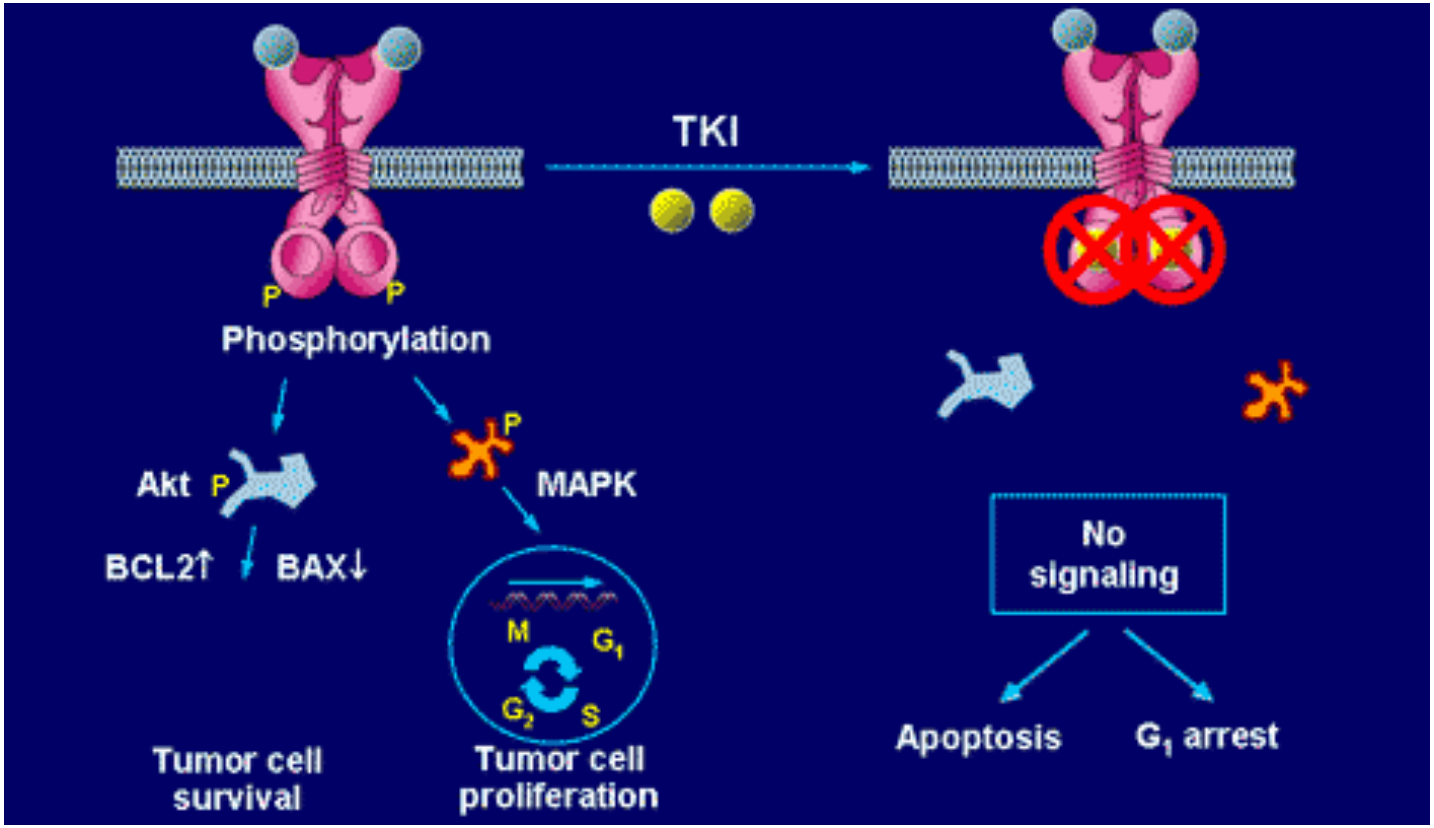
Günümüzde Hedeflenmiş Tedavide Kullanılan İlaçlar

Drug	Tumor type	Target	Detection method
Trastuzumab [3]	Metastatic breast cancer, gastric cancer	HER2	IHC, FISH, ISH
Cetuximab [3]	Metastatic colorectal cancer	EGFR	IHC, FISH
Imatinib Mesylate (Gleevec) [3]	CML, GIST with activated c-kit receptor tyrosine kinase, other sarcomas	Bcr/abl, c-kit, PDGFR,	IHC
Bevacizumab [3]	Colorectal cancer	VEGF	IHC
Gefitinib (Iressa)	Non-small-cell lung cancer	mutant EGFR	Mutational analysis, immunoblotting
G3139 (Genta, Berkley) [3]	Hematologic malignancies and malignant melanoma	Antiapoptotic gene bcl-2	Immunophenotyping by IHC
Erlotinib (Tarveca) [3]	Non-small-cell lung cancer	mutant EGFR	Mutational analysis, immunoblotting
Rapamycin RAD001 [3]	Breast, prostate, renal cancer	mTOR	ELISA
BAY43-9006 [3]	Melanoma	RAF kinase	Mutational analysis
BMS354825 [3]	GIST	Kit	IHC
Lapatinib [5]	Breast cancer	EGFR, HER2	IHC, FISH, ISH
Sunitinib [5]	Renal cell cancer	VEGFR, PDGFR, cKit, Flt-3	IHC
Pertuzumab [4]	Breast cancer	HER2	IHC, FISH, ISH
Dasatinib [4]	Breast cancer	Bcr/abl	RT-PCR

J Cancer 2011; 2:26-35

Trastuzumab (Herceptin)

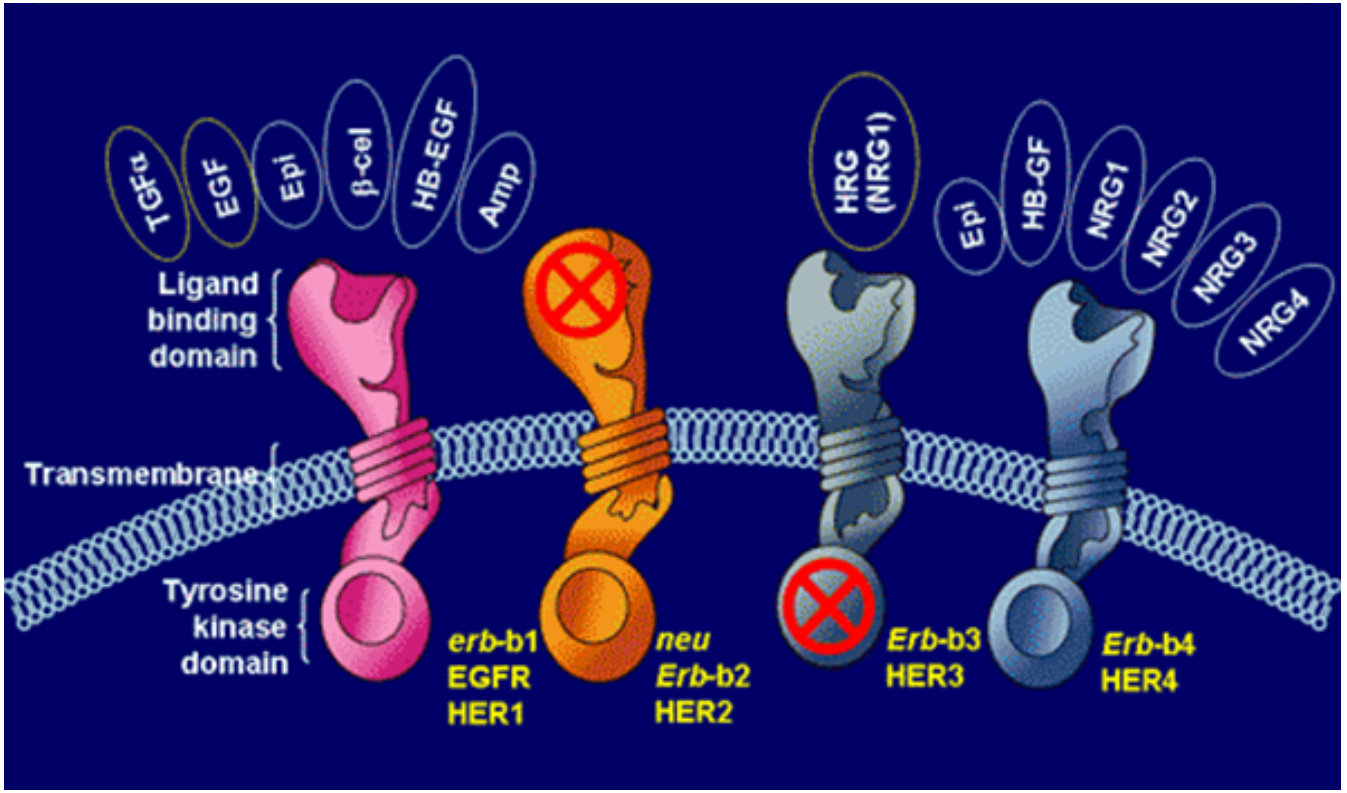
monoklonal antikor



HER2'ye yüksek özgüllüğü olan rekombinant insan monoklonal antikorudur

Moyer et al. *Cancer Res*;57:4838.

ErbB-1: EGFR
ErbB-2: HER2 ya da neu
ErbB-3: HER3
ErbB-4: HER4
ErbB protein ailesini oluşturur

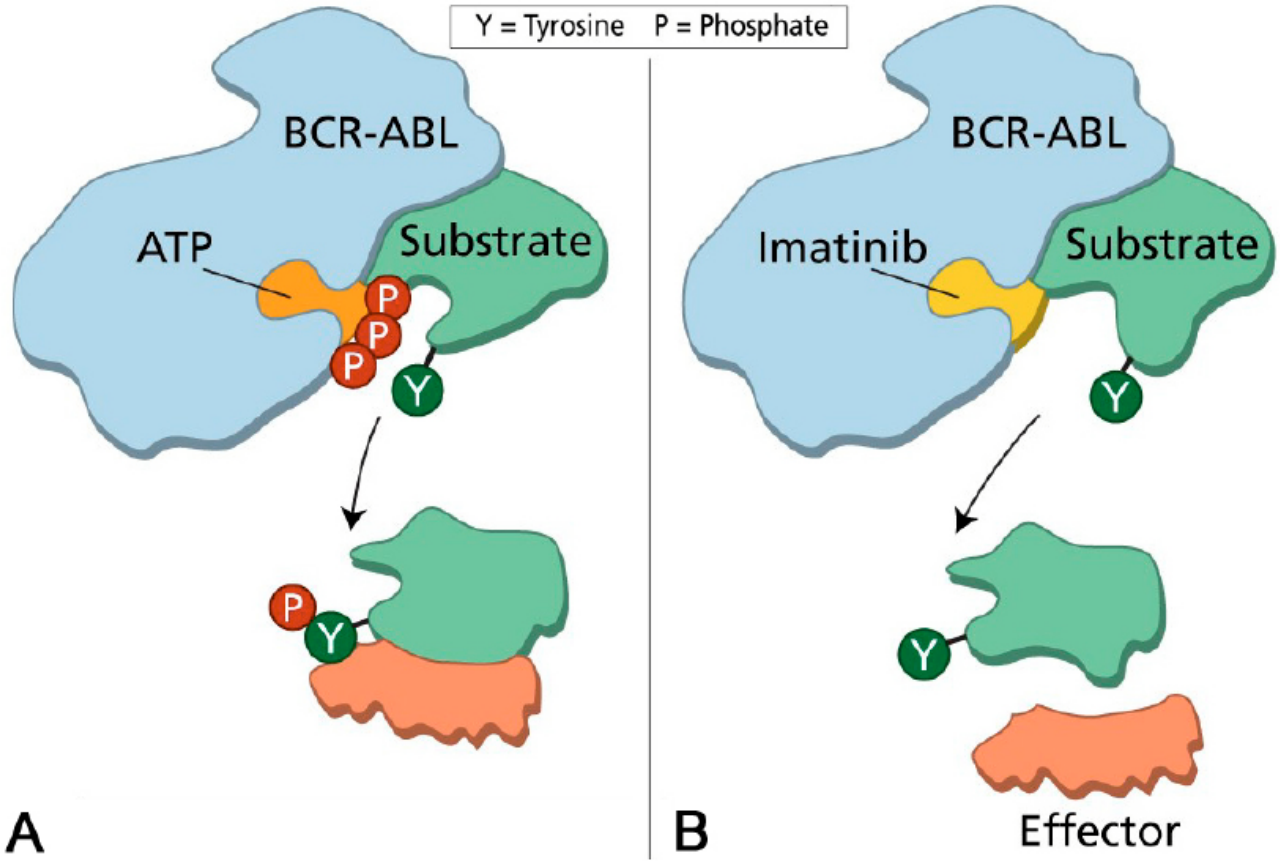


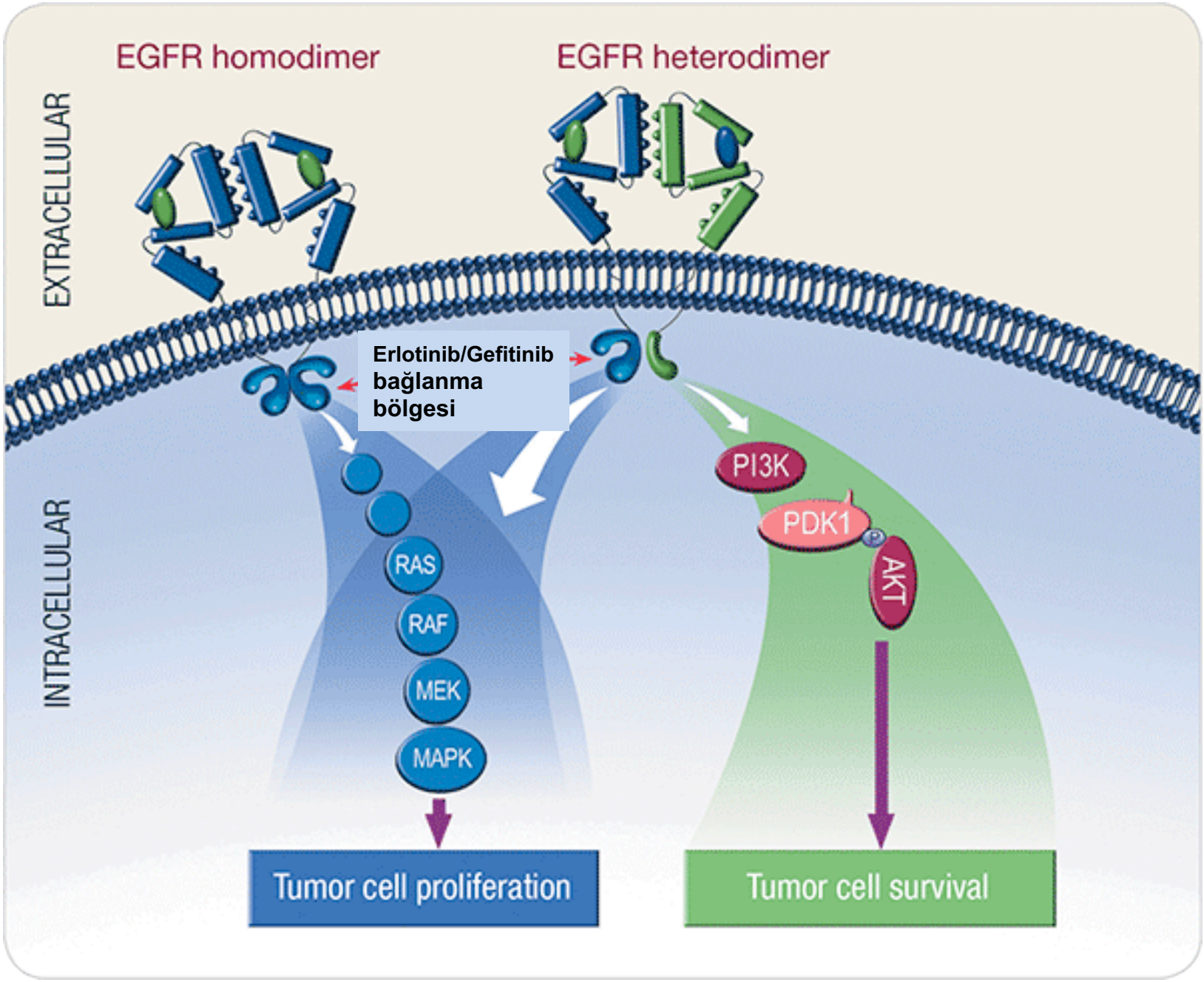
HER2 amplifikasyonu:
primer meme kanserli olguların %15'inde
metastatik kanserlerin %25-30'unda görülmekte

İmatinib

KML ve Gastrointestinal Stromal Tümör (GIST) Tedavisi

Tirozin kinaz inhibitörü




EGFR homodimer
EGFR heterodimer
EXTRACELLULAR
INTRACELLULAR
Erlotinib/Gefitinib bağlanma bölgesi
RAS
RAF
MEK
MAPK
PI3K
PDK1
P
AKT
Tumor cell proliferation
Tumor cell survival

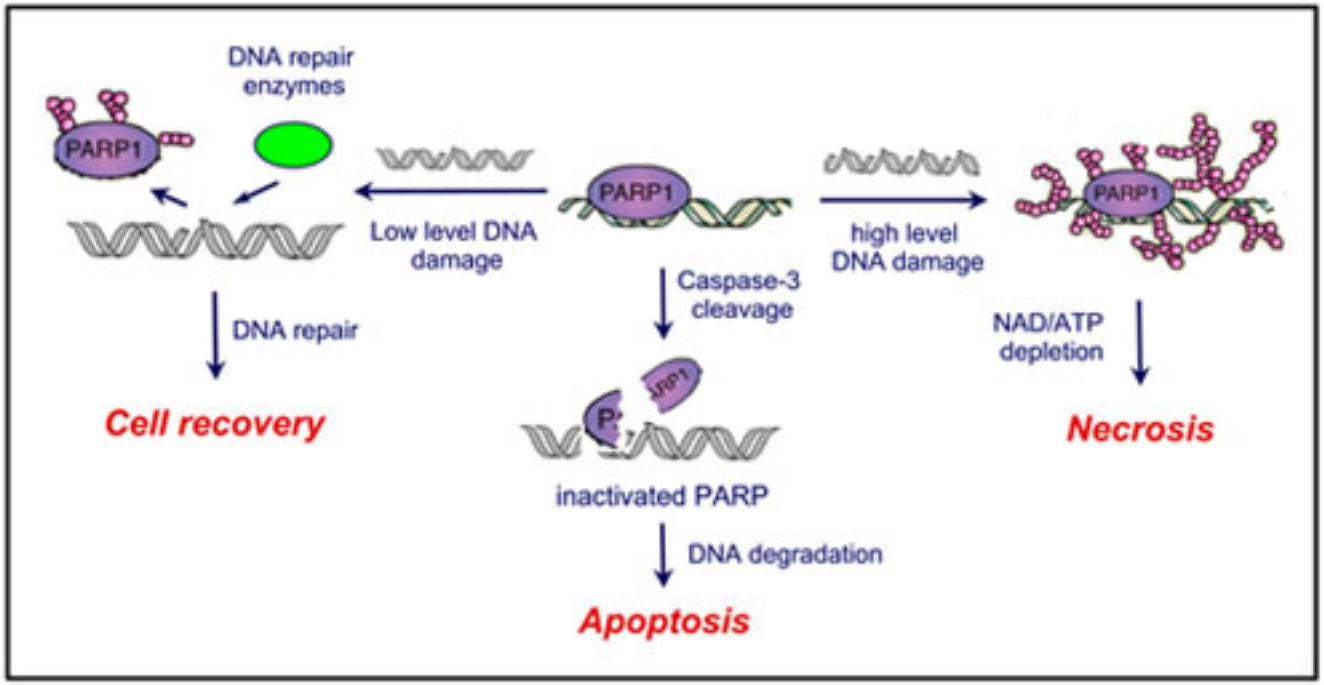
Moleküler hedefleme ile kanser tedavisinde kullanılan ilaç örnekleri

İLAÇ	TÜMÖR	HEDEF
Trastuzumab	Meme kanseri	ERBB2 (RTK) baskılama
Cetuximab	Kolon, baş boyun, vb solid doku tümörü	EGFR (RTK) baskılama
Erlotinib	NSCLC (küçük hücreli olmayan akciğer ca) pankreatik kanserler	EGFR (RTK) baskılama
Gefitinib	NSCLC %10'unda etkili	EGFR (RTK) baskılama
İmatinib	KML, GİST	BCR-ABL, PDGFR
Vemurafenib	İlerlemiş melanom	RAS yolağında BRAF baskılama (V600E mutasyonu varlığında)
Ruxolitinib	Myeloproliferatif hastalıklar	JAK/STAT yolağı - sinyal baskılama
Rapamisin (sirolimus)	Kombine tedavilerde	mTOR yolağı
Rapamisin türevi (everolimus)	İlerlemiş renal kanserler, pankreatik nöroendokrin tümörler	mTOR yolağı
Bevacizumab	İlerlemiş kolon kanserleri, NSCLC, over kanseri, renal kanserler, glioblastoma multiforme	mTOR yolağı ilişkili HIF1a>VEGFA baskılanması
Ramucirumab	ilerlemiş mide ve özofagus kanserleri	HIF1a>VEGFA baskılanması

Direnç nedeni olan genetik değişiklikler

İlaç	Tümör	Direnç mutasyonu
IMATINIB	Gastrointestinal Stromal Tümör (GIST)	cKIT geni EKZON 9, 11, 13 ve 17 mutasyonları
		PDGFRA geni EKZON 12 ve 18 mutasyonları
GEFITINIB	Küçük hücreli olmayan akciğer kanseri (NSCLC)	EGFR geni T790M
TRASTUZUMAB	Meme kanseri	PTEN kaybı
RITUKXIMAB	B-hücreli non-Hodgkin lenfoma (NHL)	FCGR3A
DOXORUBİCİN	Meme kanseri	*MRD1* C3435T
DOXORUBİCİN	Pleomorfik Liposarkom	Uzun telomer

PARP1 inhibitörleri



Olaparib, Rucaparib: BRCA ilişkili meme over kanserlerinde
Niraparib: epitelyal over, primer peritoneal kanserlerde

Baz eksizyon onarımını bozarak etkilidirler

Yapay öldürücü etki

Meme kanserinde PARP inhibisyonu tedavisi

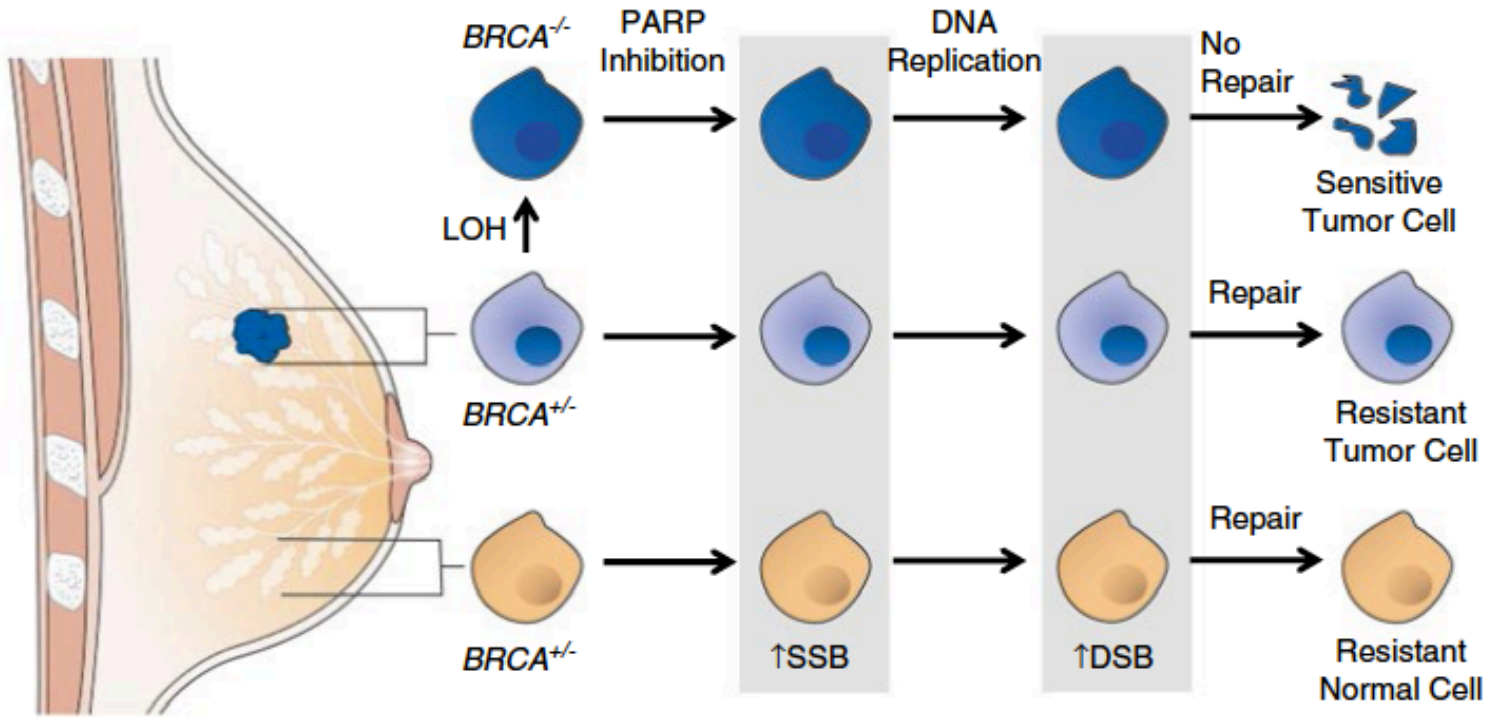


Fig. 8.3 Synthetic lethality of BRCA-deficient cancer cells treated with a PARP inhibitor. Breast cancers arise at an elevated rate in women who harbor heterozygous mutations ($BRCA^{+/-}$) in either *BRCA1* or *BRCA2*. Many tumor cells undergo loss of heterozygosity at the relevant locus and thereby become completely BRCA-deficient ($BRCA^{-/-}$). Systemic treatment with a PARP inhibitor results in the transient accumulation of single-strand breaks (*SSB*) in all cells. During DNA replication, unrepaired SSB are converted to double-strand breaks (*DSB*). Normal cells and tumor cells that retain *BRCA* heterozygosity are capable of repairing DSB via the pathway of homologous recombination. BRCA-deficient cells lack this capability, and will accumulate lethal levels of DSBs. Breast tumor image from Cancer Research UK

YENİ İLAÇ ÇALIŞMALARI ile hedeflenen yolaklar
PIK3/AKT
WNT/APC