PROTEINS INVOLVED IN CELL COMMUNICATION AS TARGET IN TREATMENT

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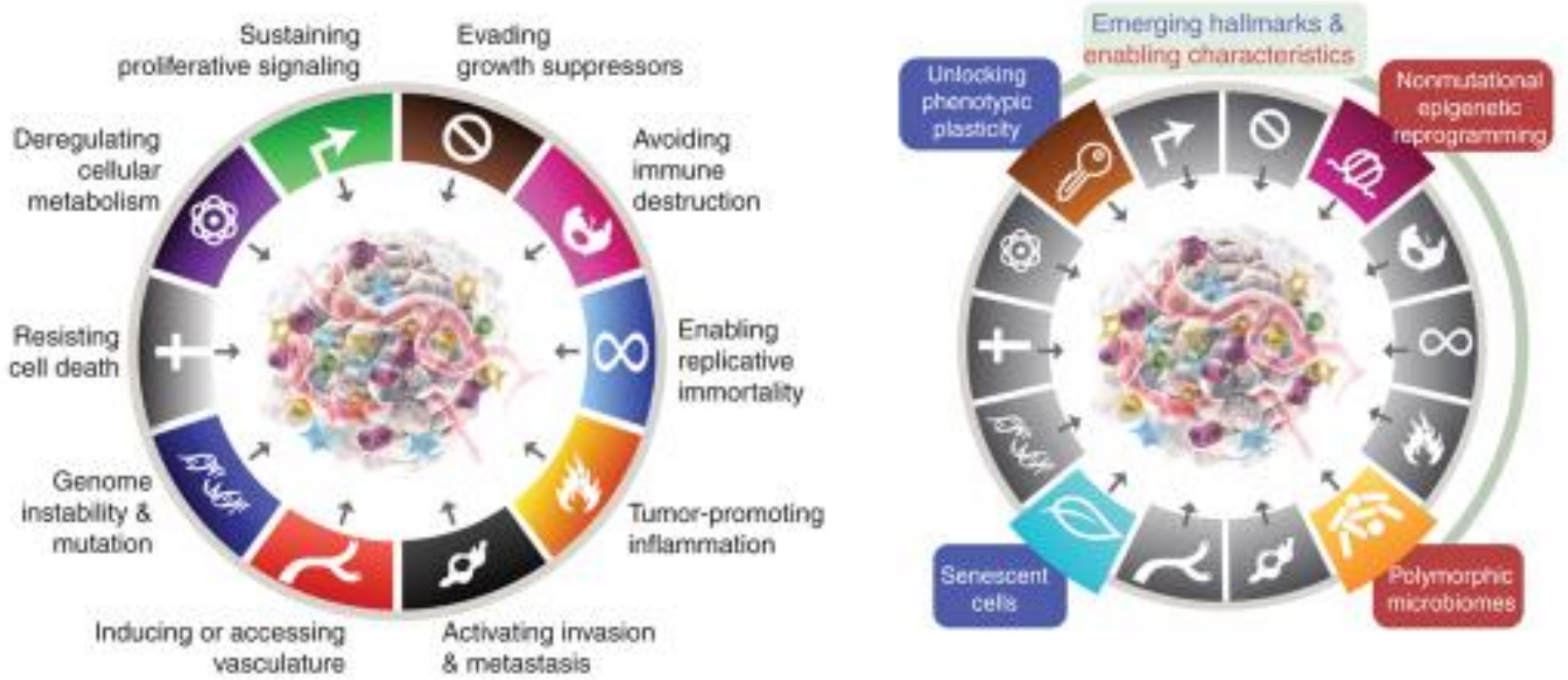
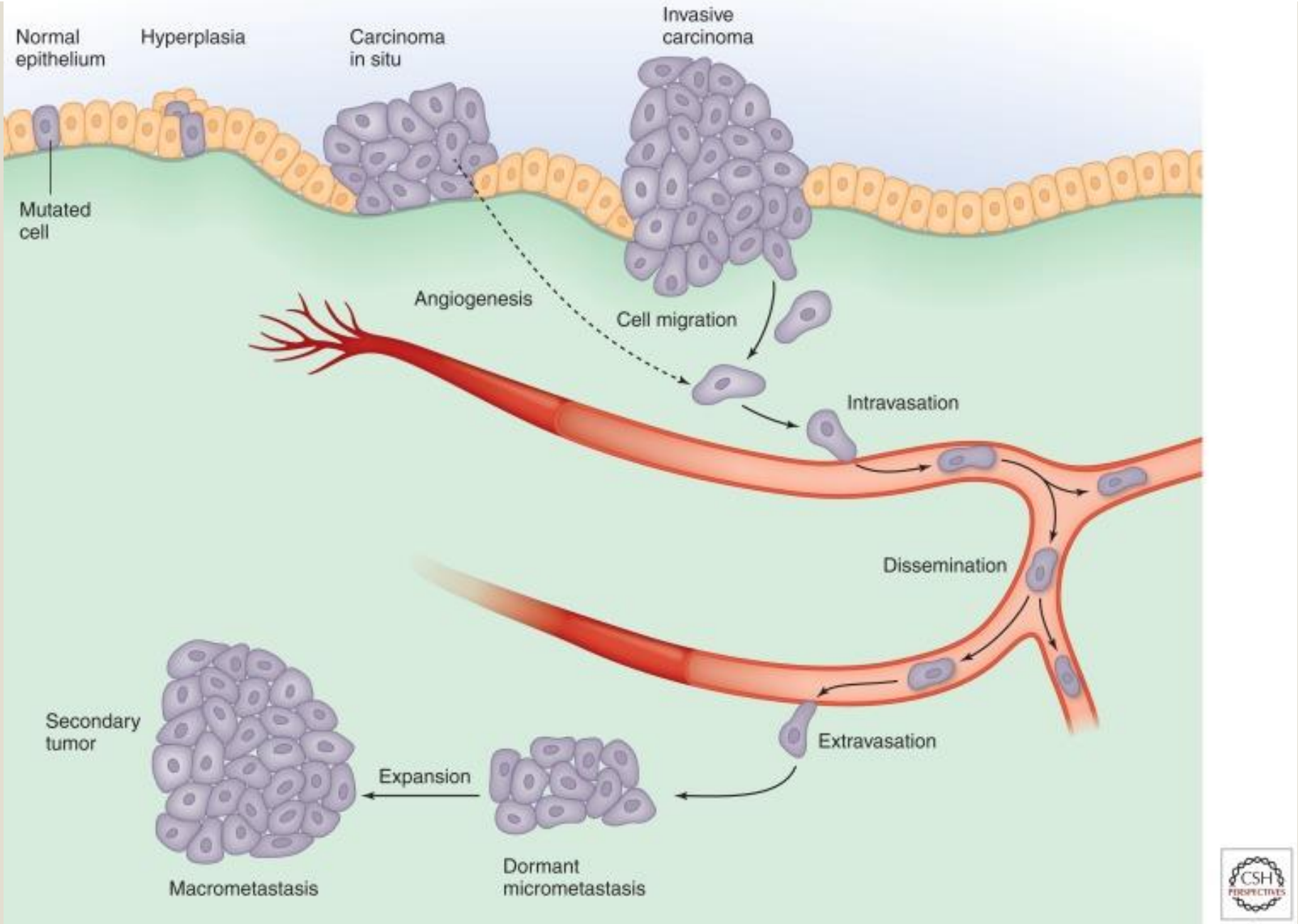
INTRODUCTION

The development of cancer involves successive genetic and epigenetic alterations that allow cells to escape homeostatic controls that ordinarily suppress inappropriate proliferation and inhibit the survival of aberrantly proliferating cells outside their normal niches.

Cancer Discov. 2022;12(1):31-46. doi:10.1158/2159-8290.CD-21-1059




Normal epithelium
Hyperplasia
Carcinoma in situ
Invasive carcinoma
Mutated cell
Angiogenesis
Cell migration
Intravasation
Dissemination
Extravasation
Secondary tumor
Expansion
Macrometastasis
Dormant micrometastasis

Gain of function(GOF)

Complex interplay between the tumor cells and surrounding non-neoplastic cells and the extracellular matrix (ECM).

DNA damage induced by environmental carcinogens or mutations arising from replication errors

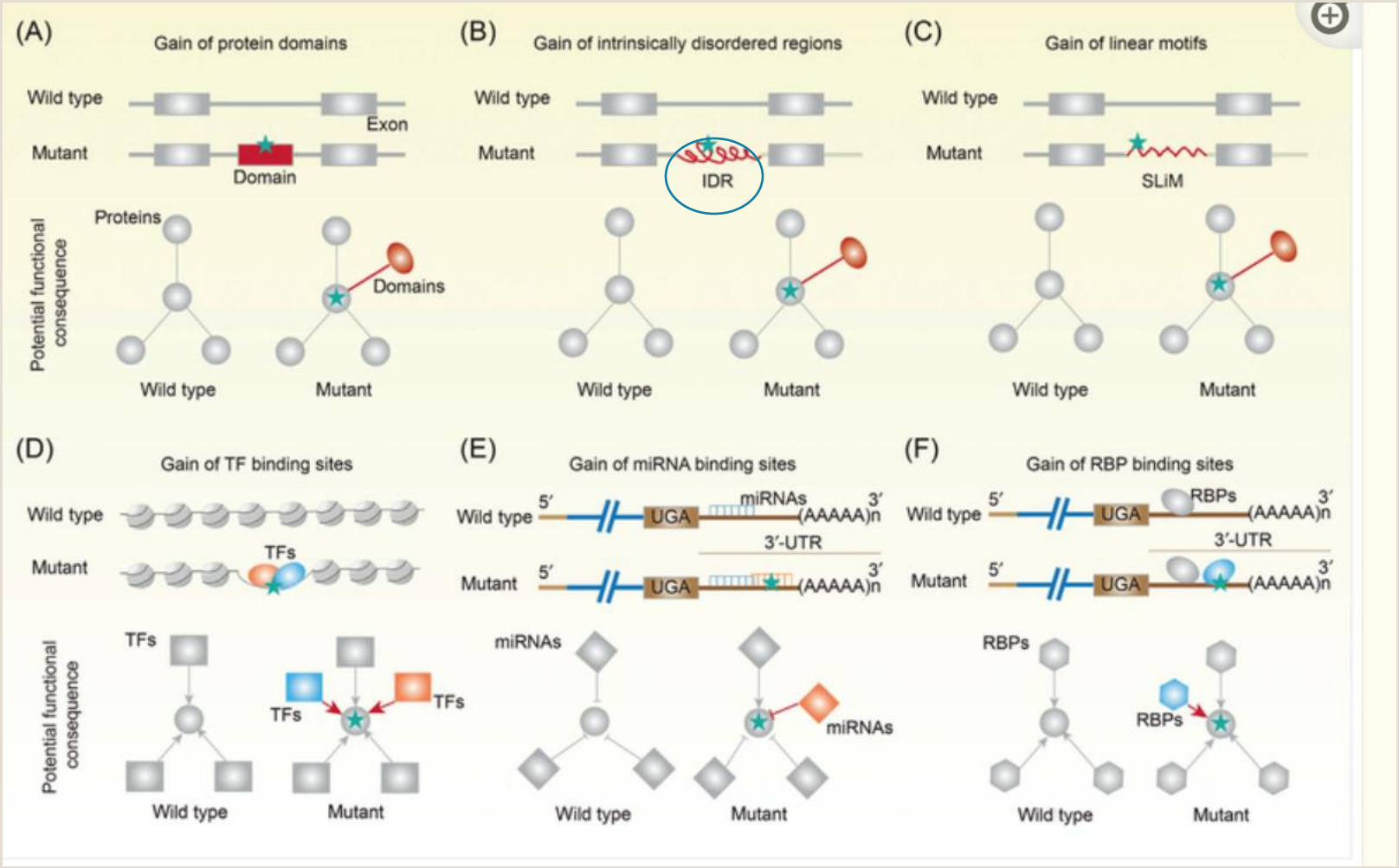
These alterations confer a selective advantage to the cells, which together with changes in the microenvironment, promote tumor growth and progression.

Gain-of-function mutations, producing so-called oncogenes that drive tumor formation.

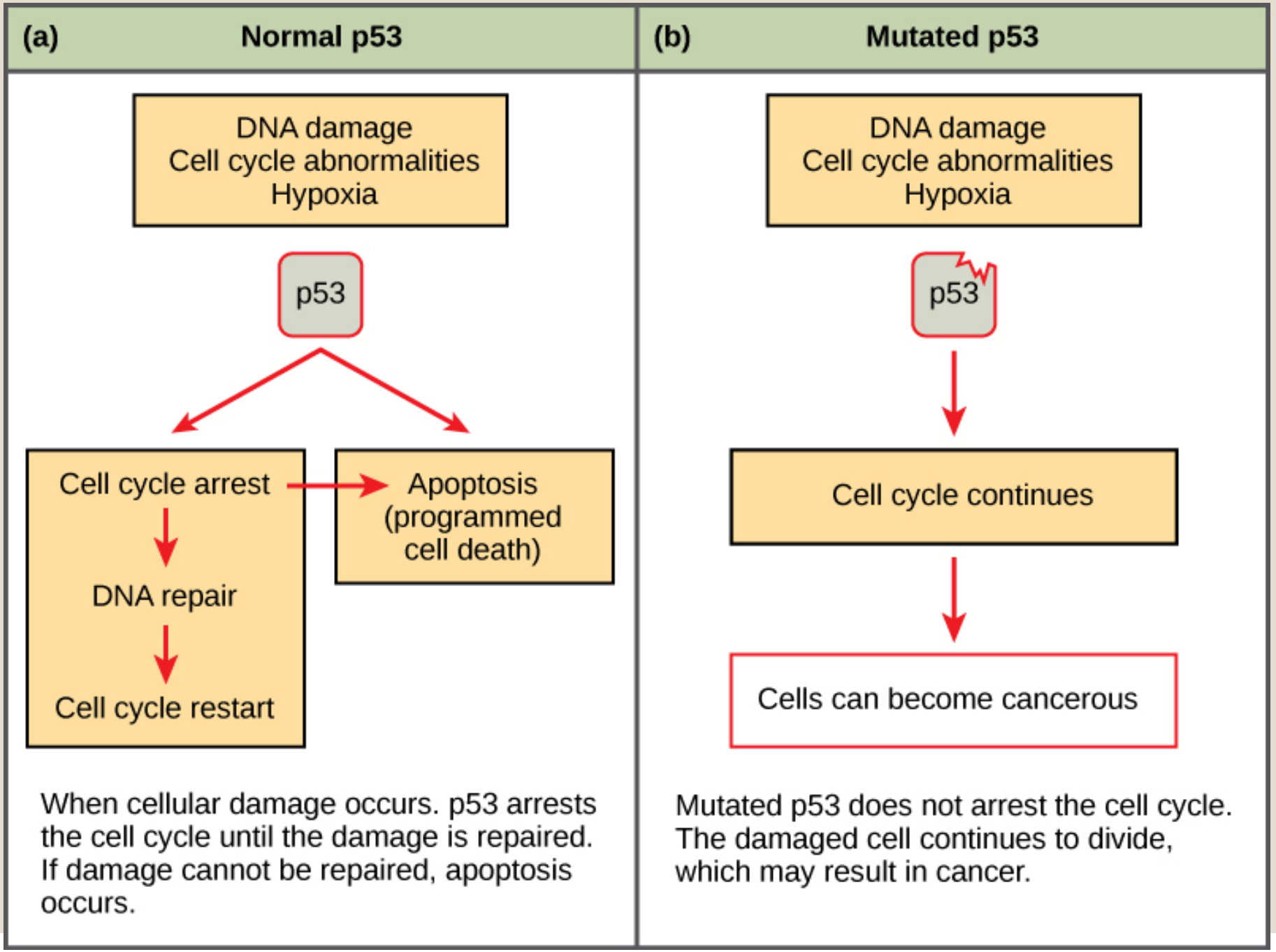
Others inactivate tumor suppressor genes that normally ensure that cells do not proliferate inappropriately or survive outside their normal niche.

GAIN OF FUNCTION MUTATION

- Driver mutation & passenger mutation



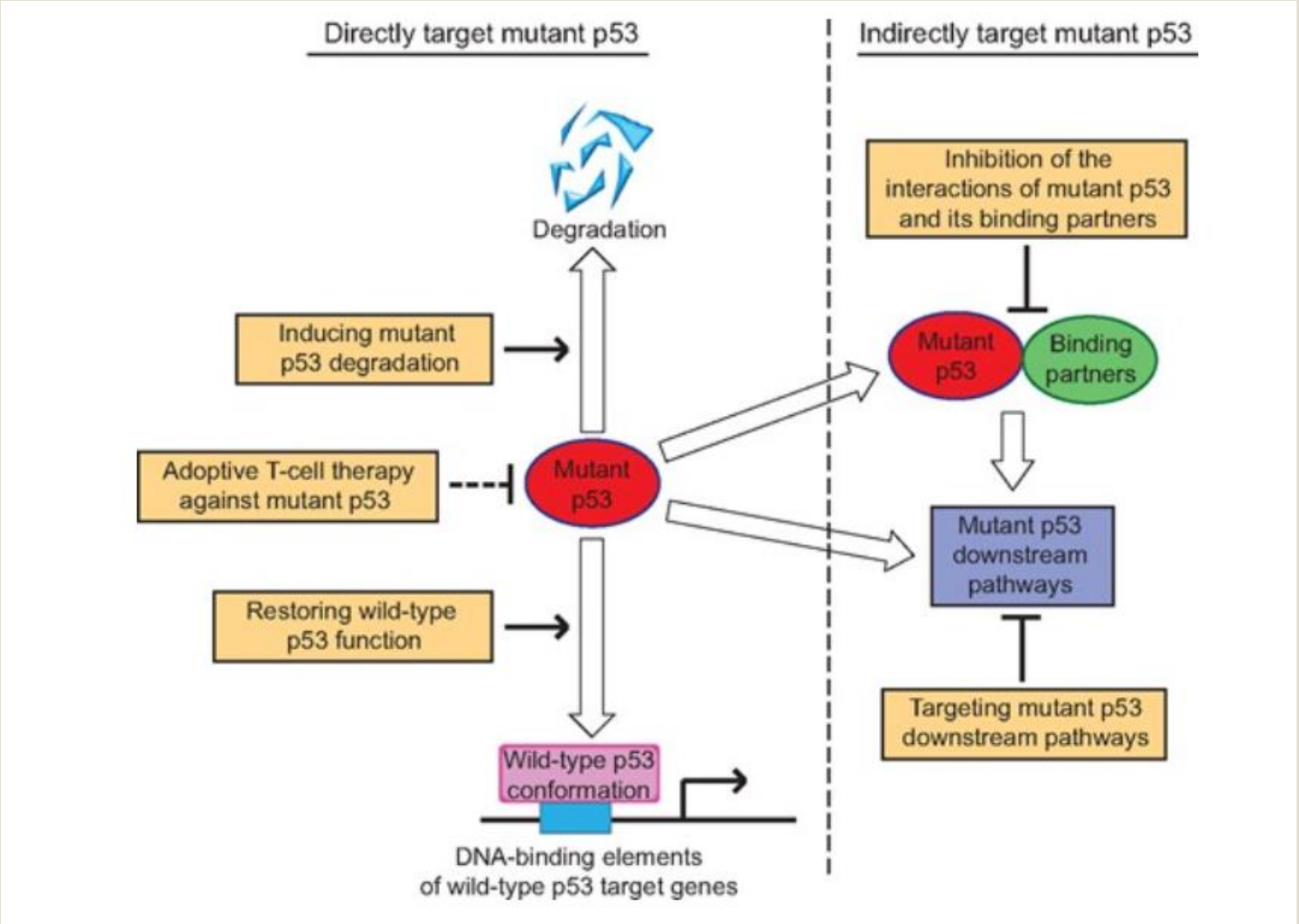
Trends Biochem Sci. 2019 Aug; 44(8): 659–674.


(a)
Normal p53
DNA damage
Cell cycle abnormalities
Hypoxia
p53
Cell cycle arrest
DNA repair
Cell cycle restart
Apoptosis
(programmed
cell death)
When cellular damage occurs. p53 arrests the cell cycle until the damage is repaired. If damage cannot be repaired, apoptosis occurs.
(b)
Mutated p53
DNA damage
Cell cycle abnormalities
Hypoxia
p53
Cell cycle continues
Cells can become cancerous
Mutated p53 does not arrest the cell cycle. The damaged cell continues to divide, which may result in cancer.

GOF-MUTANT P53

- Cell proliferation
- Metastatsis
- Genomic instability
- Cell differentiation and stemness
- Tumour microenvironment and immune response regulation
- Cancer therapy resistance

Journal of Molecular Cell Biology, Volume 12, Issue 9, September 2020, Pages 674–687


Directly target mutant p53
Indirectly target mutant p53
Degradation
Inducing mutant p53 degradation
Adoptive T-cell therapy against mutant p53
Mutant p53
Restoring wild-type p53 function
Wild-type p53 conformation
DNA-binding elements of wild-type p53 target genes
Inhibition of the interactions of mutant p53 and its binding partners
Mutant p53
Binding partners
Mutant p53 downstream pathways
Targeting mutant p53 downstream pathways

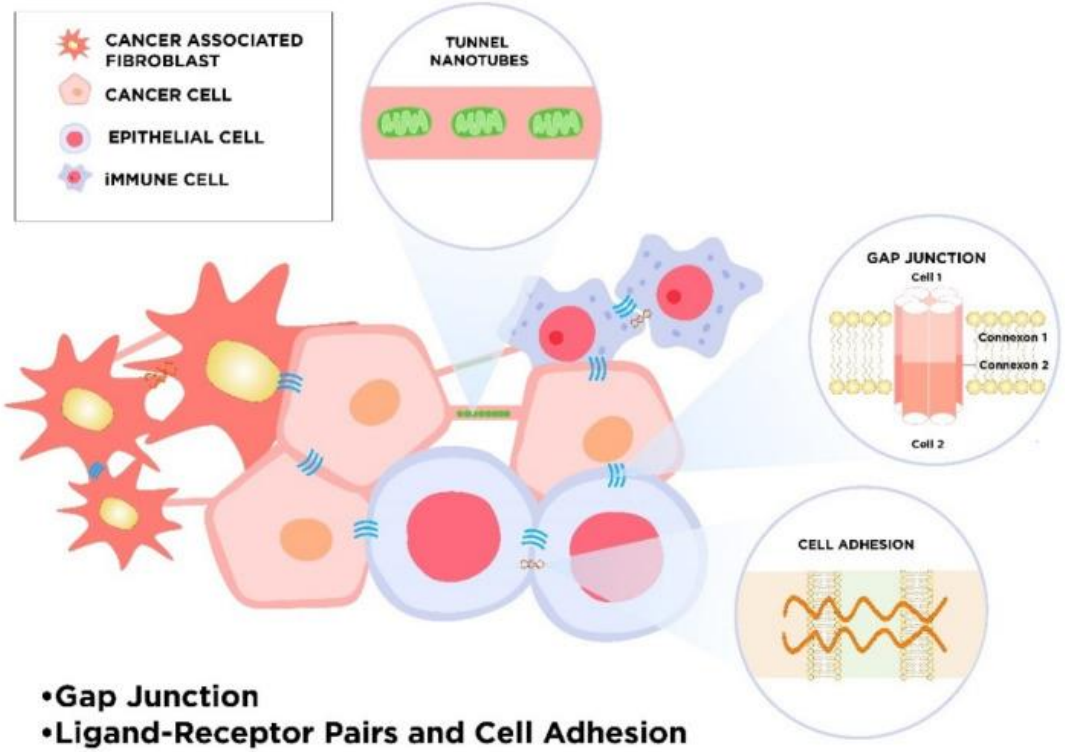
TUMOUR MICRO ENVIRONMENT

Cross-talk within the cancer microenvironment cell-to-cell contact

1. adhesion molecules,
2. electrical coupling
3. passage through gap junctions,
4. indirect through classical paracrine signaling by cytokines, growth factors, and extracellular vesicles.

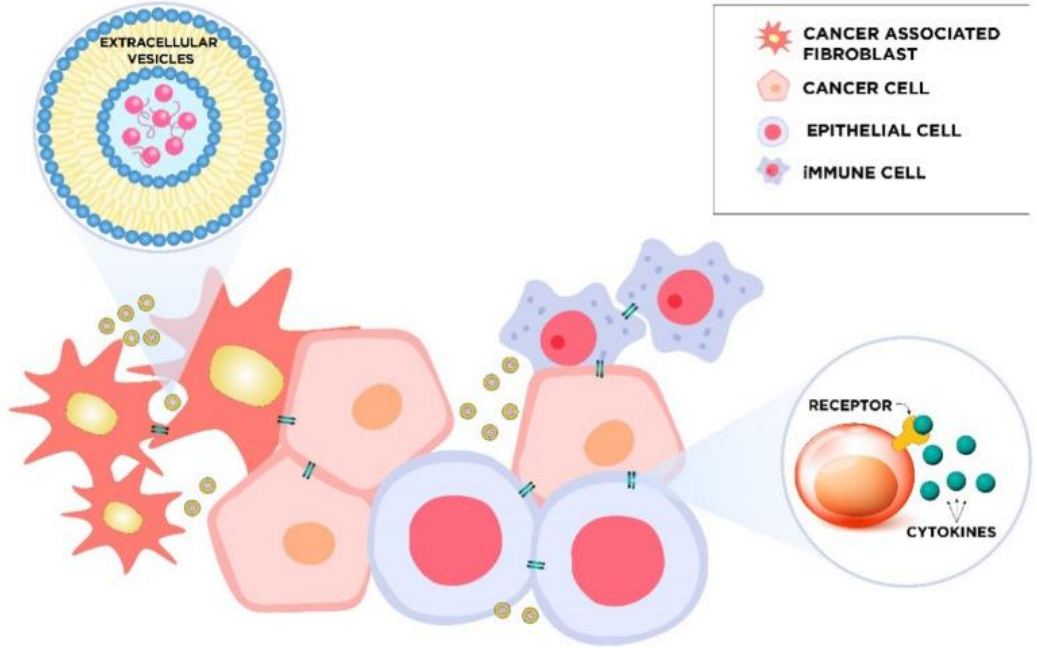
Therapeutic approaches for modulation of cell-cell communication may be a promising strategy to combat tumors.

DIRECT COMMUNICATION

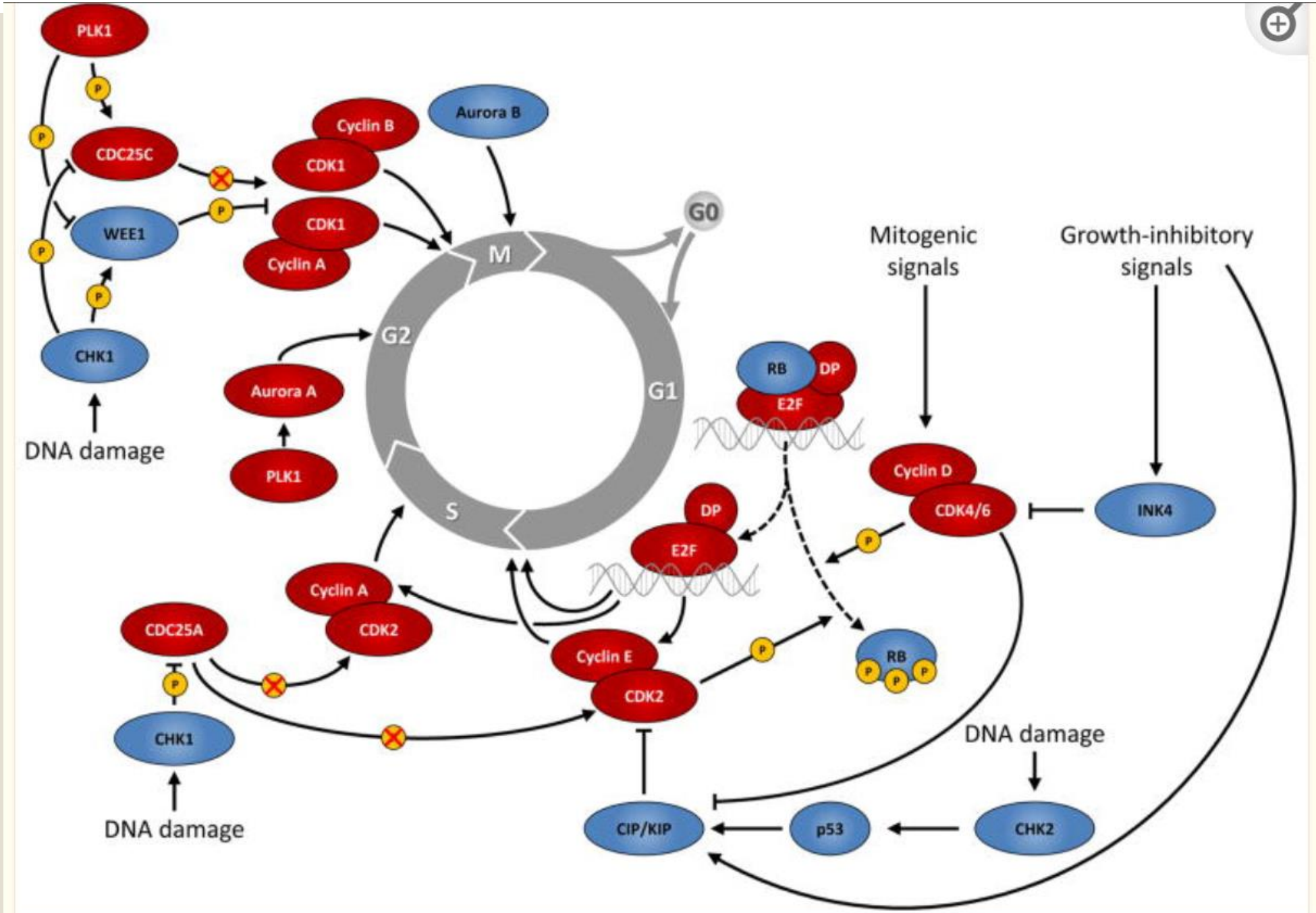


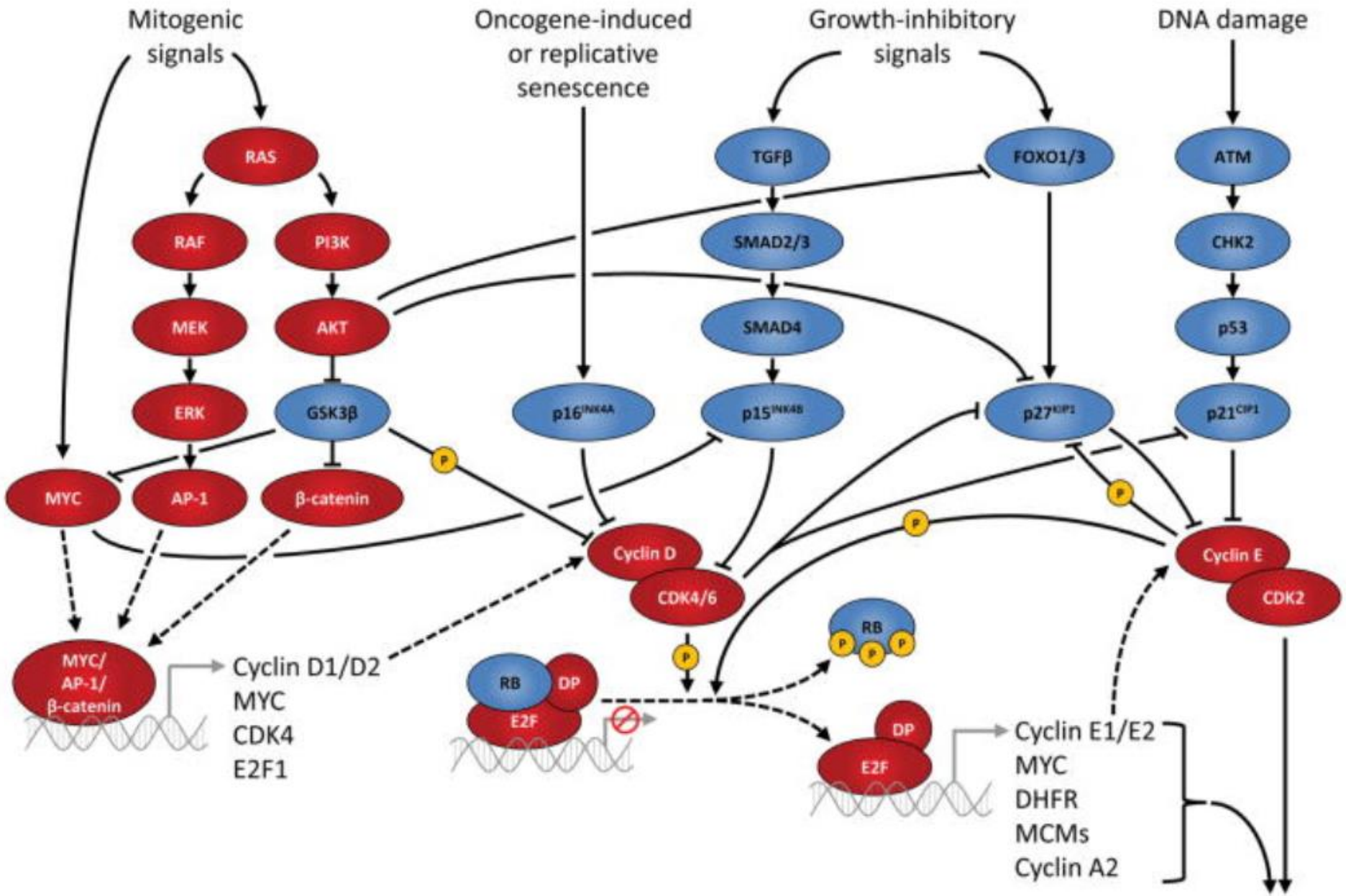
- Gap Junction
- Ligand-Receptor Pairs and Cell Adhesion
- Tunnel Nanotubes

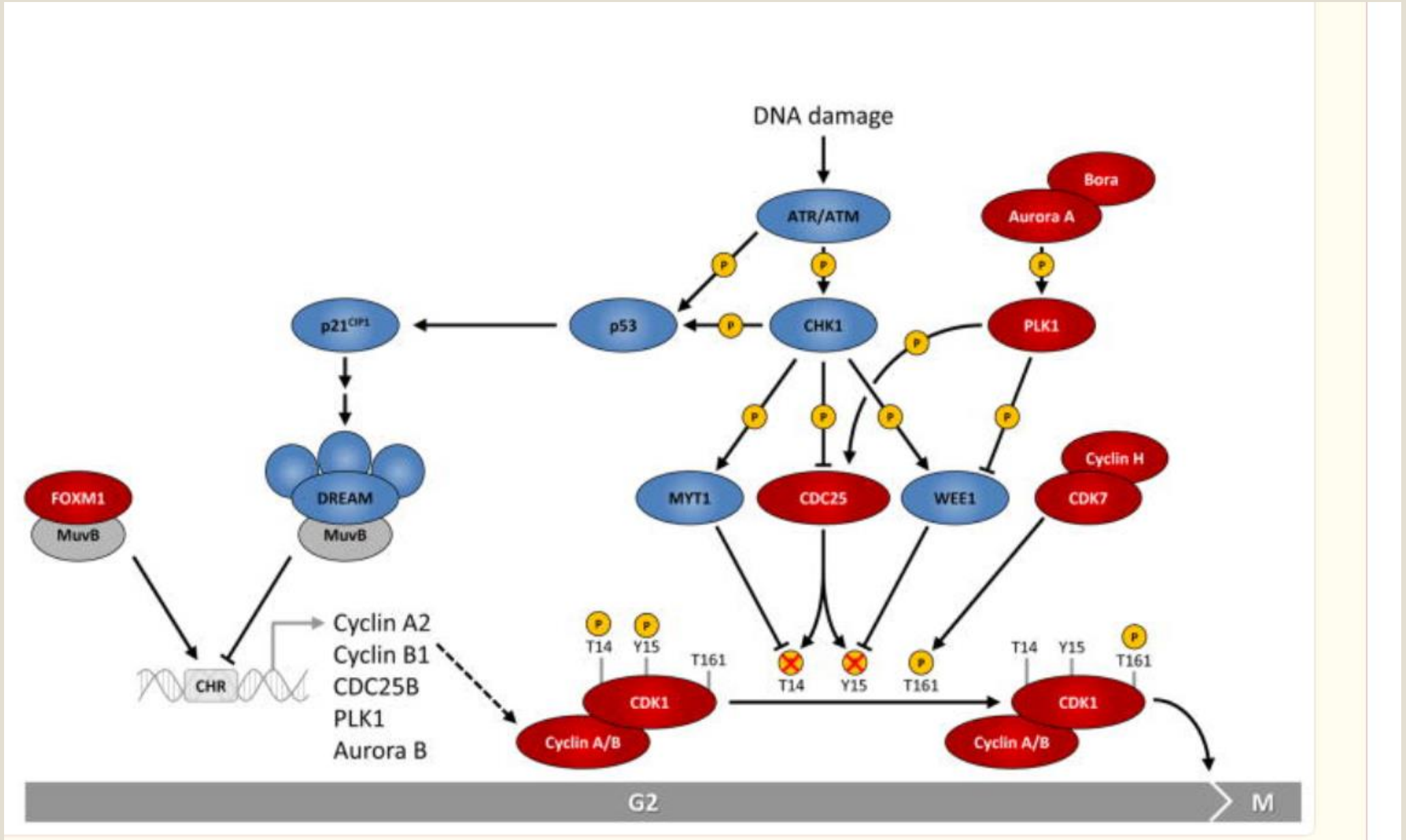
INDIRECT COMMUNICATION

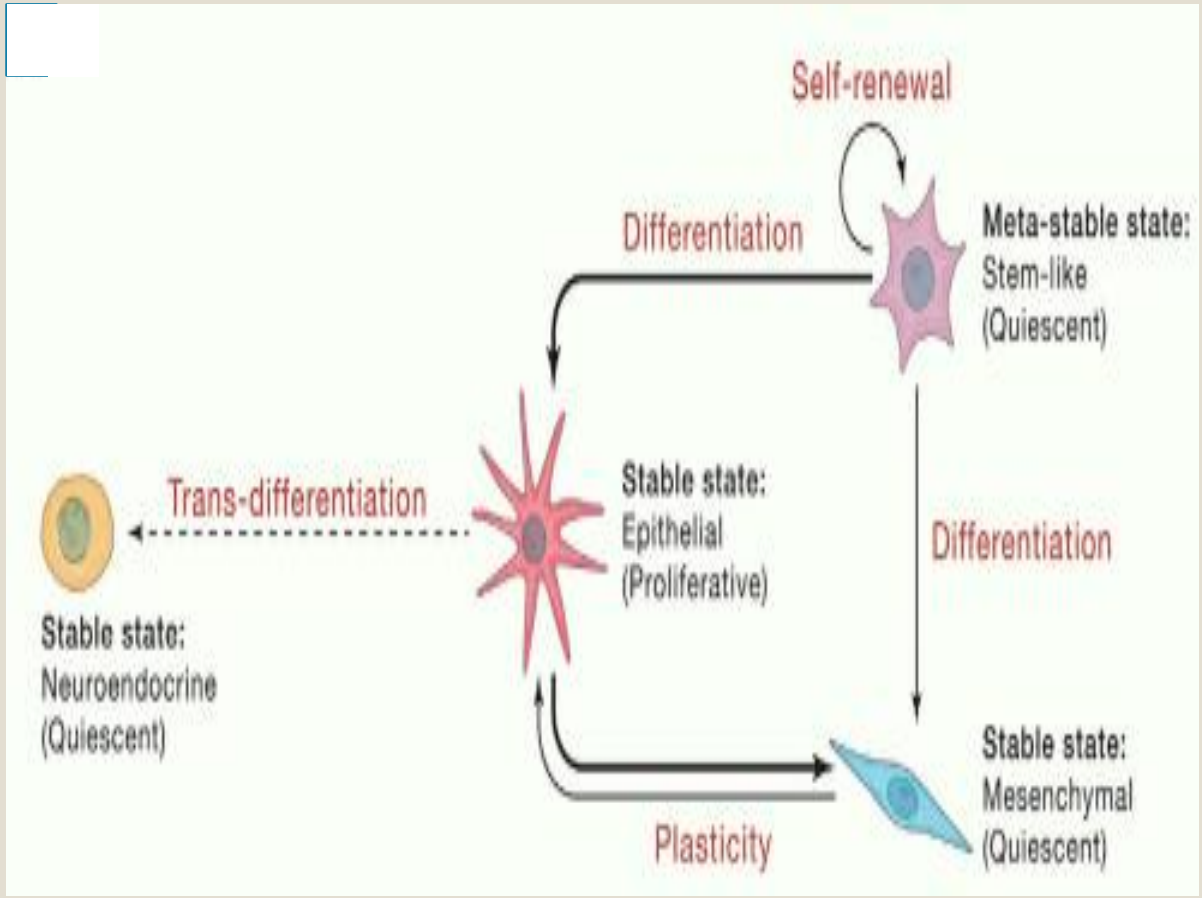


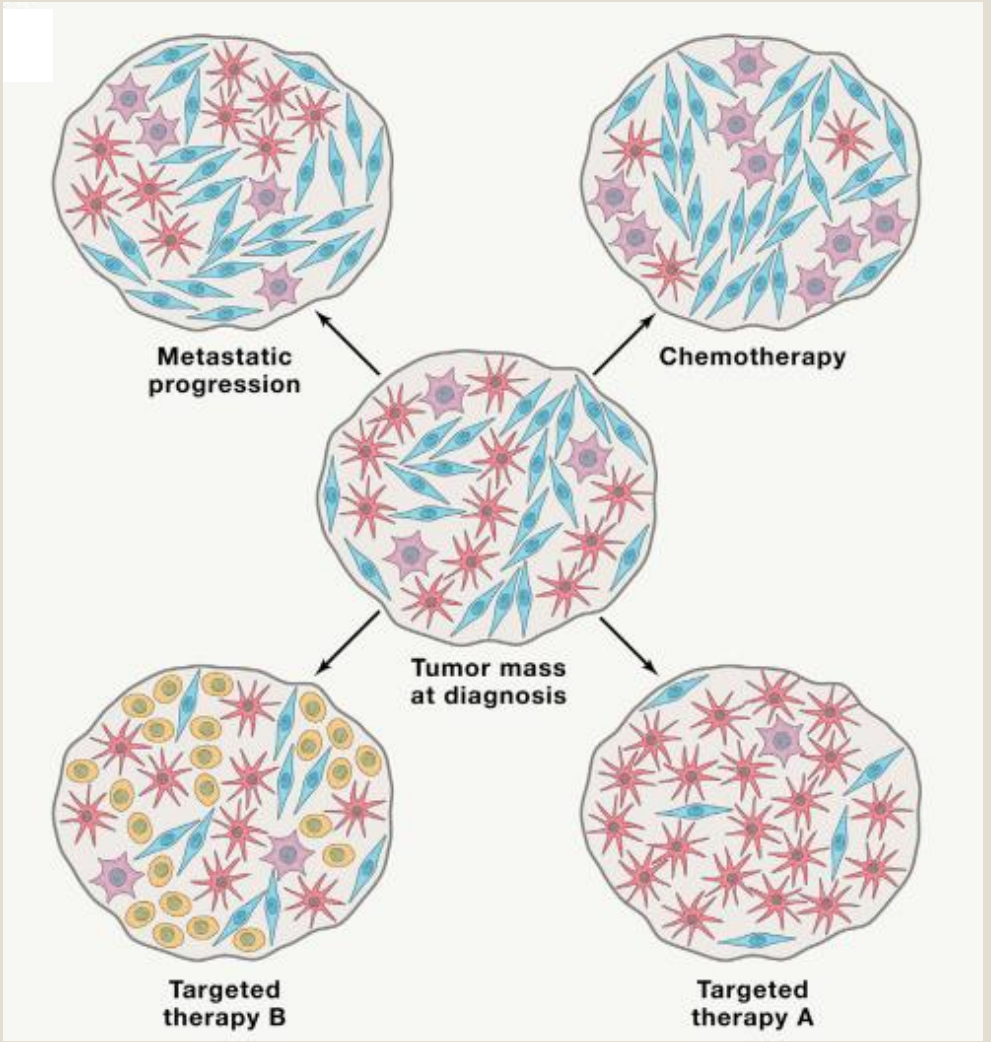
- Signaling by Extracellular Vesicles
- Signaling by Cytokines, Chemokines and Growth Factors
- Metabolites-Mediated Communication


PLK1
P
CDC25C
Cyclin B
CDK1
Aurora B
WEE1
CDK1
Cyclin A
G0
M
G2
G1
S
CHK1
DNA damage
Aurora A
PLK1
RB
DP
E2F
Mitogenic signals
Growth-inhibitory signals
Cyclin D
CDK4/6
INK4
DP
E2F
Cyclin A
CDK2
CDC25A
Cyclin E
CDK2
RB
CHK1
DNA damage
DNA damage
CIP/KIP
p53
CHK2


Mitogenic signals
Oncogene-induced or replicative senescence
Growth-inhibitory signals
DNA damage
RAS
RAF
PI3K
MEK
AKT
ERK
GSK3β
MYC
AP-1
β-catenin
TGFβ
FOXO1/3
SMAD2/3
SMAD4
p16INK4A
p15INK4B
p27KIP1
ATM
CHK2
p53
p21CIP1
P
Cyclin D
CDK4/6
Cyclin E
CDK2
RB
DP
E2F
MYC/ AP-1/ β-catenin
Cyclin D1/D2
MYC
CDK4
E2F1
Cyclin E1/E2
MYC
DHFR
MCMs
Cyclin A2

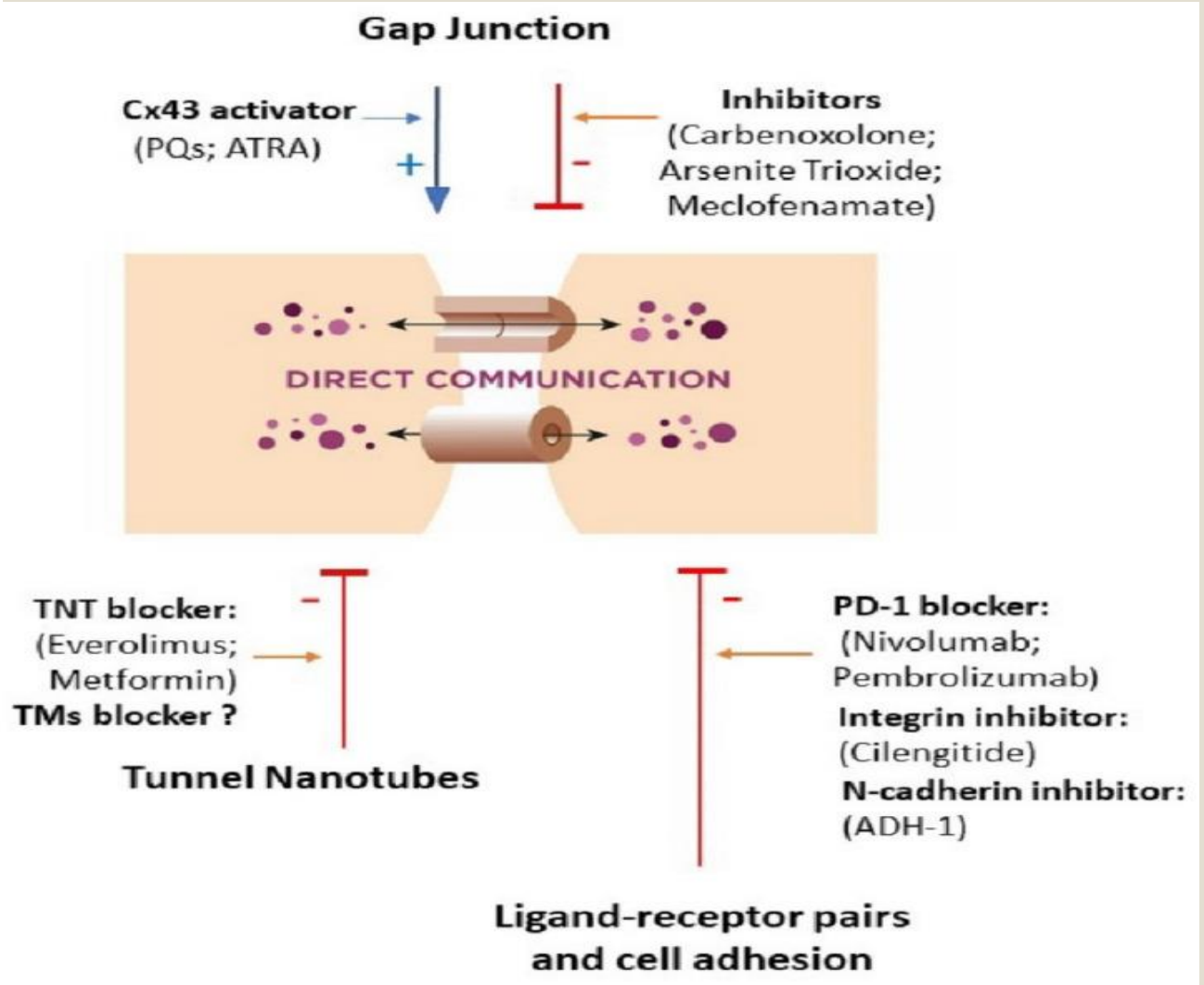

DNA damage
ATR/ATM
Bora
Aurora A
p21CIP1
p53
CHK1
PLK1
FOXM1
MuvB
DREAM
MuvB
MYT1
CDC25
WEE1
Cyclin H
CDK7
CHR
Cyclin A2
Cyclin B1
CDC25B
PLK1
Aurora B
T14
Y15
T161
CDK1
Cyclin A/B
G2
M

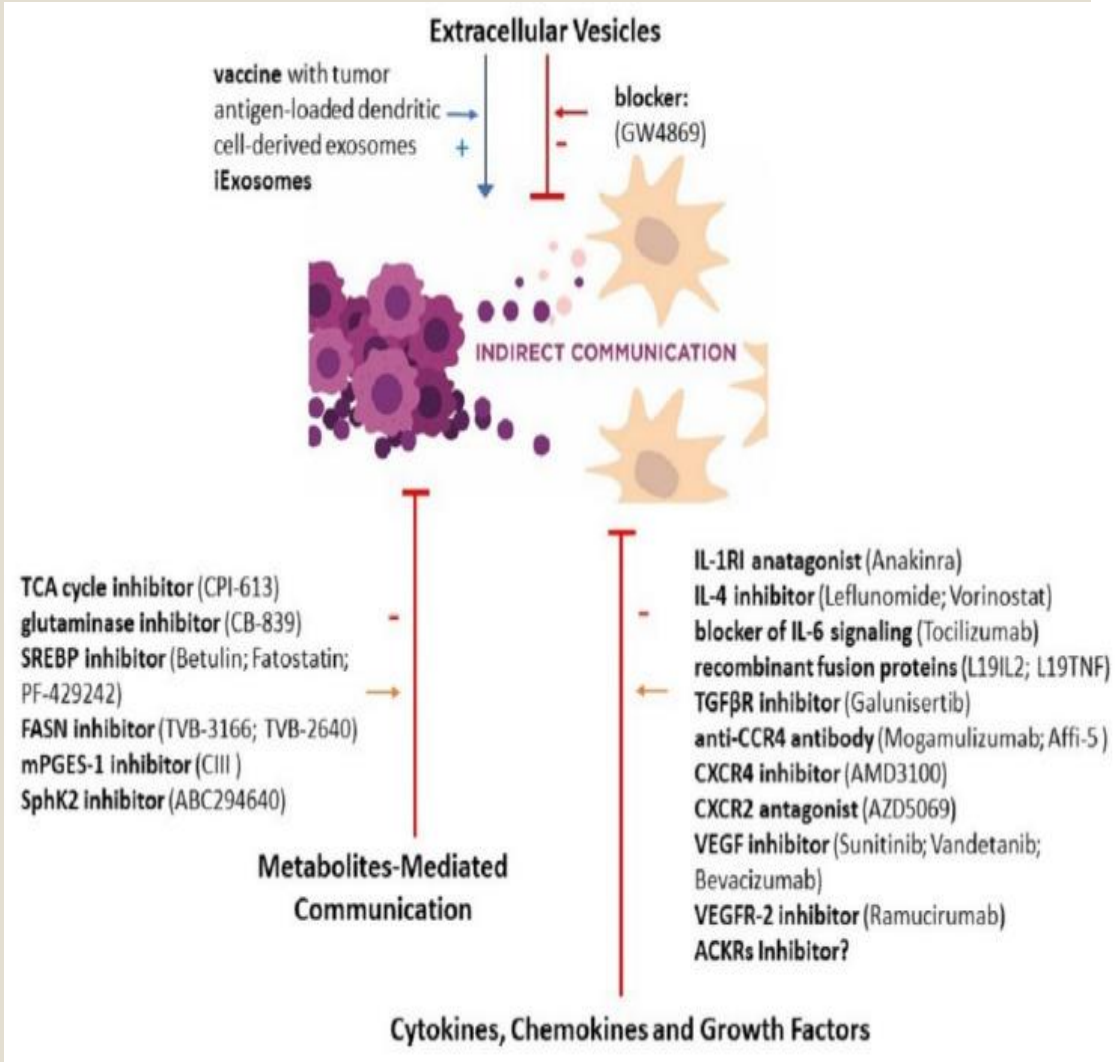

Self-renewal
Differentiation
Meta-stable state:
Stem-like
(Quiescent)
Trans-differentiation
Stable state:
Epithelial
(Proliferative)
Differentiation
Stable state:
Neuroendocrine
(Quiescent)
Stable state:
Mesenchymal
(Quiescent)
Plasticity


Metastatic progression
Chemotherapy
Tumor mass at diagnosis
Targeted therapy B
Targeted therapy A

Communication in the Cancer Microenvironment as a Target for Therapeutic Interventions

Cancers (Basel). 2020 May; 12(5): 1232





Chromatin-regulating proteins as targets for cancer therapy

Journal of Radiation Research, 2014, 55, 613–628

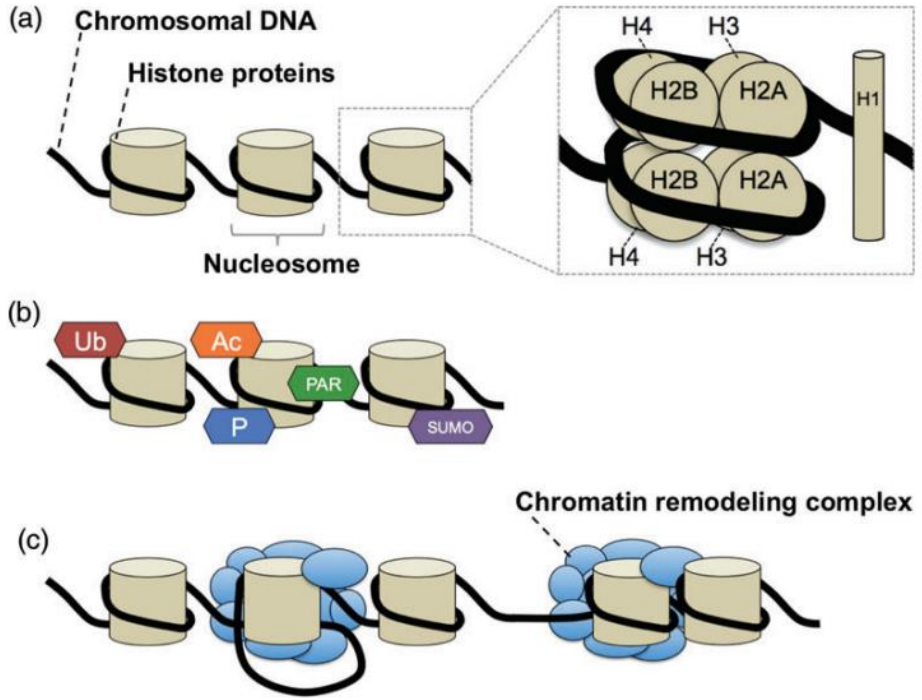


Fig. 1. Chromatin structure and its alteration by two distinct mechanisms: histone modification and chromatin remodeling. (**a**) Structure of chromatin and nucleosome. (**b**) Examples of histone modification. Ac = acetylation, PAR = poly-ADP-ribosylation, P = phosphorylation, SUMO = SUMOylation, Ub = ubiquitination. (**c**) Chromatin remodeling: DNA-loop formation (left) and nucleosome sliding (right).

Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

N Engl J Med 2019; 380:617-628

Rate of pneumonitis T-DM1, at 1.5% compared with 0.7%.(Transtuzumab)

“Radiation related skin injury” was reported in 25.4% of T-DM1 arm, compared to 27.6% on the trastuzumab arm.

Grade 1 and 2 radiation-related skin injury were significantly more common than Grade 3 toxicity, which was noted in 10 patients (1.4%) on the T-DM1, compared to 7 (1%) on the trastuzumab arm.

Cyclin dependent kinase

- The CDK4/6 act at the G_1-to-S cell cycle checkpoint.
- This checkpoint is tightly controlled by the D-type cyclins and CDK4 and CDK6.
- When CDK4 and CDK6 are activated by D-type cyclins, they phosphorylate the retinoblastoma-associated protein (pRb).
- This releases pRb's suppression of the E2F transcription factor family and ultimately allows the cell to proceed through the cell cycle and divide
- CDKs are upregulated by cyclins (A, B, D and E) and downregulated by cyclin-dependent kinase inhibitors such as p16INK4a and p21Cip1

CDK4 &6 INHIBITOR

- PALOMA 3 TRIAL

palbociclib and fulvestrant (an ER antagonist) Vs placebo and fulvestrant for women with ER+ HER2- metastatic breast cancer that have relapsed or progressed during prior hormone therapy, Including a substantial portion of patients (33%) with prior chemotherapy for metastatic disease.

The interim analysis of this study demonstrated a significantly improved median PFS (9.5 months Vs 4.6 months, respectively)

CKI

- Flavopirdol enhance cytotoxicity in glioblastoma cells was with temozolomide
- CKIs suppressing the DNA repair mechanism at the G2/M phase of the cell cycle
- small molecule CGP 75414A induced cell cycle arrest and apoptosis in human leukemic cell lines, and caused a modest G2/M arrest, apoptosis via Poly(ADP-ribose Polymerase (PARP) cleavage and mitochondrial damage in U937 monocytic human cancer cells by inhibiting the activity of CDK2 and CDK4
- small molecule (BA-12 and BP-14) of the roscovitine were shown to induce accumulation of hepatocellular carcinoma cells in G2/M and S/G2 phases of the cell cycle, suggesting that both BA-12 and BP-14 possess antiproliferative activity

Chemical component in peppers, capsaicin (that has known anti-tumor properties), resulted in the degradation of mutated p53 by activating autophagy and lead to cell death in NSCLC cells

Many mutated p53 forms can stimulate (mTOR) and block autophagic processes that could otherwise be tumor suppressive, leading to anti-apoptotic and pro-proliferative responses in breast and pancreatic cancer

small peptides that prevent the ability of mutated p53 to bind to target proteins, and such peptides enhanced the therapeutic effects of adriamycin and cisplatin by inducing apoptosis

Destabilization of mutated p53 complexes could also be achieved in cancer cells using small molecules PK-083 and PK-7088, resulting in activation of pro-apoptotic Noxa expression and apoptosis.

AURORA –A KINASE

Aurora-A regulates cell cycle progression by regulating the spindle and mitotic checkpoints.

Its main functions are mitotic regulation, promotion of mitotic entry, and cell growth arrest .

Overexpression of Aurora-A is linked to breast, ovary, and colon tumors

Moreover, overexpression of Aurora-A has been associated with radio- and chemoresistance in laryngeal cancer cells,cervical cancer and breast cancer.

Aurora-A has been suggested to induce chemoresistance in several cancers by reducing apoptosis via activation of the NF-κB/miR-21/PTEN (phosphatase and tensin homolog) signaling pathway and Akt through inhibition of the p53/PTEN cascade.

AKA-INHIBITOR

- Aurora-A kinase inhibitors currently used in preclinical and clinical studies include MLN8054, PF-03814735, AS703569, MK-0457, MK-5108, MSC1992371A and MLN8237.

- small molecule inhibitors MLN8237 was effective in treating acute myelogenous leukemia and chronic myelogenous leukemia in Phase II trials when used in combination with cytarabine and nilotinib

- Another Aurora-A kinase inhibitor, MK-5108 (Phase I), inhibits cell growth and induces G2/M arrest in chemoresistant epithelial ovarian cancer stem cells by affecting the NF-κB pathway

BRCA

- . The BRCA1/2 cell cycle checkpoint control, chromosome remodeling, transcriptional regulation, DNA repair, and apoptosis.

- BRCA1/2 are essential for both S and G2/M checkpoints in response to DNA damage caused by either radio or chemotherapy, and play important roles in multiple DNA repair pathways such as homologous recombination (HR) and transcription-coupled nucleotide excision repair (TCNER)

- Therefore, BRCA1/2-null cancers are more sensitive to platinum-based DNA damaging agents and to PARP inhibitor

- Mutations in p53 upregulate BRCA1 and induce resistance to cisplatin in breast cancer.
- BRCA1 can activate the transcriptional target TDP2 that pairs with ETS2 and mediates etoposide resistance in mutp53-bearing cells.
- Inhibition of the homologous recombination (HR) pathway proteins RAD52/51 with small molecule D-I03 can specifically inhibit the biochemical activities of RAD52 and suppress growth of BRCA1 and BRCA2 null cells .
- PARP inhibitors are also capable of sensitizing tumor cells with impaired HR activity by genomic instability and cell death.
- Since BRCA1 and BRCA2 mutated cells lack HR pathways, such inhibitors improve the effectiveness of chemotherapy in breast and ovarian cancer treatment.

WNT SIGNALLING

- Upregulation of WNT5A is associated with breast cancer, prostate cancer,melanoma and pancreatic cancer indicating its oncogenic role in these cancers.
- WNT5A is thought to induce chemoresistance in pancreatic cancer through enhanced PI3K/Akt signaling that affects the G1/S phase transition
- WNT5A was highly expressed in BRAF inhibitor (BRAFi)-resistant melanoma tumors [95]. The drug resistance mechanism appears to be that high levels of WNT5A activates signaling through Fzd7 and Ryk receptors that induce PI3K/Akt signaling resulting in increased growth and therapeutic resistance to BRAF inhibitors
- WNT5A activates the WNT/protein kinase C (PKC) signaling pathway that is highly expressed in many cancers and causes chemoresistance by partly activating WNT/β-catenin signaling

- WNT5A knockdown showed an increase of cells in G0/G1 phase and a decreased cell number in S phase, which enhanced the chemosensitivity of pancreatic cancer cells to gemcitabine

- WNT5A contributed to drug-resistance by enhancing anti-apoptosis ability in pancreatic cancer cells

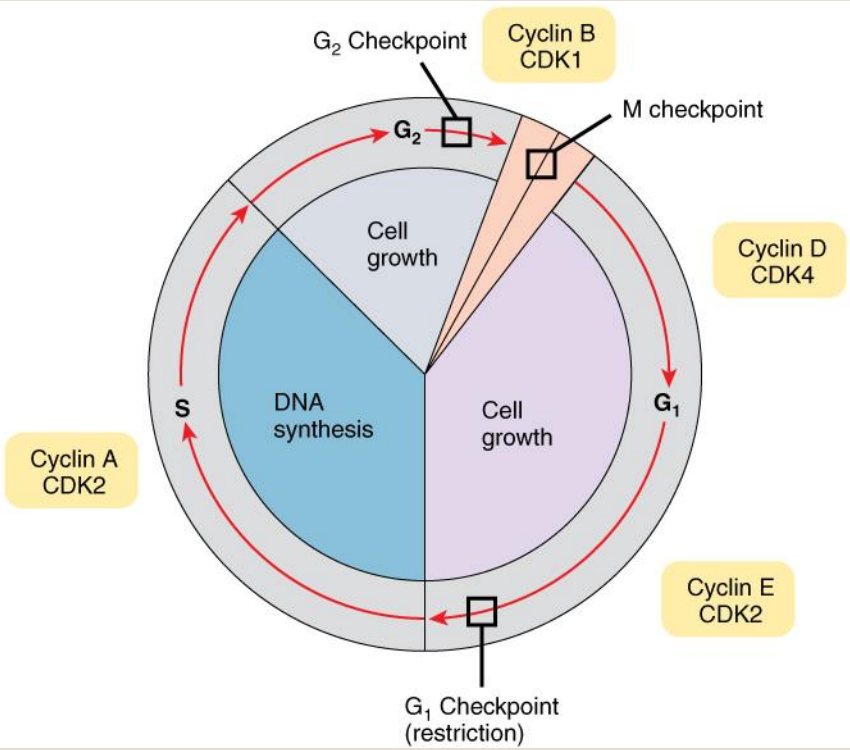
- WNT5A mediated gemcitabine chemoresistance was via the regulation of cell cycle, a target for chemotherapeutic response in pancreatic cancer.

Concurrent use of palbociclib and radiation therapy: single-centre experienceand review of the literature
British Journal of Cancer **volume 123**, pages905–908 (2020

	CDK4/6 inhibitor	Patients	Number of irradiated sites	Location metastasis	LR	RT suspension required	CDKi suspension required	Grade 2 non-haematologic toxicities	Grade ≥ 2 haematologic toxicities
Hans et al.[3] (6)	Palbociclib	5	5	Bone (4), visceral (1)	0	0	0	0	5 (100%)
Meattini et al.[4] (11)	Ribociclib	5	8	Bone (5) and visceral (3)	0	0	2 (40%)	2 (25%)	1 (20%)
Kawamoto et al.[8] (7)	Palbociclib	1	1	Bone (1)	0	1 (100%)	1 (100%)	1 (100%)	na
Kalash et al.[9] (8)	Palbociclib	3	3	Lung (3)	0	3	3 (100%)	3 (100%)	na
Chowdhary et al.[5] (12)	Palbociclib	16	23	Bone (18), brain (4) and visceral (1)	0	0	0	0	na
Messer et al.[10] (15)	Palbociclib	1	1	0	1 (L4)	1 (100%)	1 (100%)	1 (100%)	na
Figura et al.[6] (13)	Palbociclib and abemaciclib	15	42	Brain (42)	0	0	0	2 (5%)	na
Ippolito et al.[7] (14)	Palbociclib and ribociclib	16	24	Bone (23)	1 (IMC)	2 (12%)	1 (6%)	1 (4%)	31%
Our study (2019)	Palbociclib	30	35	Bone (24) and brain (2)	9	2 (6%)	3 (10%)	3 (8%)	8 (26%)

LR locoregional, *IMC* intermammary chain, *CDKi* CDK inhibitor.

check point inhibitor



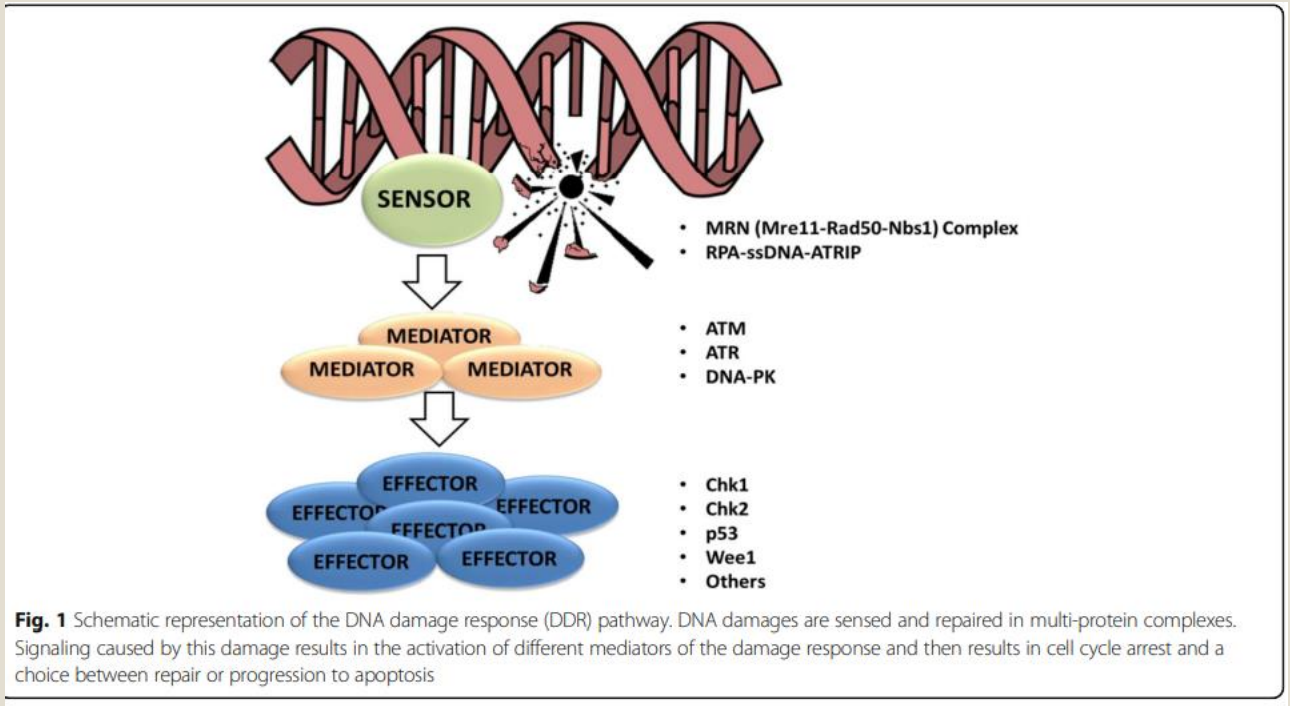


Fig. 1 Schematic representation of the DNA damage response (DDR) pathway. DNA damages are sensed and repaired in multi-protein complexes. Signaling caused by this damage results in the activation of different mediators of the damage response and then results in cell cycle arrest and a choice between repair or progression to apoptosis

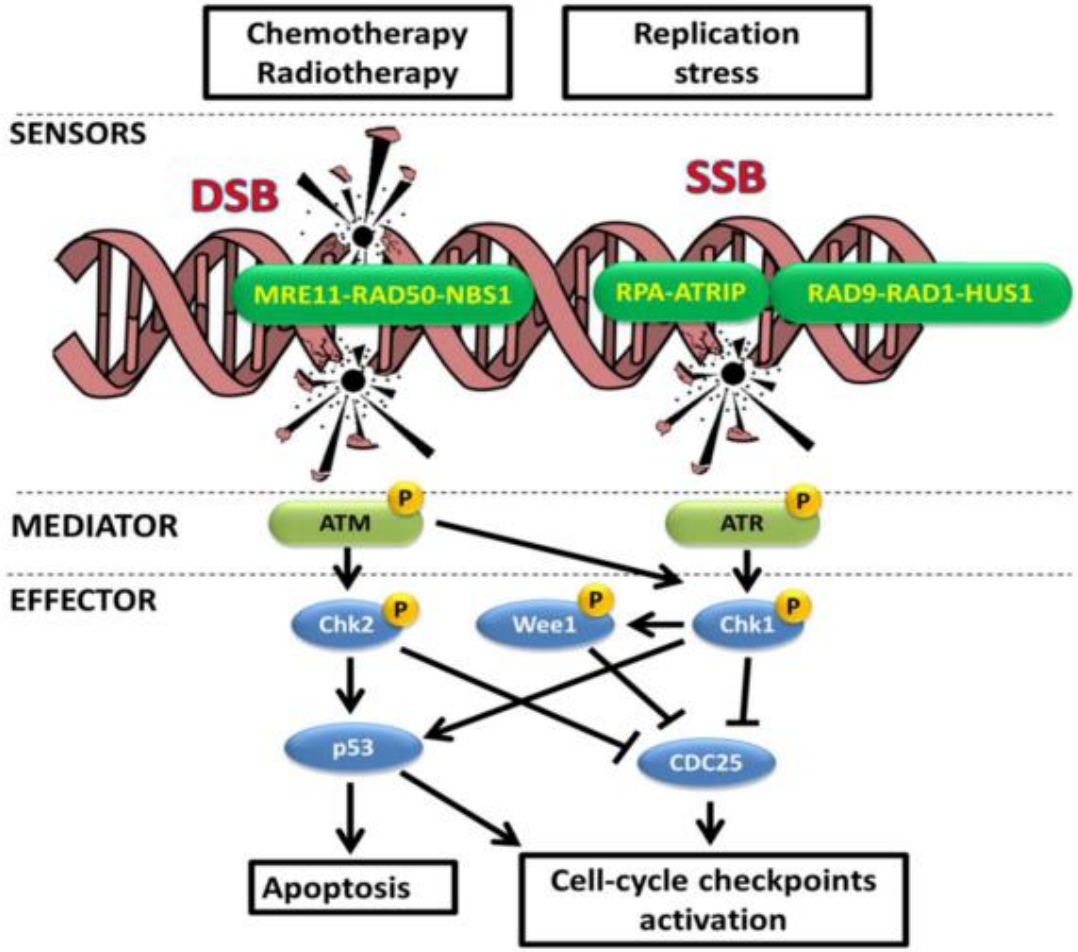


Fig. 2 DNA damages sensor and mediators in the response to DSBs and SSBs. DNA damages trigger the recruitment of specific damage sensor protein complexes. On one hand, the MRN (MRE11–RAD50–NBS1) complex is required for the activation of ataxia-telangiectasia mutated (ATM) in response to double-strand breaks (DSBs). On the other hand, the ATM- and Rad3-related (ATR)-interacting protein (ATRIP) complex, formed by ATR-ATRIP-9-1-1 complex, is recruited to sites of single-strand breaks and activates ATR. The activation of ATM and ATR promotes respectively the activation of two different effectors, CHK2 and CHK1. Although currently, the activator of WEE1 is unknown, it is believed that CHK1 promotes WEE1 activation

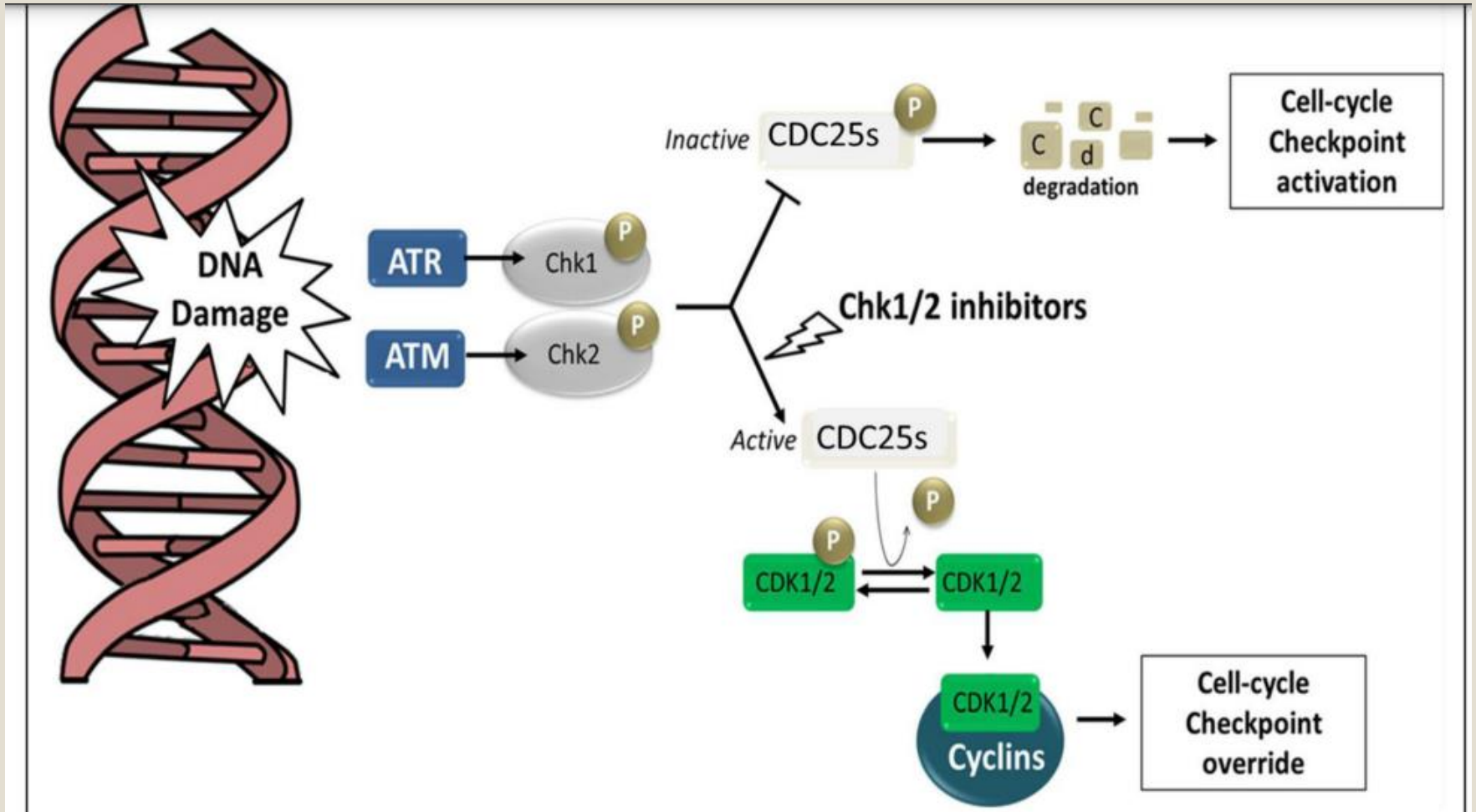


Fig. 4 Schematic representation of the mechanism of action of CHK1/CHK2 inhibitor. In both normal and tumor cells, the recognition of damages on DNA by the DDR-sensors activates different cell cycle checkpoints. The central event of checkpoint activation is the inhibition of the phosphatases CDC25s which is necessary for the activation of the complexes CDK-cyclins. Both ATR/CHK1 and ATM/CHK2 pathways promote CDC25s inhibition (ubiquitin-dependent degradation) and, consequently, they arrest cell cycle in response to DNA damages. Tumor cells can activate these pathways in response to DNA damaging agents and survive. The treatment with a CHK1/CHK2 inhibitor avoids the degradation of the phosphatase CDC25s, inducing cell cycle progression even in the presence of DNA damages. For this reason, different CHK1/CHK2 inhibitors have been developed to enhance the DNA damaging from chemotherapeutic drugs by inhibiting the cell cycle checkpoint negative signals

- **PD-1 inhibitors**
- Examples of drugs that target PD-1 include:
- Pembrolizumab
- Nivolumab
- Cemiplimab
- **PD-L1 inhibitors**
- Examples of drugs that target PD-L1 include:
- Atezolizumab
- Avelumab
- Durvalumab

CTLA-4 inhibitors

Ipilimumab&Tremelimumab.

LAG-3 inhibitors

Relatlimab

Apoptosis as Target

There are three main known mechanisms by which cancer cells acquire apoptosis resistance:

(1) a disruption in the balance between pro- and anti-apoptotic proteins.

(2) an impairment of signaling through death receptors.

(3) a reduction in the function of caspases.

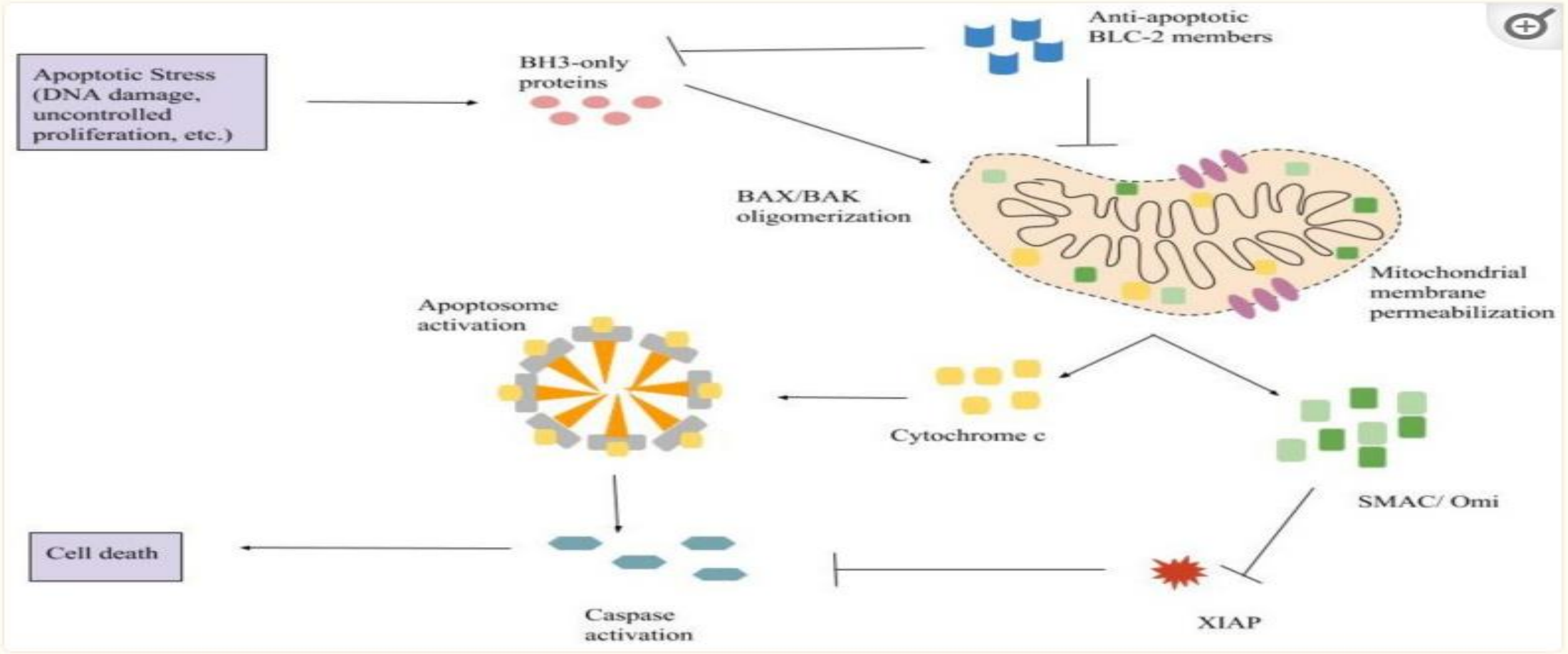


Figure 1

The pathway of intrinsic apoptosis. BH3-only proteins are upregulated in response to apoptotic stress. They activate BAX (BCL-2-associated X protein) and BAK (BCL-2 homologous antagonist killer) which oligomerize and results in mitochondrial membrane permeabilization. Cytochrome c, SMAC (second mitochondria-derived activator of caspase), and Omi are released and the apoptosome is formed from procaspase-9, dATP, cytochrome c, and APAF-1. Caspases are then activated and begin to cleave cellular proteins resulting in apoptosis. Arrows represent activation and T bars represent inhibition.

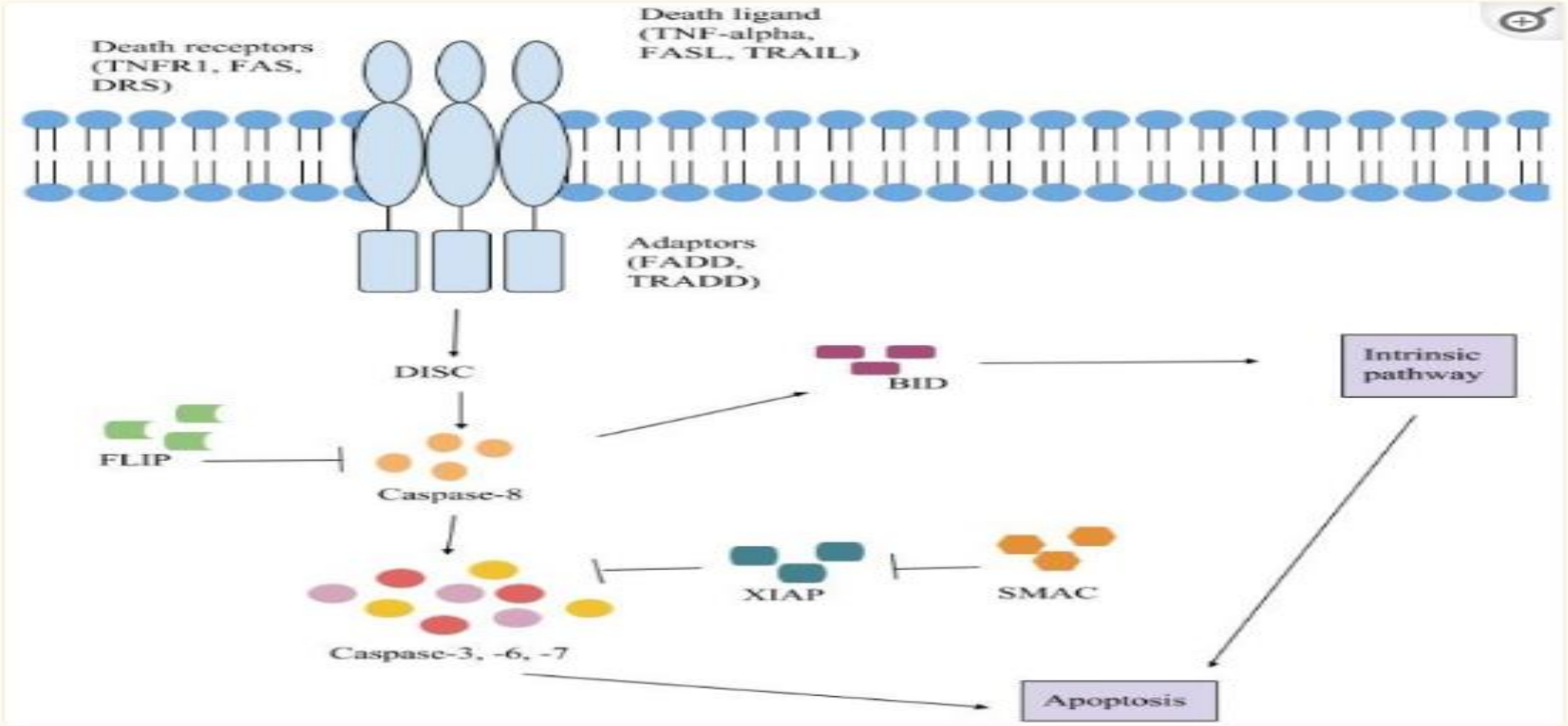
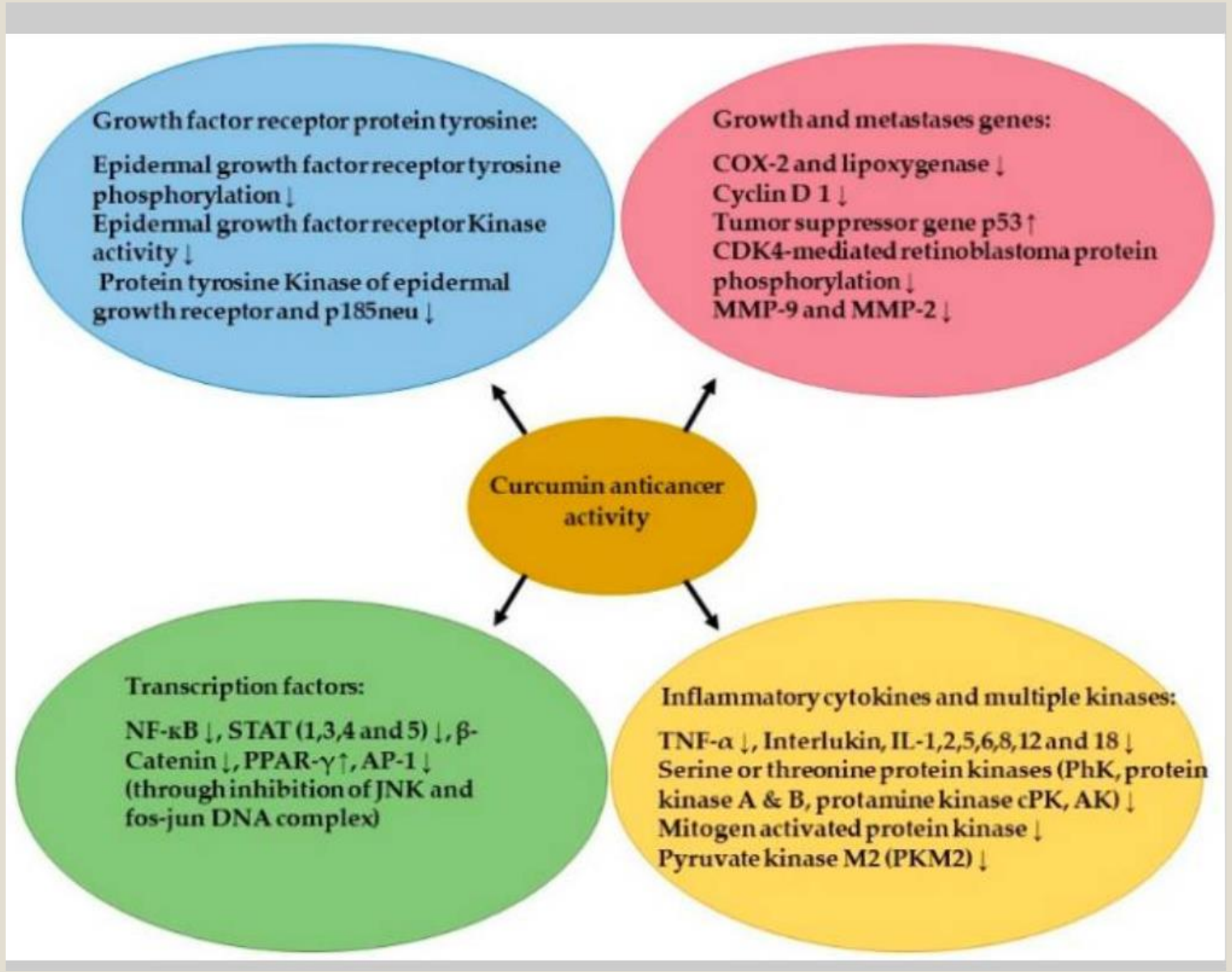


Figure 2

The extrinsic pathway begins with a death ligand docking on a death receptor. An adaptor protein binds to the receptor. DISC (death-inducing signaling complex) is formed from the adaptor protein and procaspases-8 and -10. Caspase-8 becomes activated which activates caspases-3, -6 and -7 and BID (BH3 interacting-domain death agonist). BID goes on to activate BAX and BAK which activates the intrinsic pathway. Caspases-3, -6 and -7 are the executioner caspases that result in cell death. Arrows represent activation and T bars represent inhibition.


Growth factor receptor protein tyrosine:
Epidermal growth factor receptor tyrosine phosphorylation ↓
Epidermal growth factor receptor Kinase activity ↓
Protein tyrosine Kinase of epidermal growth receptor and p185neu ↓
Growth and metastases genes:
COX-2 and lipoxygenase ↓
Cyclin D 1 ↓
Tumor suppressor gene p53 ↑
CDK4-mediated retinoblastoma protein phosphorylation ↓
MMP-9 and MMP-2 ↓
Curcumin anticancer activity
Transcription factors:
NF-κB ↓, STAT (1,3,4 and 5) ↓, β-Catenin ↓, PPAR-γ ↑, AP-1 ↓ (through inhibition of JNK and fos-jun DNA complex)
Inflammatory cytokines and multiple kinases:
TNF-α ↓, Interlukin, IL-1,2,5,6,8,12 and 18 ↓
Serine or threonine protein kinases (PhK, protein kinase A & B, protamine kinase cPK, AK) ↓
Mitogen activated protein kinase ↓
Pyruvate kinase M2 (PKM2) ↓

Clinical studies of curcumin in the prevention/treatment of different types of cancer.

Type of Cancer	Type of Study	No of Patients	Dose of Curcumin	Endpoints	Results	R
BPH [a]	Pilot product evaluation study	61	1g/day for 24 weeks	Signs and symptoms, quality of life	Reduced signs and symptoms, improved quality of life	
Breast	Phase I clinical trial	14	0.5–8 g/day for 7 days plus docetaxel	Maximal tolerated dose of curcumin, toxicity, safety, efficacy, levels of VEGF [b] and tumor markers	No cancer progression, partial response in some patients, low frequency of toxic effects, decreased levels of VEGF	
CML [c]	Randomized controlled trial	50	5 g TID [d] for 6 weeks plus imatinib (400 mg BD [e])	Plasma nitric oxide levels	Reduced nitric oxide levels	
Colorectal	dose-escalation pilot study	15	40–200 mg/day for 29 days	Blood COX-2 [f] activity and PGE2 [g] levels	Dose-dependent decrease in PGE2 levels	
	Phase I does-escalation trial	15	0.45–3.6 g/day for 4 months	Levels of curcumin and its metabolites in plasma urine, and feces; levels of PGE2 and glutathione *S*-transferase activity in blood	Dose-dependent decrease in PGE2 levels, low concentrations of curcumin and its metabolites in plasma and urine	
	Phase I does-escalation trial	12	0.45 g, 1.8 g, 3.6 g per day for 7 days	Concentration of curcumin and its metabolites in plasma and colorectal tissue	Biologically active concentrations of curcumin in the colorectal tissue	
	Phase I clinical trial	126	360 mg TID for 10–30 days	Serum levels of TNF-α [h], *p53* expression in tumor tissue	Decreased serum levels of TNF-α, increased expression of *p53* in colorectal tissue	
	Phase II clinical trial	44	2 g/day and 4 g/day for 1 month	Concentration of PGE2 and 5-HETE [i] within ACF [j] and normal mucosa, total ACF number	Reduced number of ACF with dose of 4 g	
	Pilot study	26	2.35 g/day for 14 days	Safety, tolerance, levels of curcumin in colonic mucosa	Safe and well tolerated, Prolonged biologically active levels of curcumin achieved in colon tissue	

HNSCC [k]	Pilot study	21	1 g single dose	IκKβ [l] kinase activity, cytokine levels in saliva	Reduced IκKβ activity in the salivary cells
Intestinal Adenoma	Randomized controlled trial	44	1.5 g BID for 12 months	total number of polyps, mean polyp size, adverse effects	No significant clinical response, very few adverse effects
Pancreatic	Phase II clinical trial	25	8 g/day for 8 weeks	Tumor response, tumor markers, adverse effects	Poor oral bioavailability, biological response in only 2 patients, no toxicities
	Phase II clinical trial	17	8 g/day for 4 weeks	Time to tumor progression (TTP) and toxicity profile	TTP of 1–12 months (median 2 months), high frequency of side effects
	Phase I/II clinical trial	21	8 g/day for 14 days plus gemcitabine	patient compliance, toxicity, efficacy	Safe and well tolerated, median overall survival time of 161 days
	Phase I clinical trial	16	200–400 mg/day for 9 months	Safety, pharmacokinetics, NF-κB [m] activity, cytokine levels, efficacy and quality of life	Safe, highly bioavailable, no significant changes in NF-κB activity or cytokine levels, improved quality of life
Prostate	Randomized controlled trial	85	100 mg plus 40 mg soy isoflavones for 6 months	Serum PSA [n] levels	Decreased levels of PSA in patients with an initial PSA ≥ 10 μg/mL
	Randomized controlled trial	40	3 g/day for 3 months as a supplement to radiotherapy	biochemical and clinical progression-free survivals, alterations in the activity of antioxidant enzymes	Considerable antioxidant effect, decreased levels of PSA
Solid tumors	Randomized controlled trial	80	180 mg/day for 8 weeks	Changes in quality of life, serum levels of inflammatory mediators	Improved quality of life, reduced levels of inflammatory mediators

CAM AS TARGET

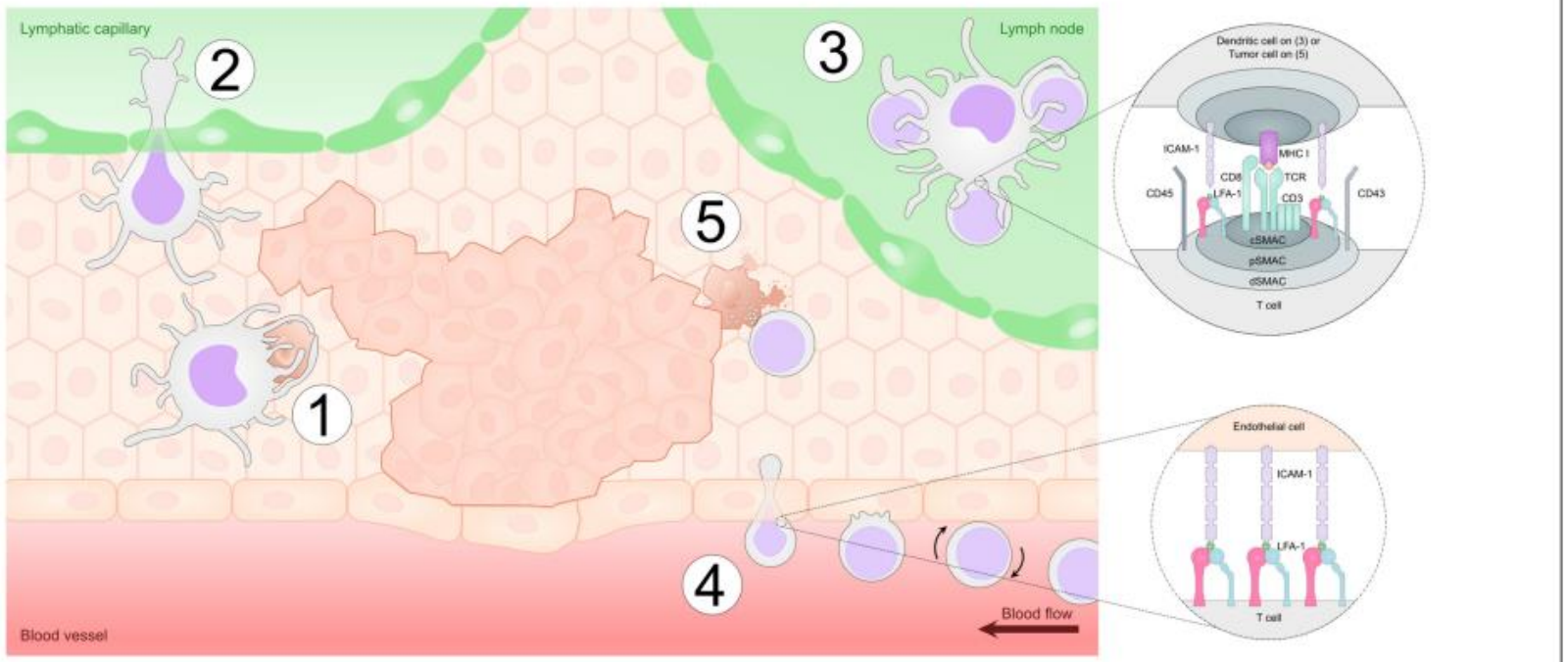


FIGURE 3 | Integrins play a vital role in anti-tumor immunity. Dendritic cells (DCs) take up tumor antigens in the tumor microenvironment by phagocytosing dying tumor cells in a process mediated by adhesion molecules such as $\alpha_v\beta_5$ integrins (Step 1). DCs then enter the lymphatic vessels partly in an LFA-1/ICAM-1-dependent manner and migrate to the draining lymph node (Step 2). In the lymph node, DCs form an immunological synapse with $CD8^+$ T cells in order to present the tumor antigen. LFA-1-ICAM interactions mediate adhesion in the immunological synapse and also provide an additional co-stimulatory signal to the T cells (Step 3). Once activated, T cells travel via the blood stream and enter the tumor site by interacting with adhesion molecules including E-selectin, ICAMs and VCAM-1 on endothelial cells in a process termed leukocyte adhesion cascade. This process is regulated by sequential expression of selectins (L-selectin) and integrins (LFA-1, VLA-4) on the migrating T cell (Step 4). Finally, after reaching the tumor microenvironment, $CD8^+$ T cells form an immunological synapse with tumor cells and kill the malignant cells via the release of cytotoxic granules (Step 5).

Cell-Cell Communications: New Insights in Targeting Tight Junctions through Phytochemicals for Potential Cancer Therapeutic Adjuvants

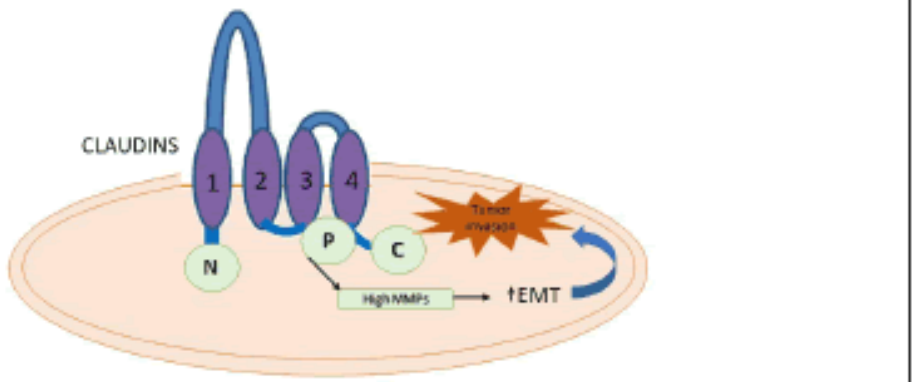
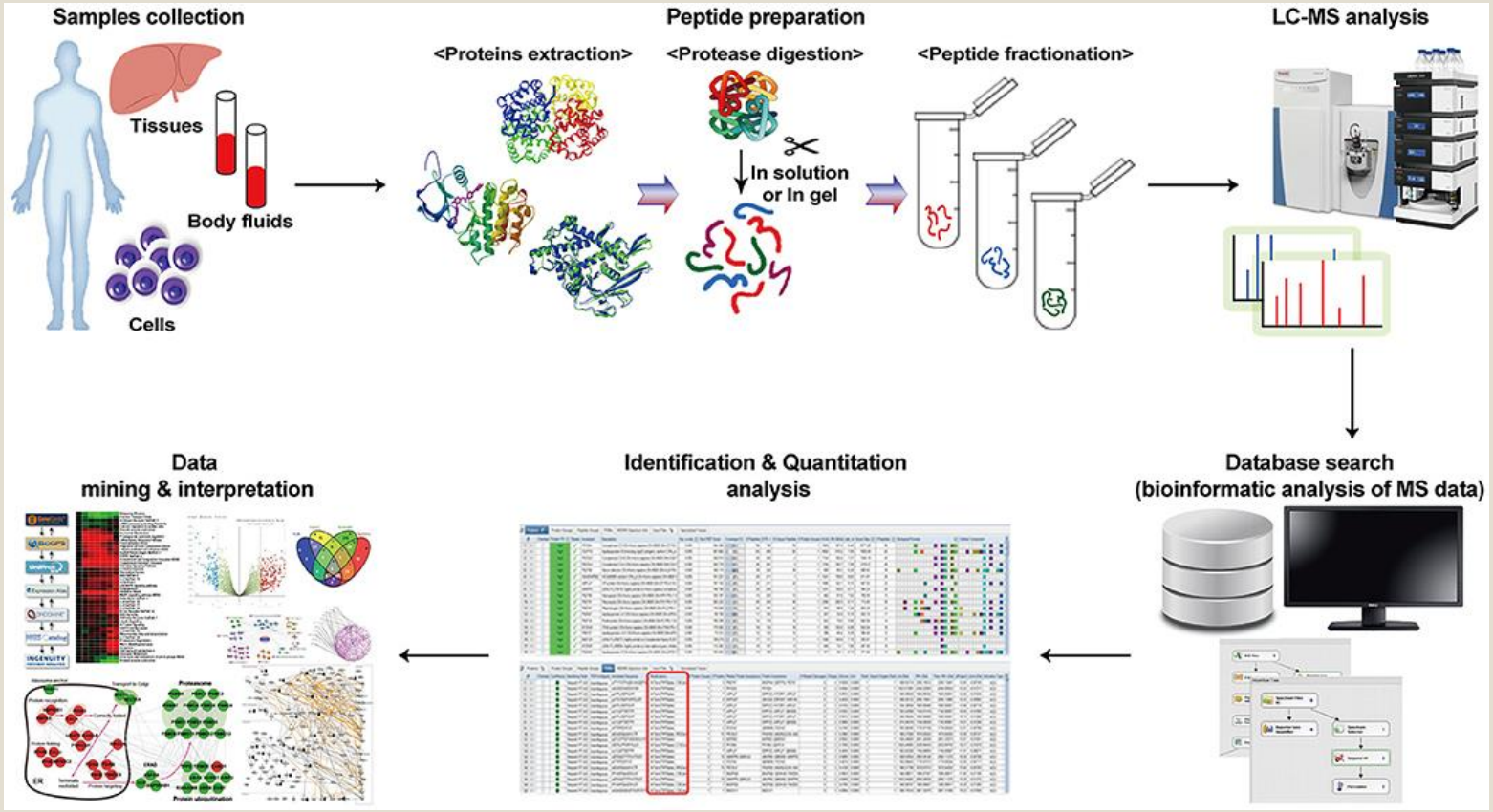


Figure 1: Impact of TJ disruption on tumor invasion and metastasis. Claudins are the group of TJ proteins that play a critical role in tumor invasion, migration, and metastasis. Activation of claudins by phosphorylation induces synthesis of bulk quantities of Matrix Matallo Proteinase (MMPs) which aids in tumor cell invasion by enhancing Epithelial Mesenchymal Transition (EMT).

plant derived bioactive compounds such as quercetin, berberine, genistein, capsaicin, curcumin, and many more natural compounds have been shown to be effective in enhancing the TJ integrity *via* TJ proteins and inflammatory signalling pathways,

proteomics

- Proteomics involves a wide range of processes such as protein expression profiling, protein modifications, protein-protein interactions, protein structure, and protein function



Type of Cancer	Sample Type	Method of target discovery	MS-based strategy	Target	Biomarker/ Target Type	Features of biomarker
Liver (HCC)	Patient's tissue	- Proteomics - Phosphoproteomics	In-solution digestion and LC-MS/MS	PYCR2, ADH1A	- Prognostic	HCC metabolic reprogramming
Pancreas	Primary Pancreatic Epithelial cells	- Proteomics	In-solution digestion and LC-MS/MS	LKB1	- Prognostic	Regulate pathways associated with glycolysis, serine metabolism, and DNA methylation
	PDAC cell lines	- Proteomics	In-gel digestion and LC-MS/MS	MAP2	- Prognostic	Proteins involved in microtubule synthesis are upregulated in gemcitabine-resistant cells. Microtubule stabilizing has an effective anti-cancer effect, particularly in MAP2 overexpressed cells.
Ovary	Patients Tissue	- Proteomics	In-solution digestion and LC-MS/MS	NNMT	- Therapeutic	Central metabolic regulator of CAF differentiation and cancer progression in the stroma
Breast	Patients Tissue, Breast cancer cell lines	- Proteomics - Metabolomics	in-solution digestion and LC-MS/MS	PYCR1	- Prognostic	The higher the expression of PYCR1, the lower the patient's survival rate. Expression of PYCR1 is involved in acquiring resistance
	Breast CSCs, Breast cancer cell line	- Proteomics	In-solution digestion and LC-MS/MS	CD66c	- Therapeutic	Proposed as a novel breast CSC marker by modulating the cell viability of CSCs under hypoxic condition.
	Breast cancer cell lines	- Proteomics	In-solution digestion and LC-MS/MS	NEDD4	- Therapeutic	Presenting as a novel therapeutic target by regulating the expression of ALDH1A1 and CD44, which are characteristic of CSCs
Lung	EGFR-mutant cell lines	- Proteomics - Phosphoproteomics	In-solution digestion and LC-MS/MS	PI3K/ MTOR	- Therapeutic	In lung cancer resistant to EGFR tyrosine kinase inhibitor, PI3K/MTOR inhibitor was used in combination to overcome resistance
Myeloid leukemia	Patient-derived AML stem cells	- Proteomics	In-solution digestion and LC-MS/MS	IL3RA, CD99	- Therapeutic	Providing proteomic resources to design leukemic stem cells-targeted therapies by presenting leukemic stem cells-specific markers

AML, acute myeloid leukemia; CAF, cancer-associated fibroblast; CSC, cancer stem cell; EGFR, epidermal growth factor receptor; HCC, hepatocellular carcinoma; chromatography-tandem mass spectrometry; PDAC, pancreatic ductal adenocarcinoma; PDX, patient-derived xenografts.

Type of cancer	Sample type	Biomarker of immunotherapy	Description	Therapeutic monitoring
Liver	Patient's tissue	SLC10A1	Provide predominantly downregulated immune protein cluster between tumor and non-tumor liver	-
Melanoma	Patient's tissue	MHC	Provide linking melanoma metabolism to immunogenicity and immunotherapy	-
Lung	Patient's tissue	LAIR1, TIM3	Identify intratumorally collagen that are major source of immune suppression related to murine and human lung cancer	+
Glioblastoma	Patient's tissue	FAK	Provide glioblastoma factors related to immunotherapy using proteomics/miRNomics	+
Colon	Patient's tissue	IGF2BP3	Provide a novel information of putative tumor-specific biomarkers that are potentially ideal targets for immunotherapy	-
Clear cell renal cell carcinoma	Patient's tissue	OXPHOS, PRDX4, BAP1, STAT1	Provide microenvironment cell signatures, four immune-based clear cell renal cell carcinoma	-
Endometrial carcinoma	Patient's tissue	CDK12	Suggest alternative mechanism for repressing anti-tumor immune response	-

Type of cancer	Sample type	Method of target discovery	MS-based strategy	Target	Biomarker/ target type	Features of biomarker
Glioblastoma	Patient's tissue	- Proteomics	In-solution digestion and LC-MS/MS	YBX1	- Prognostic - Therapeutic	Major tumor invasion-regulated proteins
Glioblastoma	Primary GBM subtypes	- Proteomics	In-solution digestion and LC-MS/MS	CD9	- Therapeutic	Highly expressed in primary GNS cells
Glioblastoma	Glioma cells	- Proteomics	In-gel digestion and LC-MS/MS	EGFRvIII	- Therapeutic	EGFRvIII expression is associated with pro-invasive proteins through EV profile
Glioblastoma	Blood	- Proteomics	In-solution digestion and LC-MS/MS	LRG1, CRP, C9	- Prognostic	Concentration in plasma correlated significantly with tumor size
Glioblastoma	Patient's tissue, Fluid	- Proteomics	In-solution digestion and LC-MS/MS	CCT6A	- Prognostic	CCT6A in EV is associated with induction of expression and amplification and negative survival in glioblastoma
Glioma	Plasma	- Proteomics	In-solution digestion and LC-MS/MS	SDC1	- Diagnostic	High-grade glioma and low-grade glioma through SDC1 present in EV in the patient's plasma
Glioma	Patient's tissue	- Proteomics	In-solution digestion and LC-MS/MS	CDH18	- Prognostic	Role of tumor-suppressor
Astrocytoma	Urine from tumor model	- Proteomics	In-solution digestion and LC-MS/MS	109 proteins	- Prognostic	Protein alteration by date, diagnosis before tumor is seen in MRI

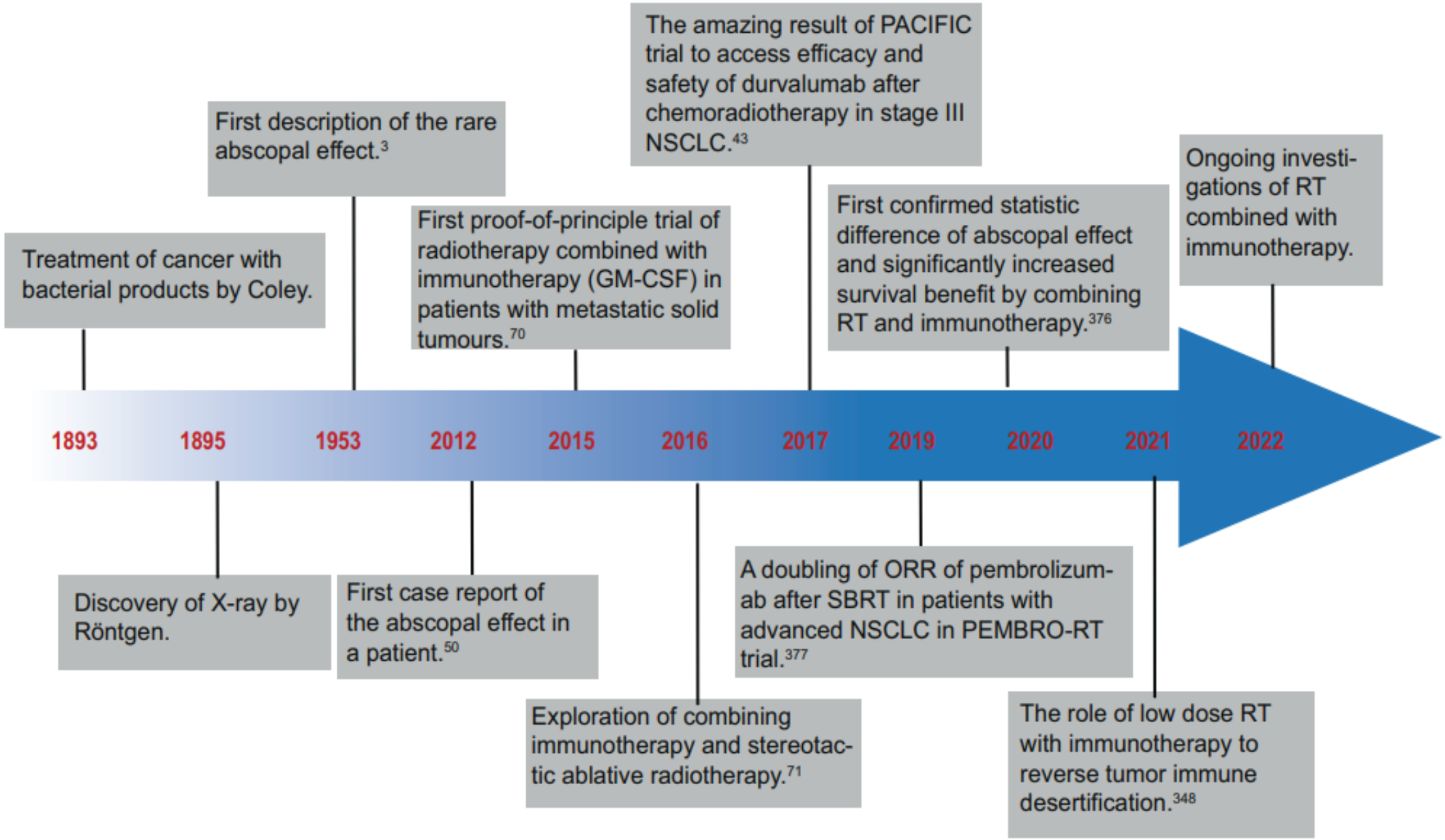
EGFR, epidermal growth factor receptor; EV, extracellular vesicle GBM, glioblastoma multiforme; GNS, GBM-derived neural stem; LC-MS/MS, liquid chromatograp spectrometry; MS/MS, tandem mass spectrometry.

TOXICOPROTEOMICS

- Toxicoproteomics is a new scientific method that combines proteomic technologies with bioinformatics.

- Liver carcinogen N-nitrosomorpholine (NNM) cause,up regulation of stress proteins, including caspase-8 precursor, vimentin, and Rho GDP dissociation inhibitor.

- Toxicogenomics, a discipline that determines genetic susceptibility of a particular individual following exposure to a carcinogenetic agent, toxicoproteomics allow the monitoring of the body’s response to a specific toxicant


Treatment of cancer with bacterial products by Coley.
First description of the rare abscopal effect.[3]
First proof-of-principle trial of radiotherapy combined with immunotherapy (GM-CSF) in patients with metastatic solid tumours.[70]
The amazing result of PACIFIC trial to access efficacy and safety of durvalumab after chemoradiotherapy in stage III NSCLC.[43]
First confirmed statistic difference of abscopal effect and significantly increased survival benefit by combining RT and immunotherapy.[376]
Ongoing investigations of RT combined with immunotherapy.
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Discovery of X-ray by Röntgen.
First case report of the abscopal effect in a patient.[50]
Exploration of combining immunotherapy and stereotactic ablative radiotherapy.[71]
A doubling of ORR of pembrolizumab after SBRT in patients with advanced NSCLC in PEMBRO-RT trial.[377]
The role of low dose RT with immunotherapy to reverse tumor immune desertification.[348]

TAKE HOME MESSAGE

- Multi omic approach.
- Proteomics,Genomics,metabolomics,transcriptomics,epigenomics,Radiomics.
- Personalised medicine (tumour cell biology)

Thank You