Exploring Tumor Immune Microenvironment " TIME"

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Functional Medicine Consultant, IFM, USA

Advisory board, Keto Live Centre, Switzerland

Tumor-Immune- MicroEnvironment “TIME”

- Understanding cancer behavior
- Meet our Mighty Immune system
- Cancer-Immune Interaction
- Understanding Tumor Microenvironment Barriers
- Optimizing Tumor Immune Microenvironment
- Nature is here to help, just a few examples

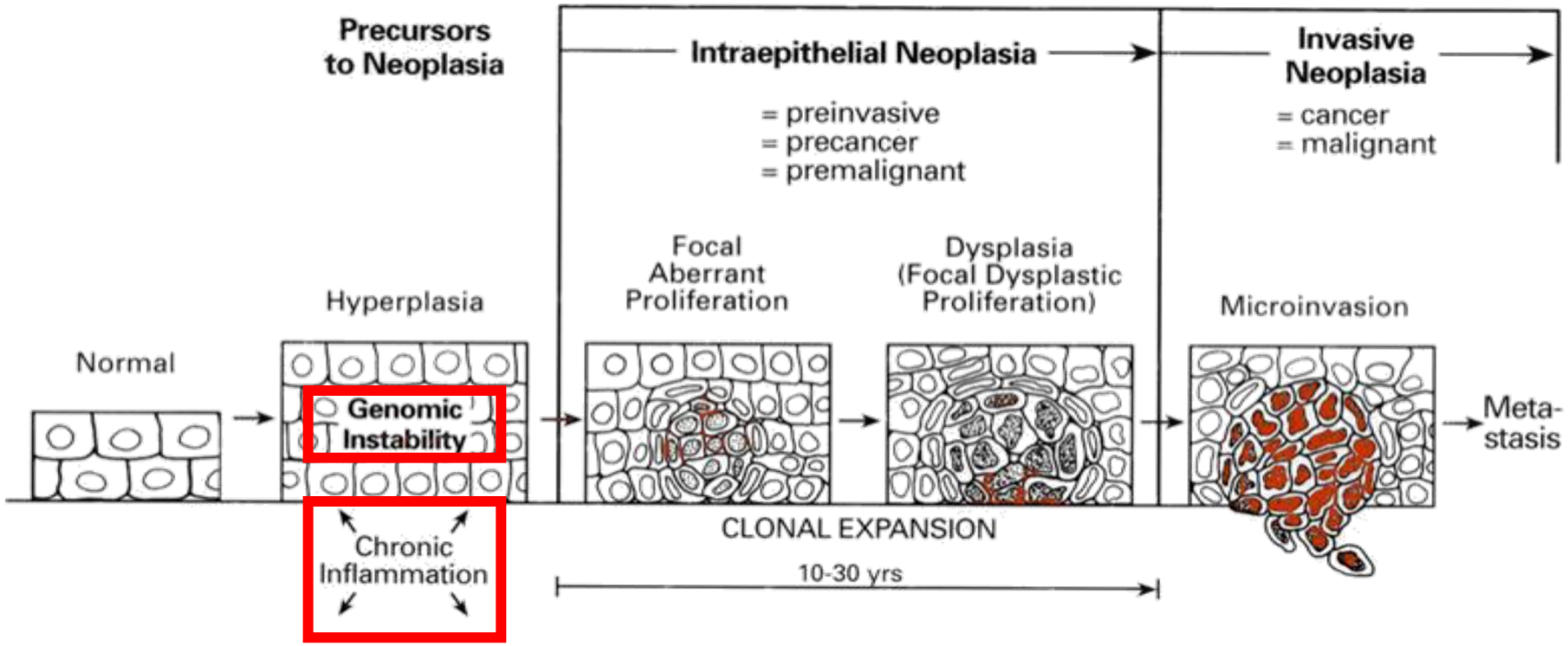
Understanding Cancer?

- Neo plasia = New Growth
- Tumor = Swelling
- Cancer = Crab " in Greek- Karkinos → *Karkinoma*

Definition:

- *Abnormal mass/ growth* of tissue with,
- *Autonomous uncontrolled* growth,
- *Exceeds* that of normal tissues,
- The growth *persists* after stopping the growth signal
- Tumors are either Benign or Malignant.

Carcinogenesis

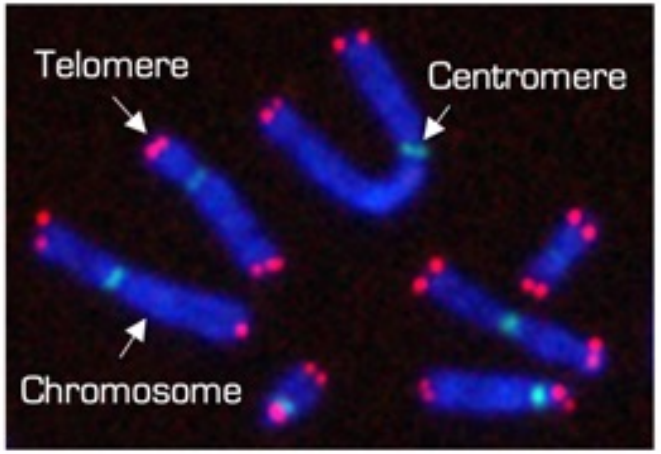


- **Proto-Oncogenes:** normal genes involved in modulation of cell growth
- **When mutated → Oncogenes:** activate the cells to grow indefinitely!!
- **Tumor Suppressor Genes:** normal **genes** that:
  - Slow down cell division,
  - Repair DNA mistakes,
  - Tell cells when to die (apoptosis or programmed cell death)

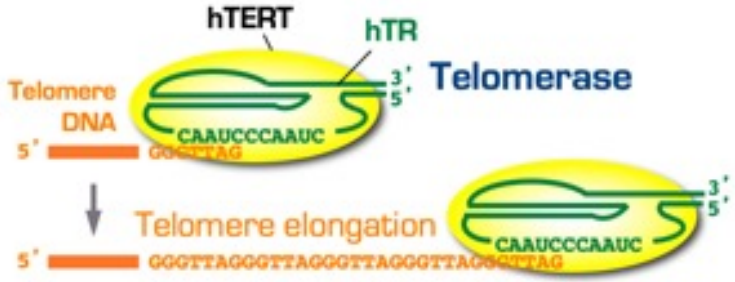
TP53 & BRCA

Telomeres & Cancer

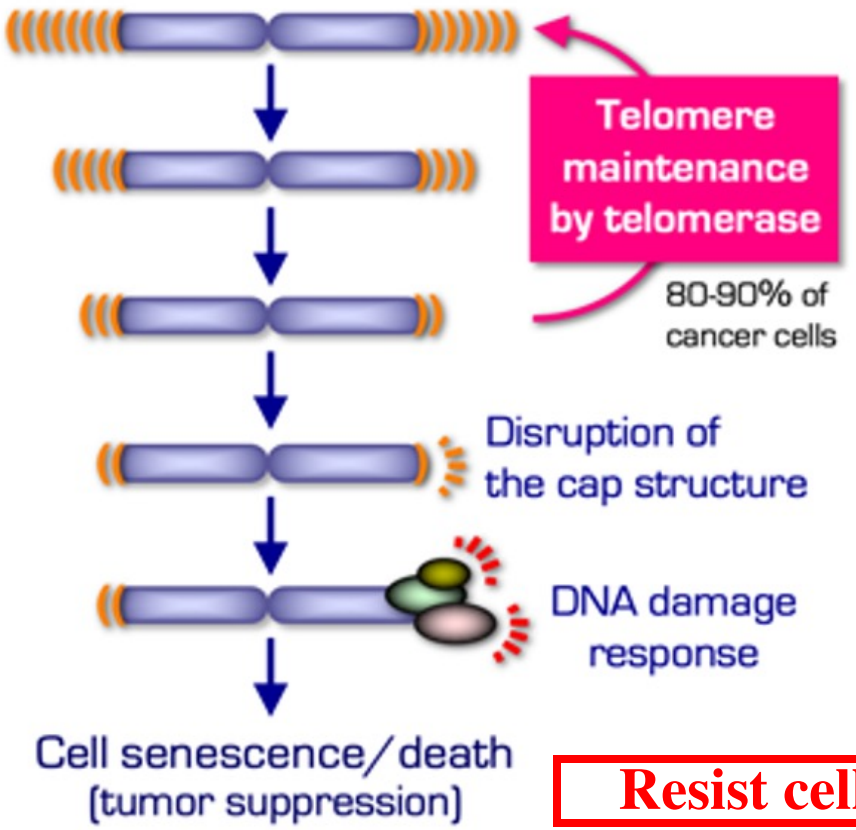
Chromosome caps



Telomerase, the telomere-synthesizing enzyme



Telomere shortening in a dividing cell

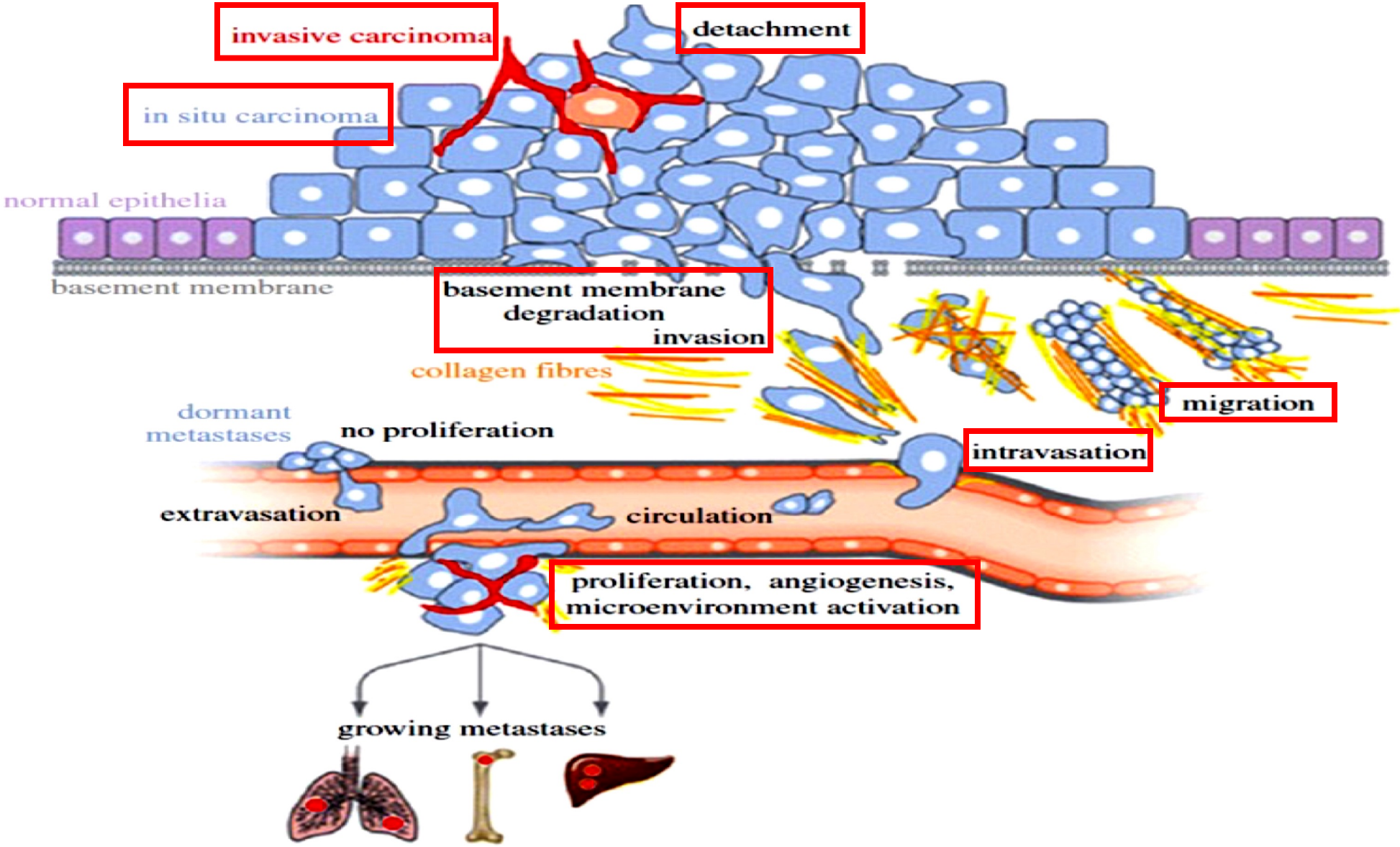


Resist cell death

Most cancer cells maintain telomeres by telomerase activation & proliferate infinitely

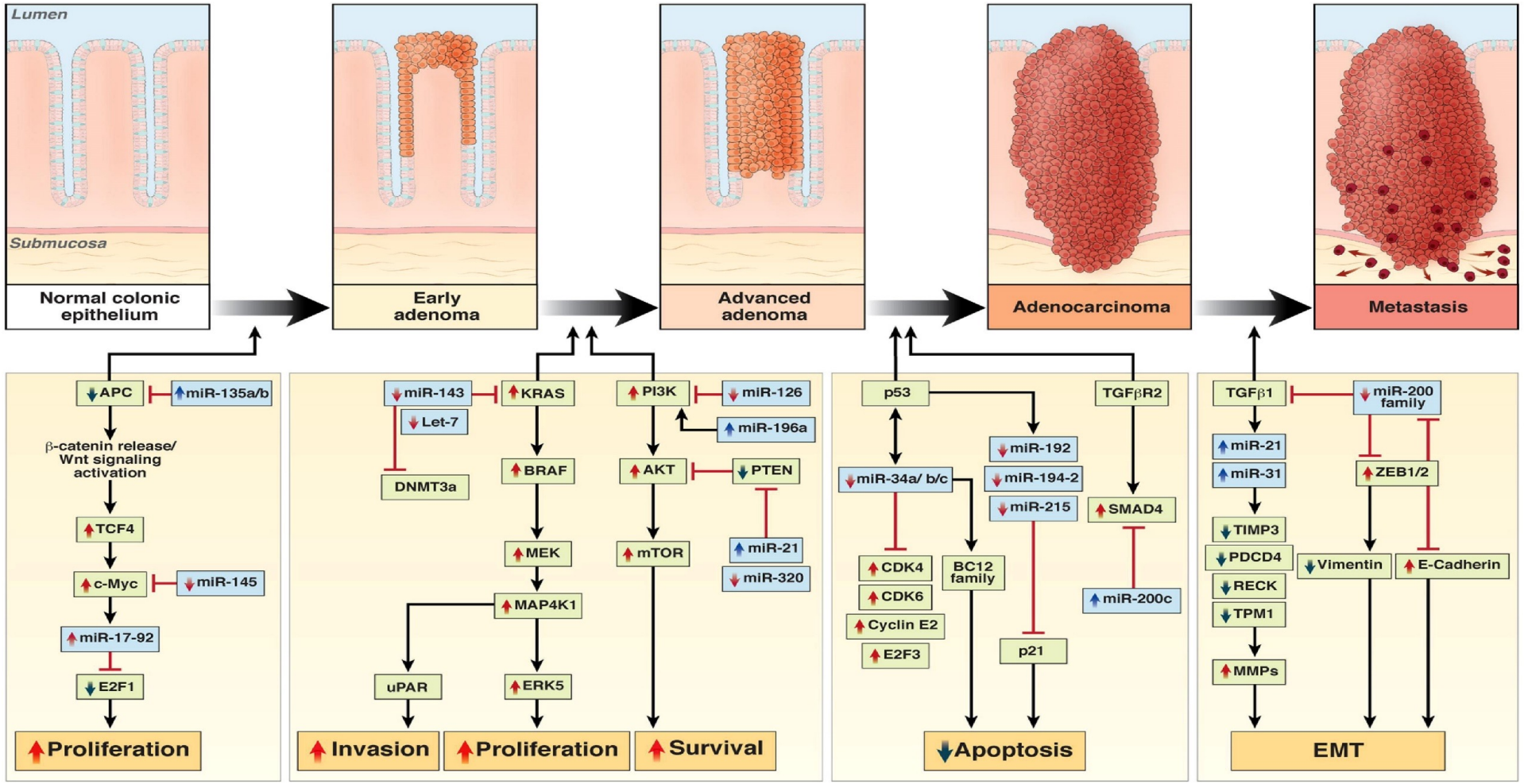
Replicative immortality

Angiogenesis & Metastases

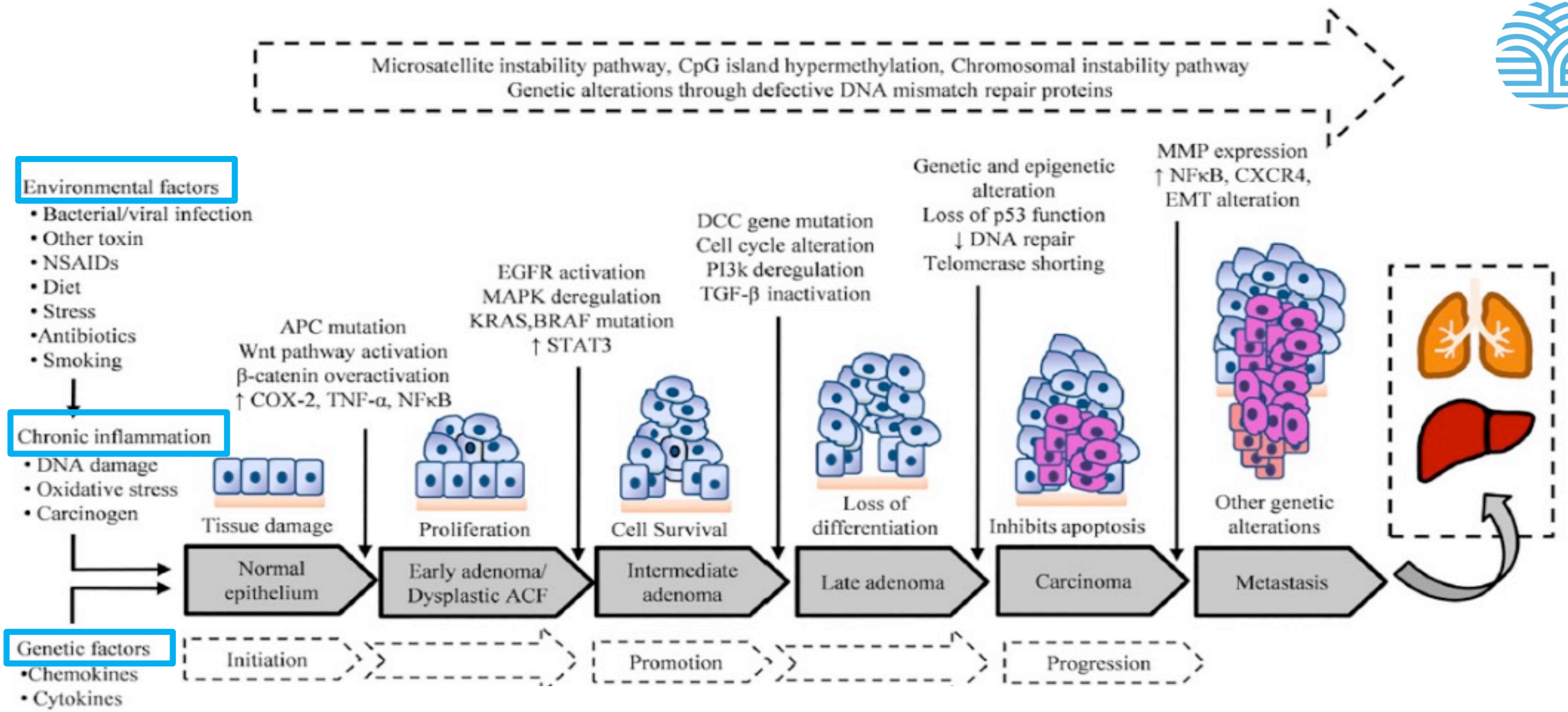


Ion transport and cancer: from initiation to metastasis. Phil. Trans. R. Soc. B 369: 20130092.

Epigenetics for Cancer Initiation & Progression in CRC



Epigenetics of Colorectal cancer. .Gastroenterology 2012 143, 1442-1460.e1



Dietary phytochemicals in colorectal cancer prevention and treatment: A focus on the molecular mechanisms involved. Biotechnol Adv. 2020 Jan-Feb;38:107322

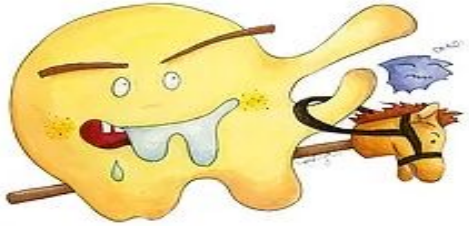
Meet our mighty Immune system


NK Cell


Cytotoxic T Cell


Helper T Cell

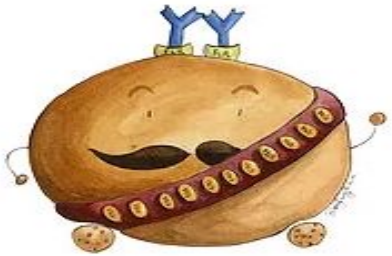

Follicular Dendritic Cell


Macrophage


Treg


B Cell


Plasma Cell


Mast Cell


Basophil

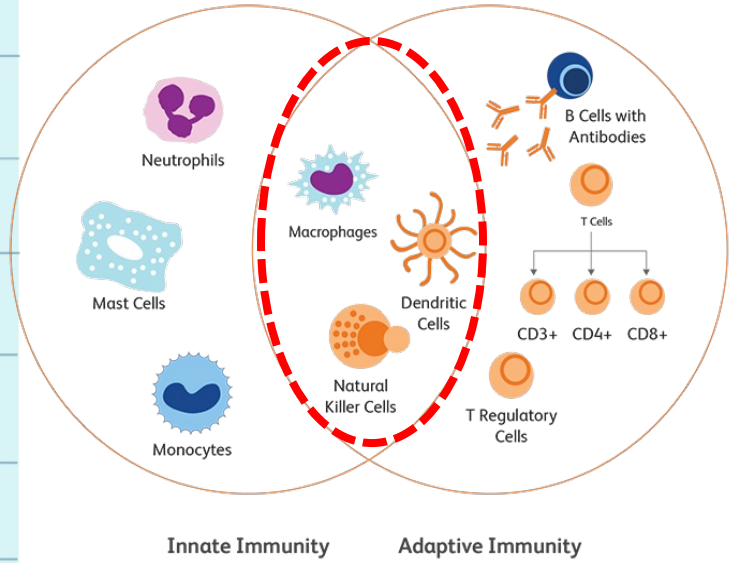

Neutrophil


Eosinophil

HEMATOPOIETIC STEM CELL		
	SELF-RENEWAL CYTOKINES	EXPANSION CYTOKINES
Hematopoietic stem cell	SCF; TPO	Flt3-Ligand; SCF; TPO; IL-3; IL-6

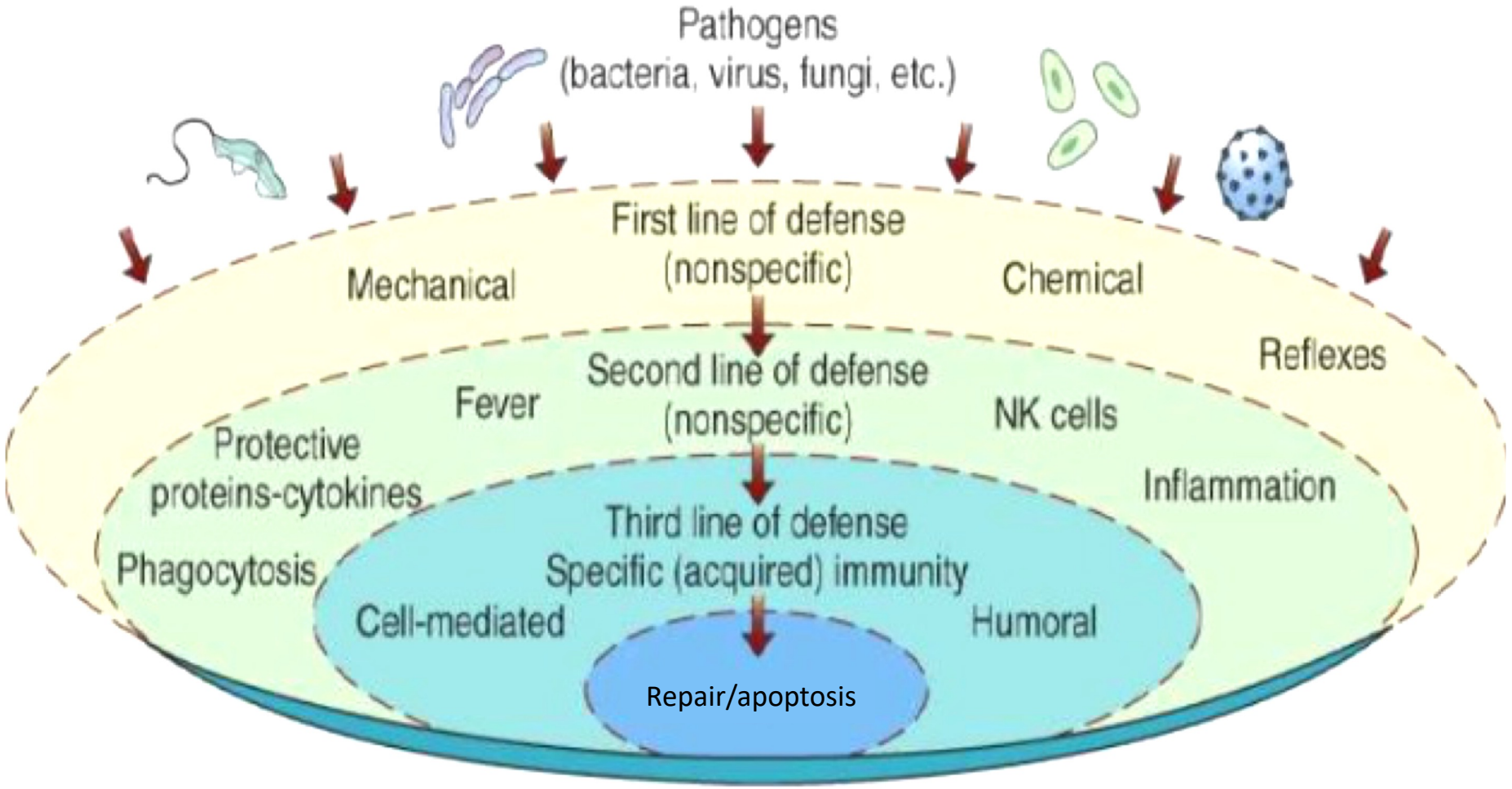
THE INNATE IMMUNE SYSTEM		
	DIFFERENTIATING CYTOKINES	SECRETED CYTOKINES
Myeloid progenitor	IL-3; IL-6; EPO; GM-CSF; G-CSF	
Monocyte	GM-CSF; G-CSF	
Macrophage	IFN-γ; IL-6; IL-10; M-CSF	TGF-β; TNF-α; VEGF; IL-1β; IL-6; IL-10; IL-12
Dendritic cell	Flt3-Ligand; GM-CSF; IFN-α; IL-4	IL-1α; IL-1β; IL-4; IL-6; IL-10; IL-12; TGF-β; IFN-α; IFN-γ
Eosinophil	IL-3; IL-5; GM-CSF	TGF-β; VEGF; PDGF-BB; TNF-α; IL-1α; IL-1β; IL-2; IL-4; IL-5; IL-6; IL-8; IL-12; IL-13
Basophil	IL-3; IL-6; GM-CSF; G-CSF	TNF-α; IL-4; IL-6; IL-13
Mast cell	IL-3; IL-6; GM-CSF; G-CSF	TNF-α; GM-CSF; IL-3; IL-4; IL-5; IL-6; IL-8; IL-13
Neutrophil	IL-6; GM-CSF; G-CSF; SCF	APRIL; RANKL; TNF-α; TGF- β; VEGF; IL-1α; IL-1β; IL-6; IL-12; IL-18; IL-21
NK cell	IL-15	GM-CSF; IFN-γ; TNF-α; MIP-1α; MIP-1β; IL-5; IL-10; IL-17; IL-22

THE ADAPTIVE IMMUNE SYSTEM		
	DIFFERENTIATING CYTOKINES	SECRETED CYTOKINES
Lymphoid progenitor	IL-7	
B cell progenitor	IL-3; IL-4; IL-6; IL-7; SCF	
Plasma cell	IL-4; IL-5; IL-10; IL-21; TGF-β; IFN-γ	
T cell progenitor	IL-2; IL-7; Notch	GM-CSF; TGF-β; TNF-α; IL-4; IL-6; IL-10; IL-12
Helper T cell	IL-2; IL-4; IL-6; IL-12; TGF-β; IFN-γ	* IFN-γ; TNF-α; TGF-β; IL-4; IL-5; IL-6; IL-9; IL-10; IL-13; IL-17; IL-21; IL-22
Cytotoxic T cell	IL-2; IL-5; IL-7; IL-12	IFN-γ; TNF-α; TNF-β; IL-2; sFas Ligand

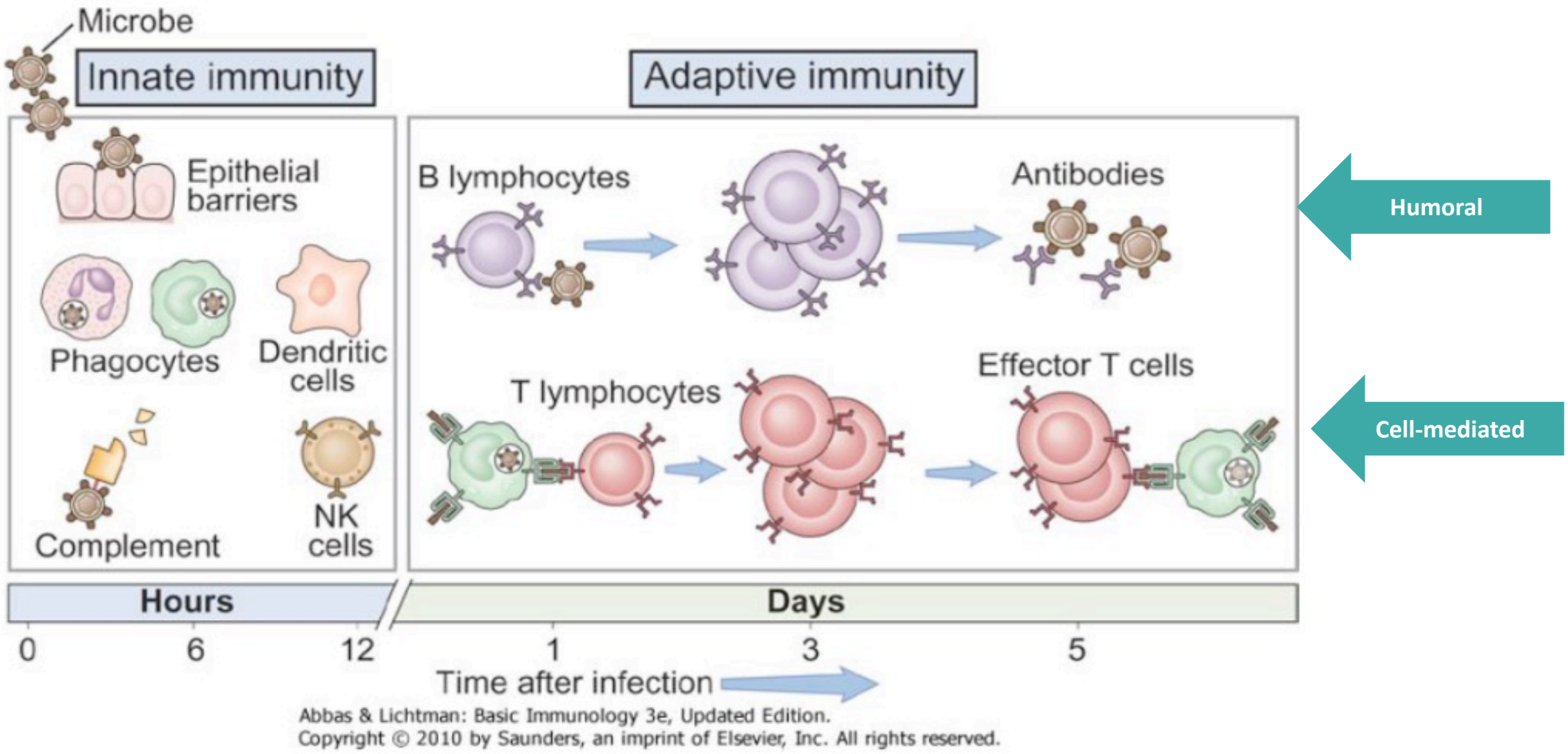


Reference: Peprotech Inc, 2021

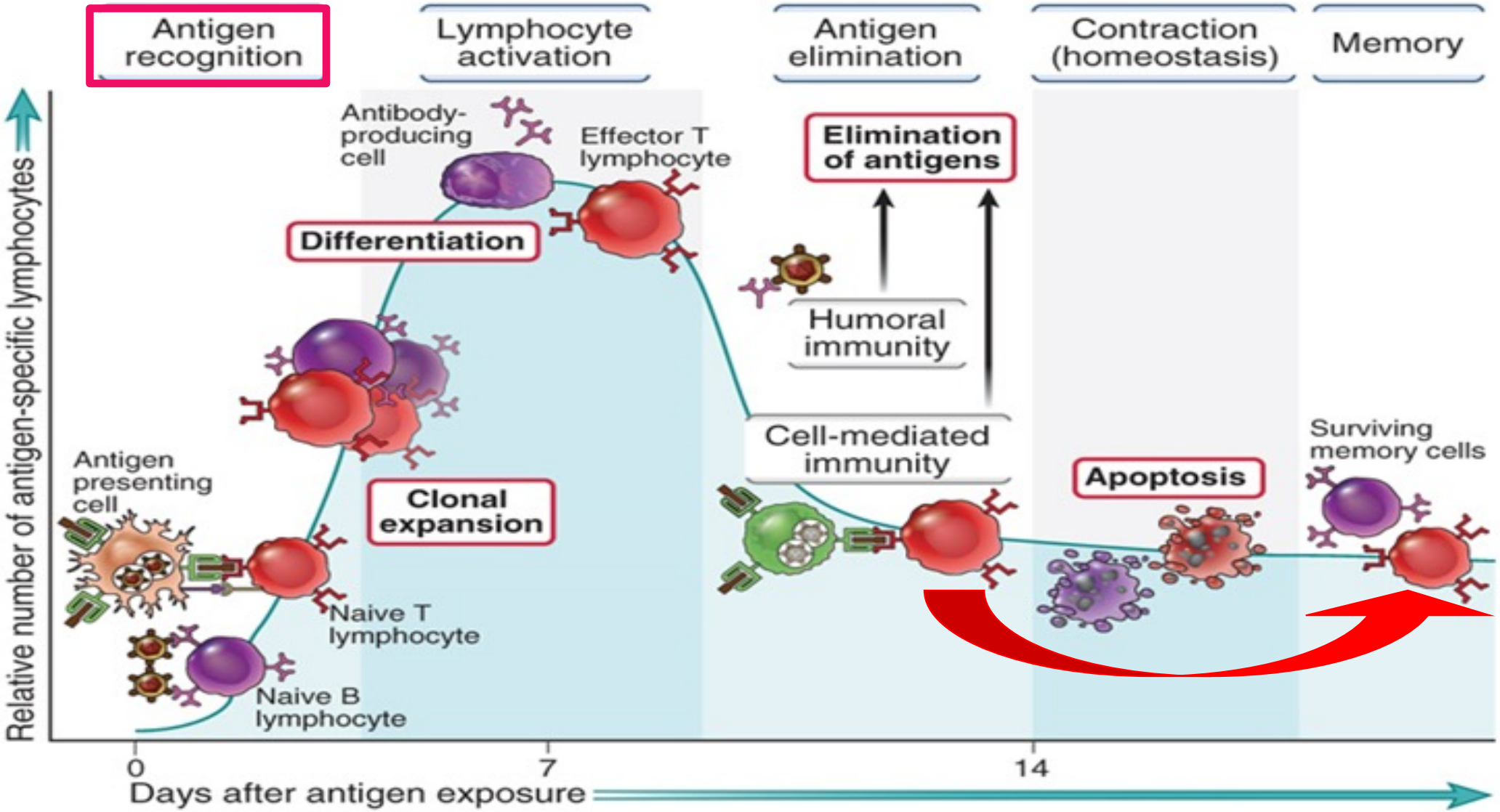
Timeline of a Pathogen



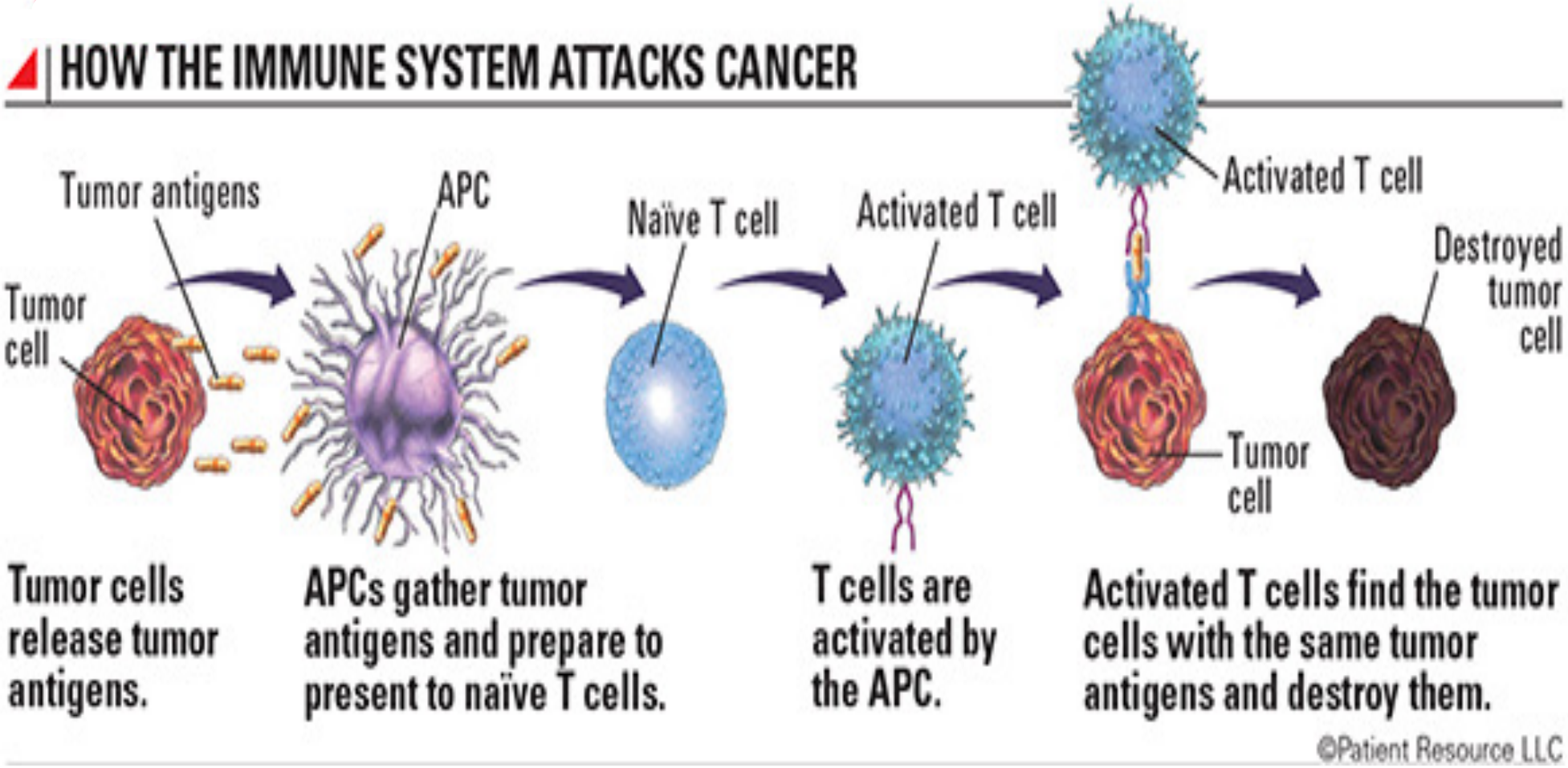
Timeline of a Pathogen



Timeline of a Pathogen

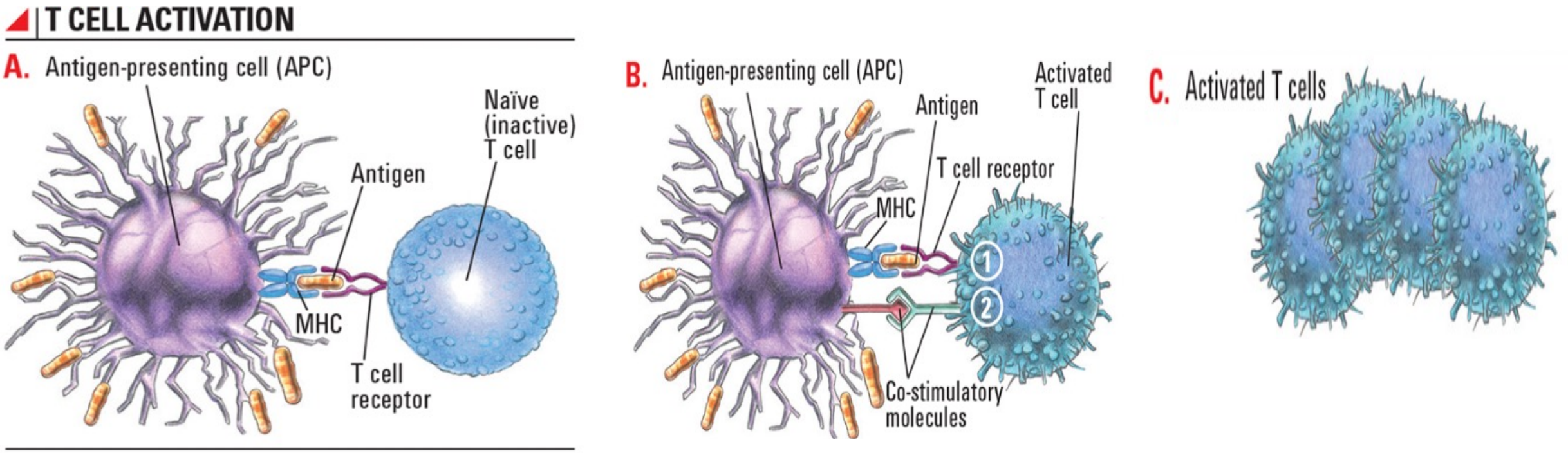


Immune- Cancer Interactions



https://www.sitcancer.org/clinician/resources/melanoma/immune-system

Immune- Cancer Interactions



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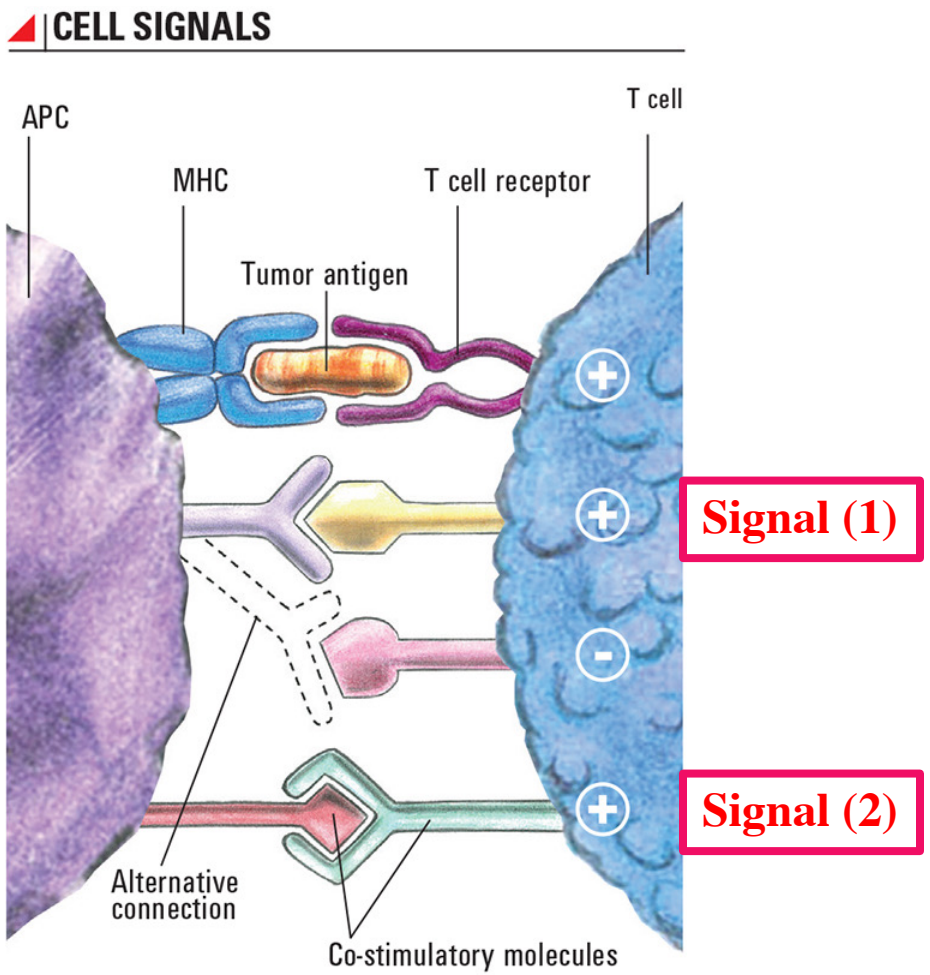
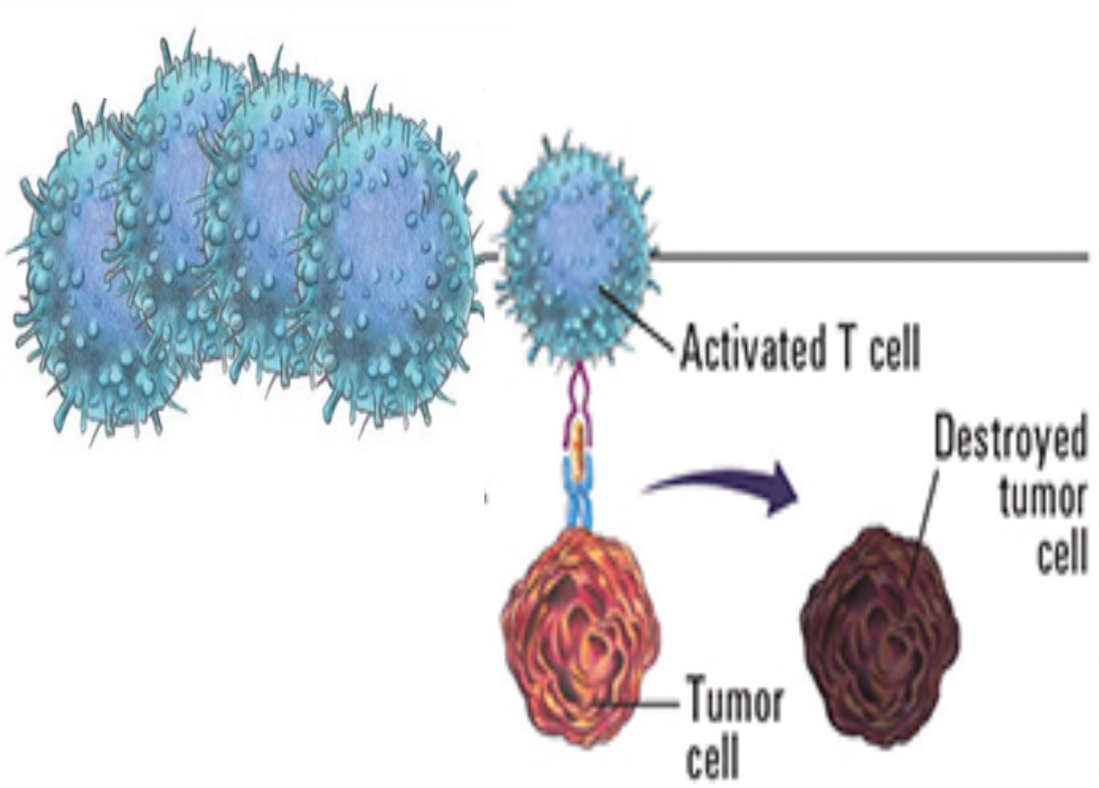
Immune- Cancer Interactions



Signal (1)

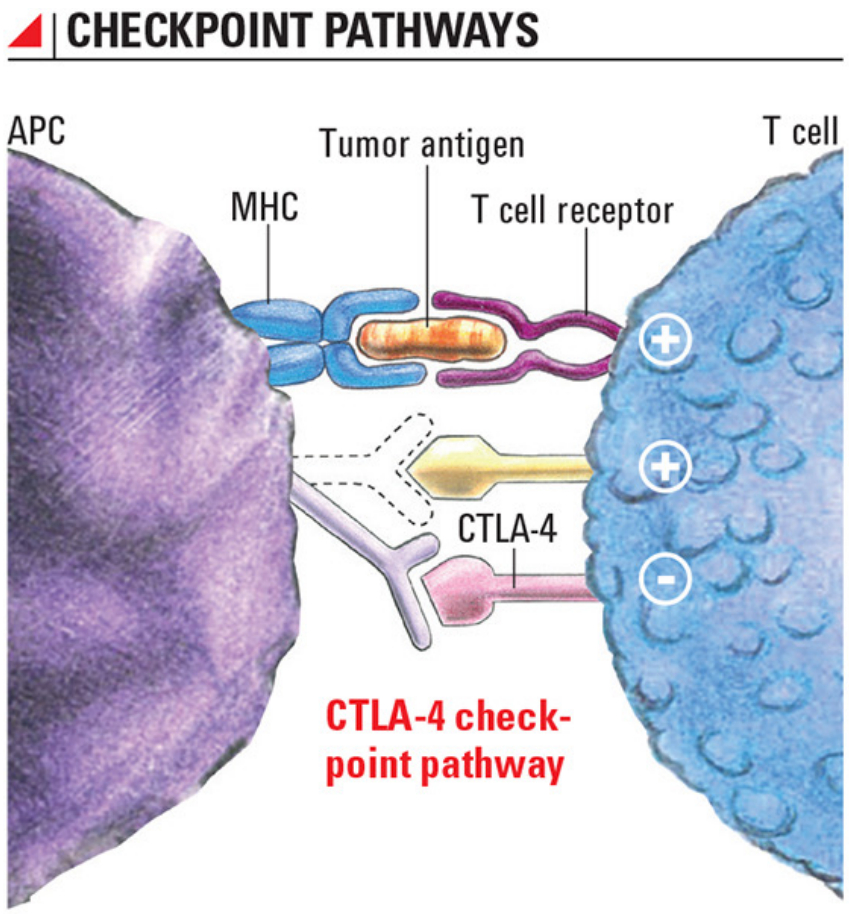
Signal (2)



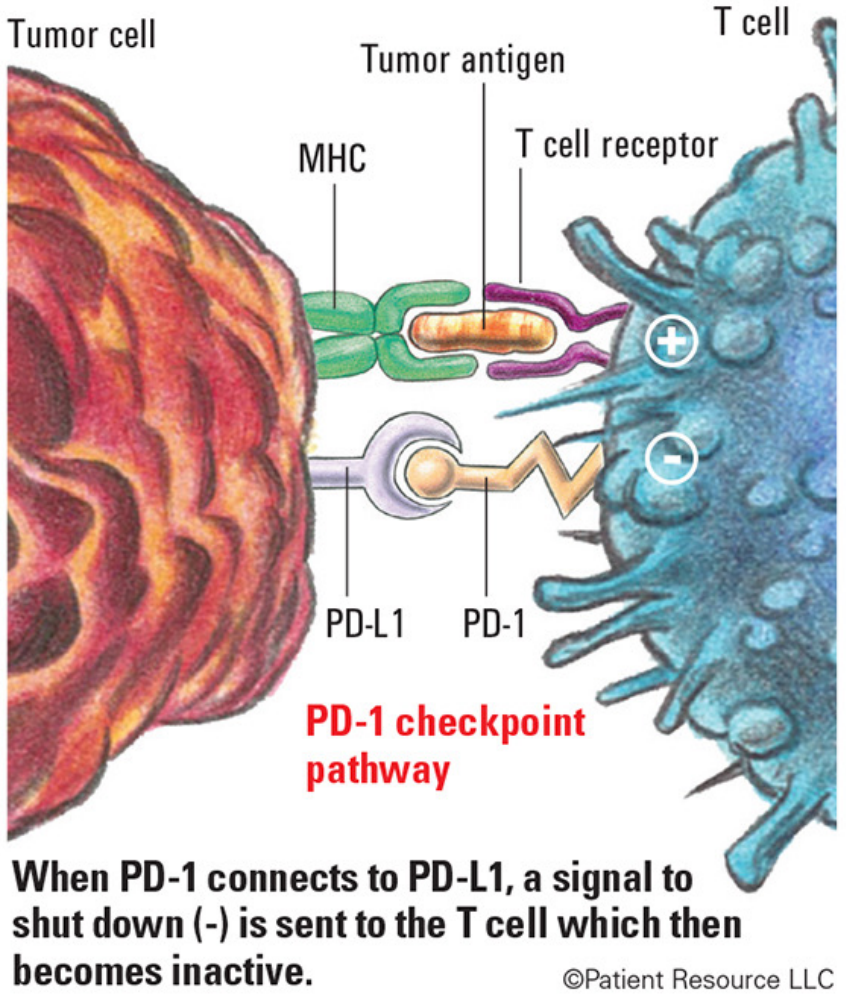
https://www.sitcancer.org/clinician/resources/melanoma/immune-system

Immune- Cancer Interactions

Evading the Immune System



When the CTLA-4 molecule connects instead of other molecules, a signal to shut down (-) is sent to the T Cell.

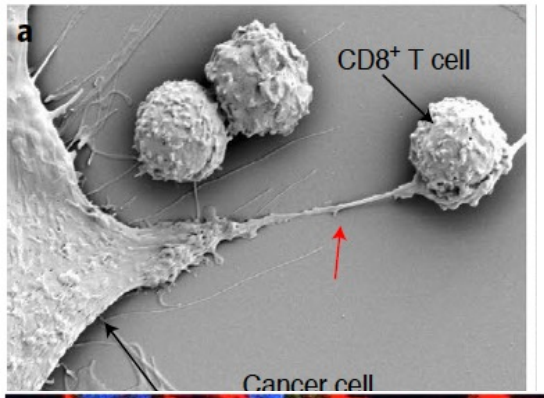


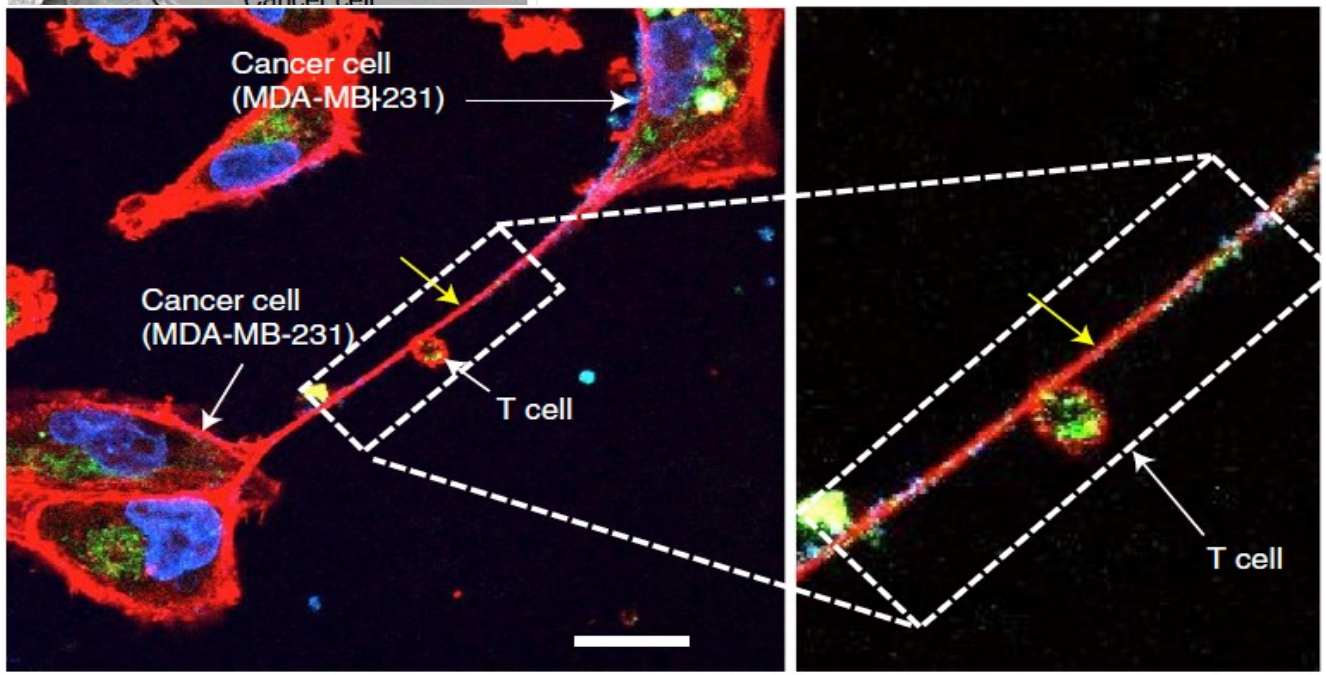
When PD-1 connects to PD-L1, a signal to shut down (-) is sent to the T cell which then becomes inactive.

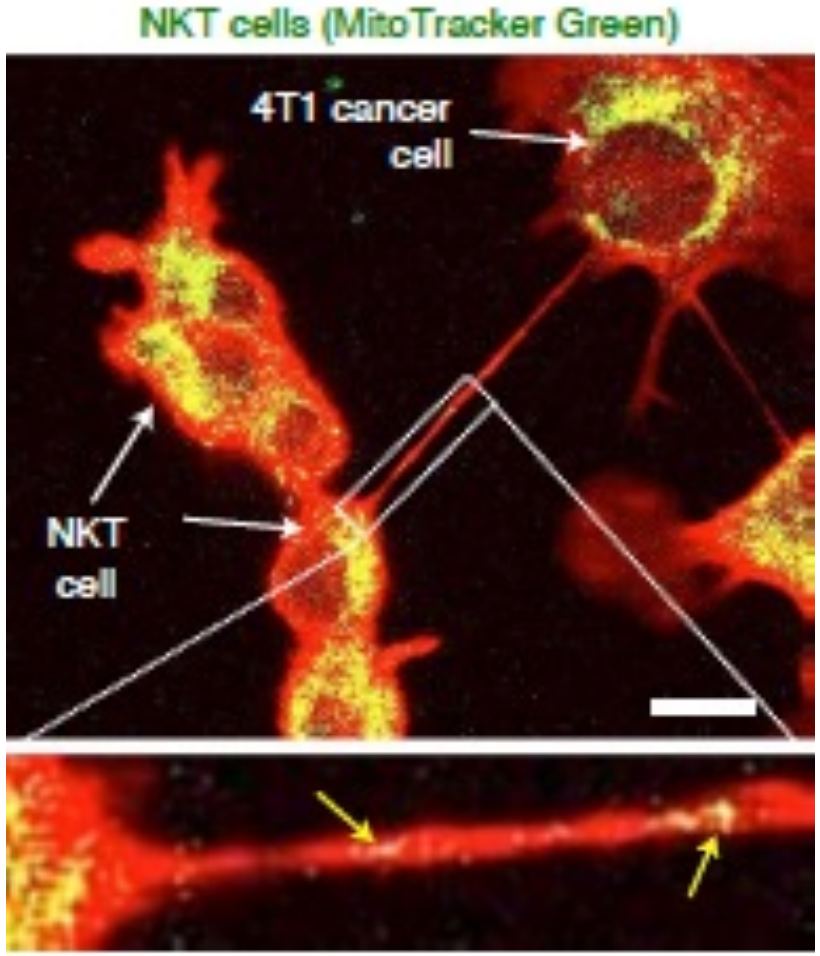
https://www.sitcancer.org/clinician/resources/melanoma/immune-system

Immune- Cancer Interactions

Stealing- Cellular Energetics

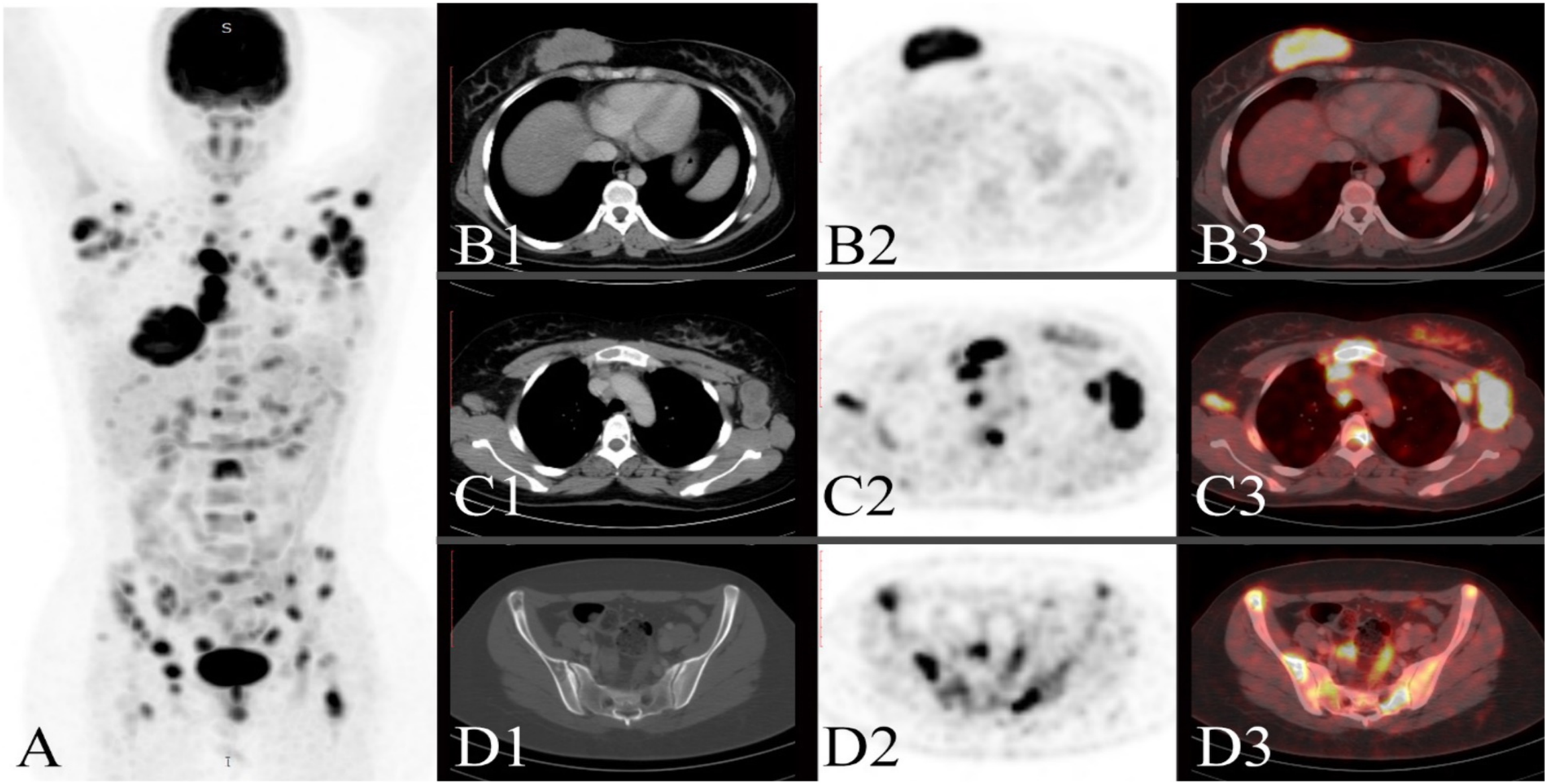






Nature Nanotechnology | VOL 17 | JanuarY 2022 | 98–106 |

A note on Cellular energetics



Just a few words about Lactate…

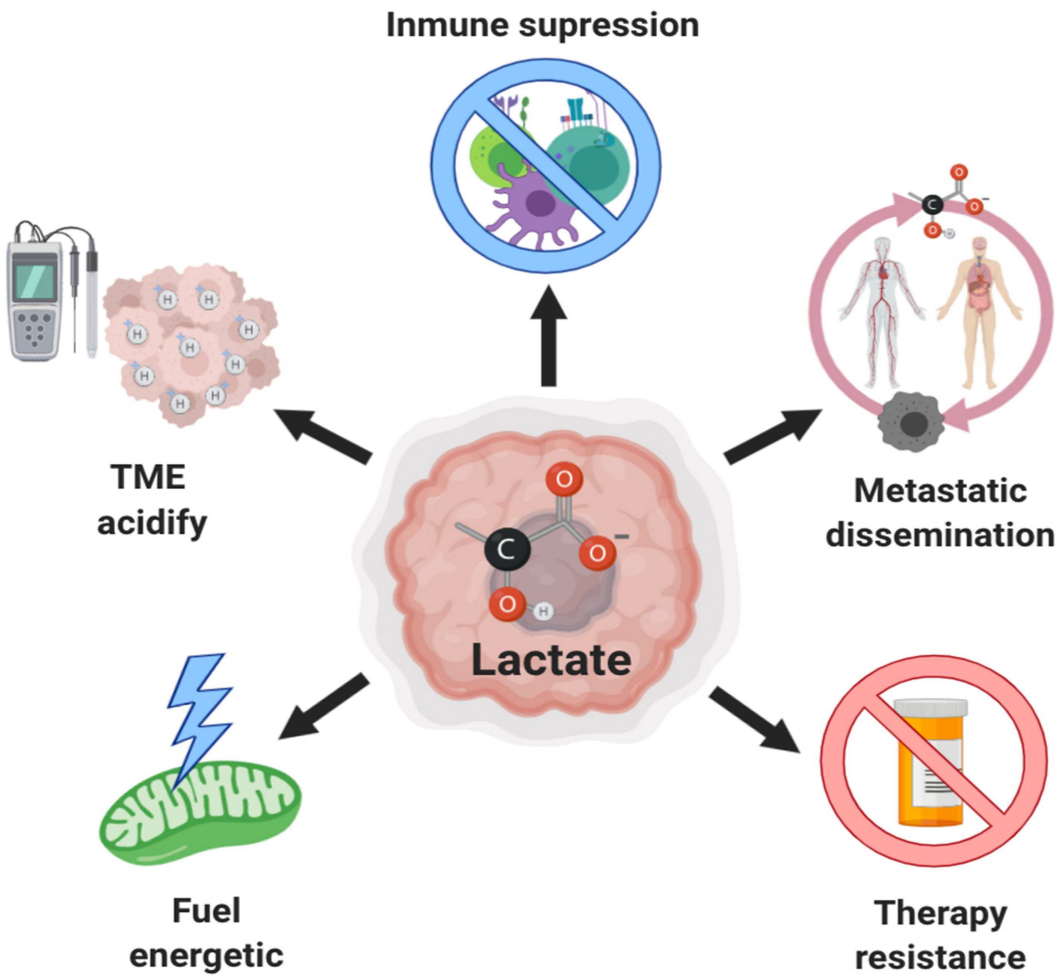
frontiers in Oncology

REVIEW
published: 01 November 2019
doi: 10.3389/fonc.2019.01143

Lactate in the Regulation of Tumor Microenvironment and Therapeutic Approaches

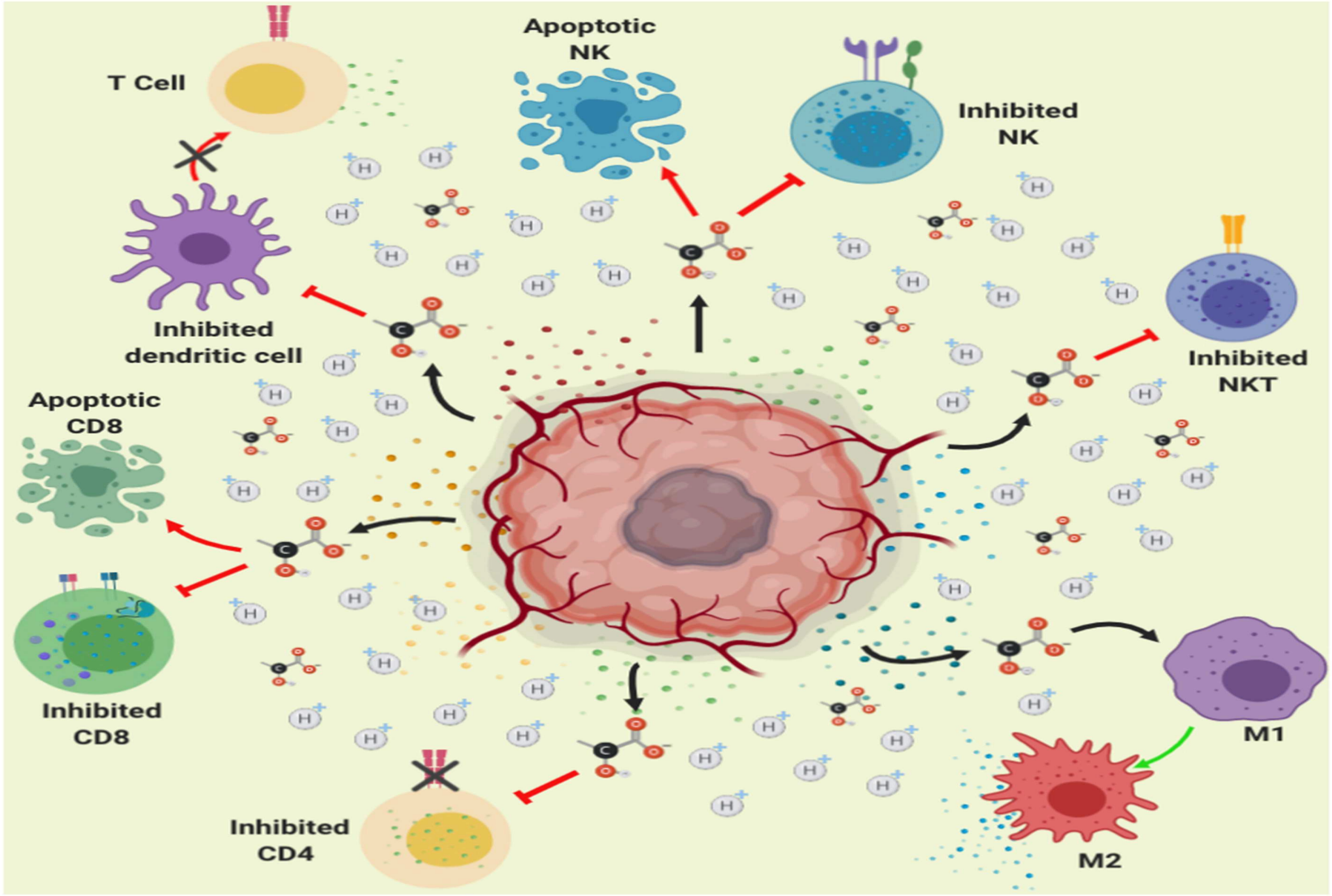
Karen G. de la Cruz-López[1,2,3], Leonardo Josué Castro-Muñoz[1,2], Diego O. Reyes-Hernández[4,5], Alejandro García-Carrancá[2,3] and Joaquín Manzo-Merino[2,5,6]*

[1] *Programa de Doctorado en Ciencias Biomédicas, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Ciudad Universitaria, Mexico City, Mexico,* [2] *Unidad de Investigación Biomédica en Cáncer, Instituto Nacional de Cancerología, México/Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Mexico City, Mexico,* [3] *Laboratory of Virus and Cancer, Subdirección de Investigación Básica, Instituto Nacional de Cancerología, Mexico City, Mexico,* [4] *Programa de Maestría y Doctorado en Ciencias Médicas, Odontológicas y de la Salud, Maestría en Investigación Clínica Experimental, Universidad Nacional Autónoma de Mexico, Mexico City, Mexico,* [5] *Biological Cancer Causing Agents Group, Instituto Nacional de Cancerología, Mexico City, Mexico,* [6] *Cátedras CONACyT-Instituto Nacional de Cancerología, Mexico City, Mexico*



Lactate in the Regulation of Tumor Microenvironment and Therapeutic Approaches. Front Oncol. 2019 Nov 1;9:1143.

Just a few words about Lactate



Lactate in the Regulation of Tumor Microenvironment and Therapeutic Approaches. Front Oncol. 2019 Nov 1;9:1143.

Tumor Microenvironment milieu

- **Weak/Leaky Vasculature**
→ Hypoxia,angiogenesis, metastasis, …

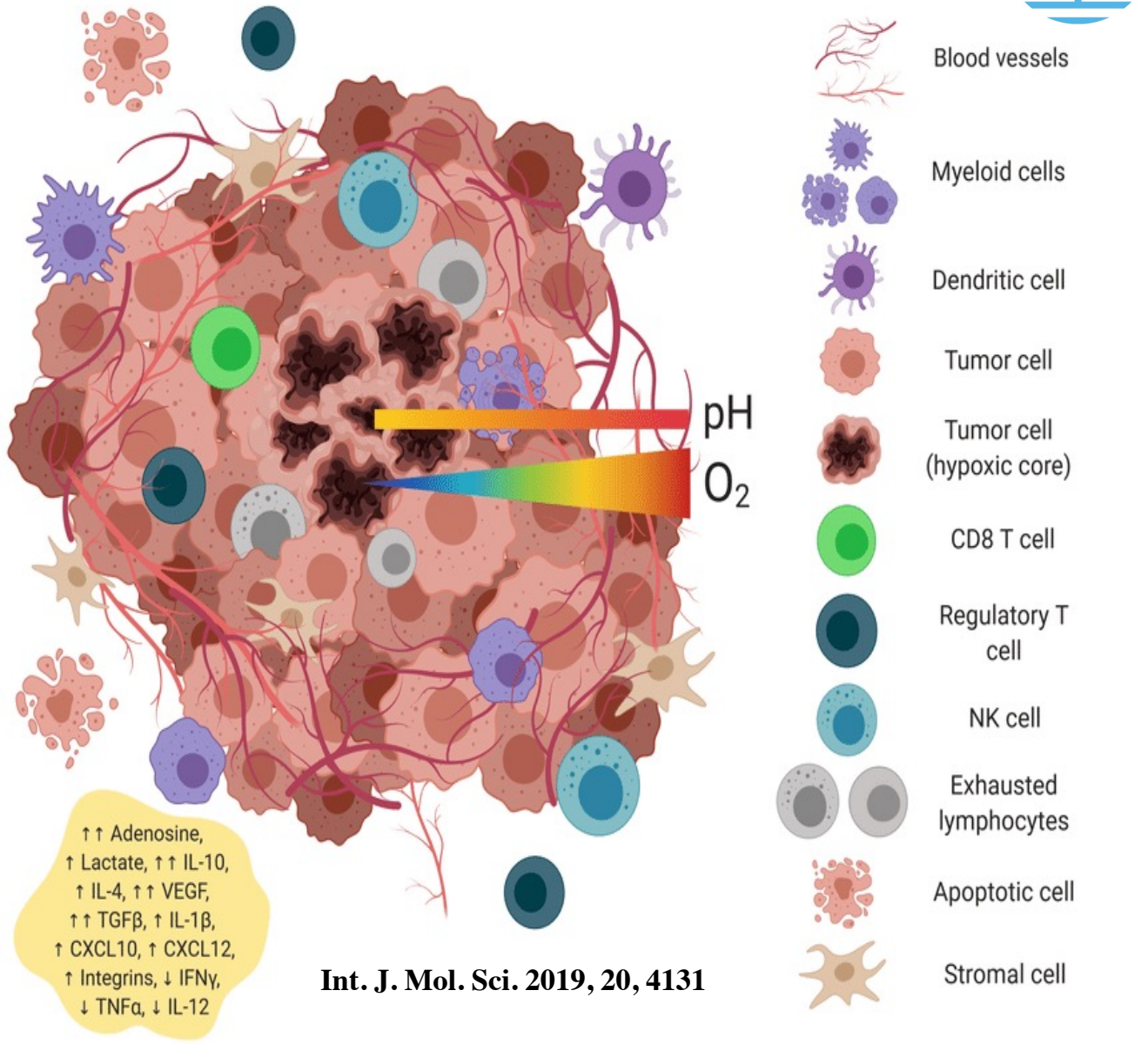
- **Disturbed Immune cells**
→ suppressed Cytotoxic T cells, NK, …

- **Dissolved Extracellular matrix**
→ acting on fibroblasts, collagen, MMP , …

- **Various Proteins & metabolic molecules**
→ lactate, pyruvate, glutamate, …

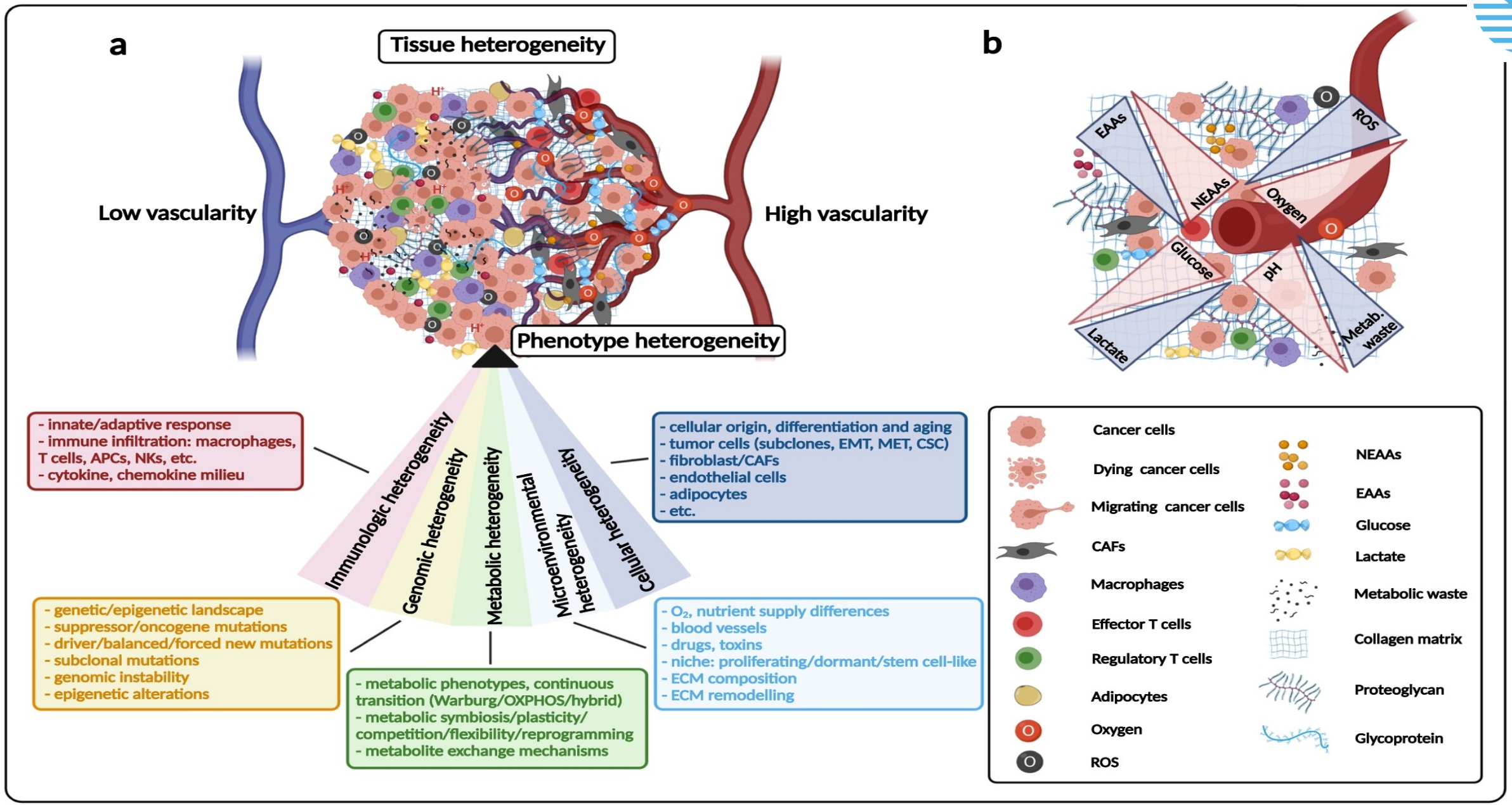
- **Inflammation, toxic burden & acidity**

- **Mitochondropathy, ROS, …**



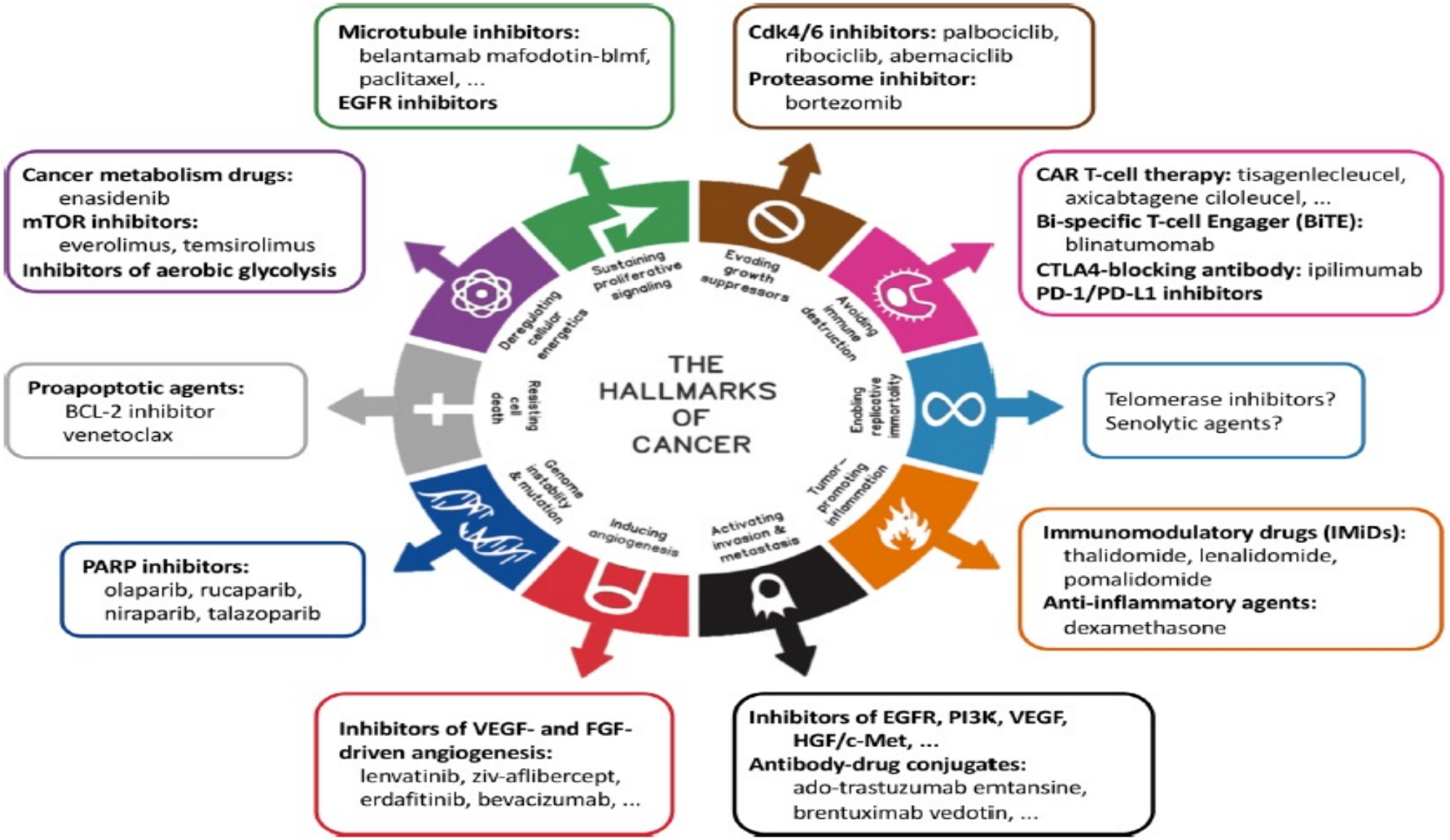
Int. J. Mol. Sci. 2019, 20, 4131

Tumor Microenvironment & Hallmarks of cancer



Cancer Metastasis Rev 40, 989–1033 (2021)

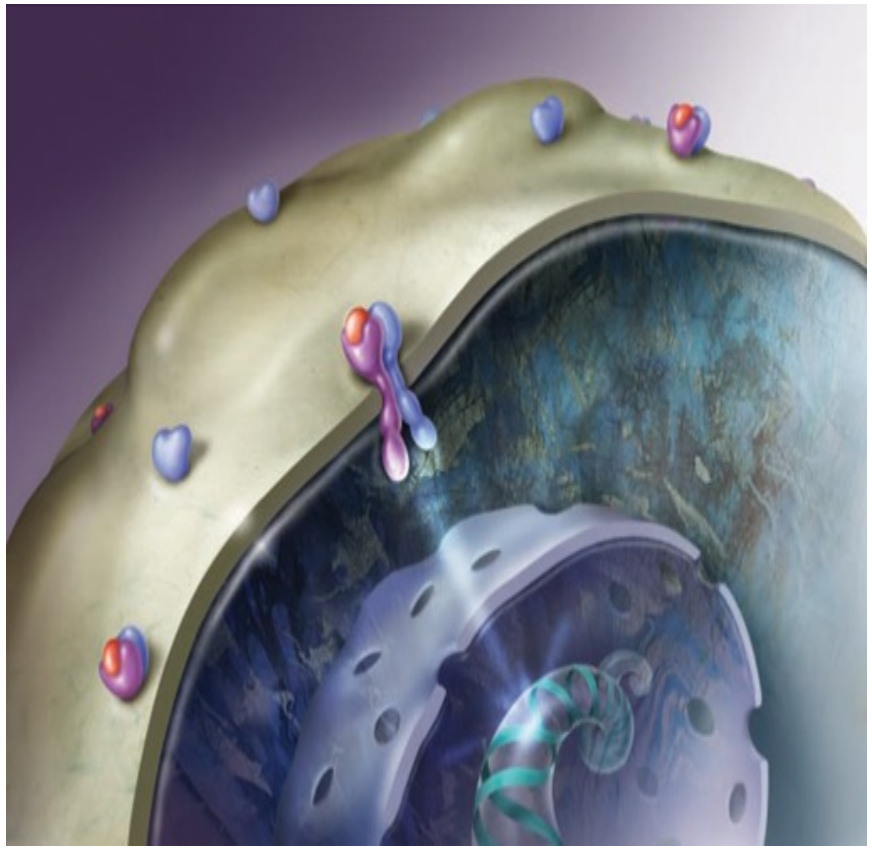
Targeted Therapy, is it?



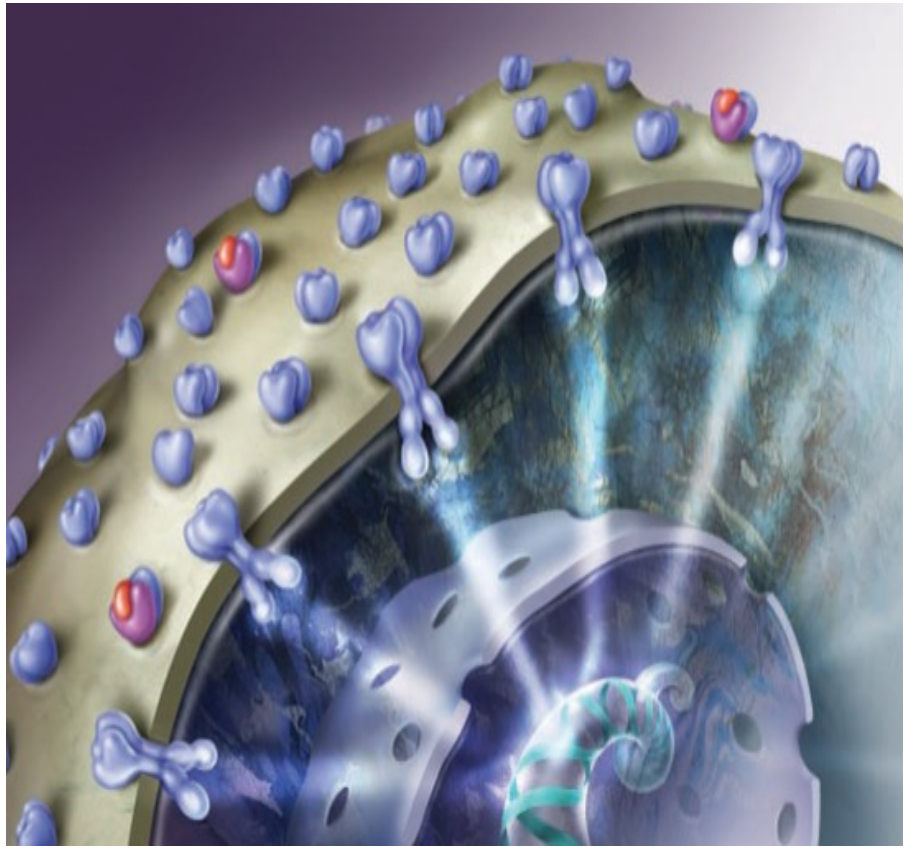
Druggable genome and precision medicine in cancer: current challenges. FEBS J. 2021 Nov;288(21):6142-6158

Examples of Cancer Genetics HER2-*neu* Gene (ERBB2)

Normal HER2 Expression
20 000 receptors/cell



HER2 Over Expression
2 000 000 receptors/cell

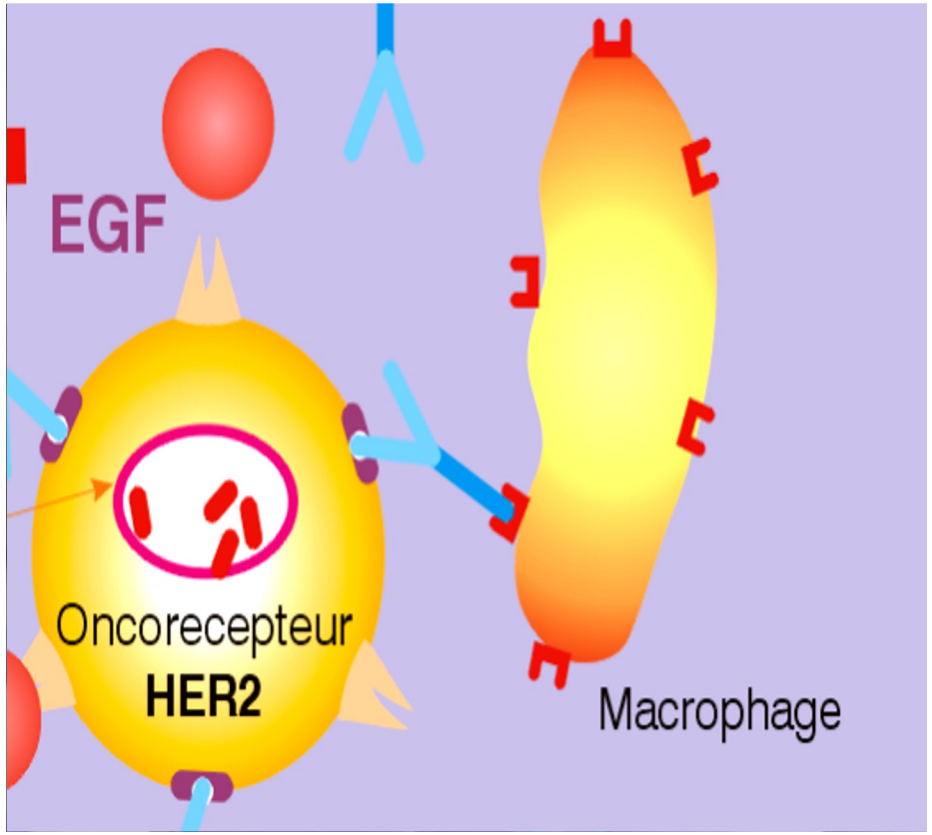


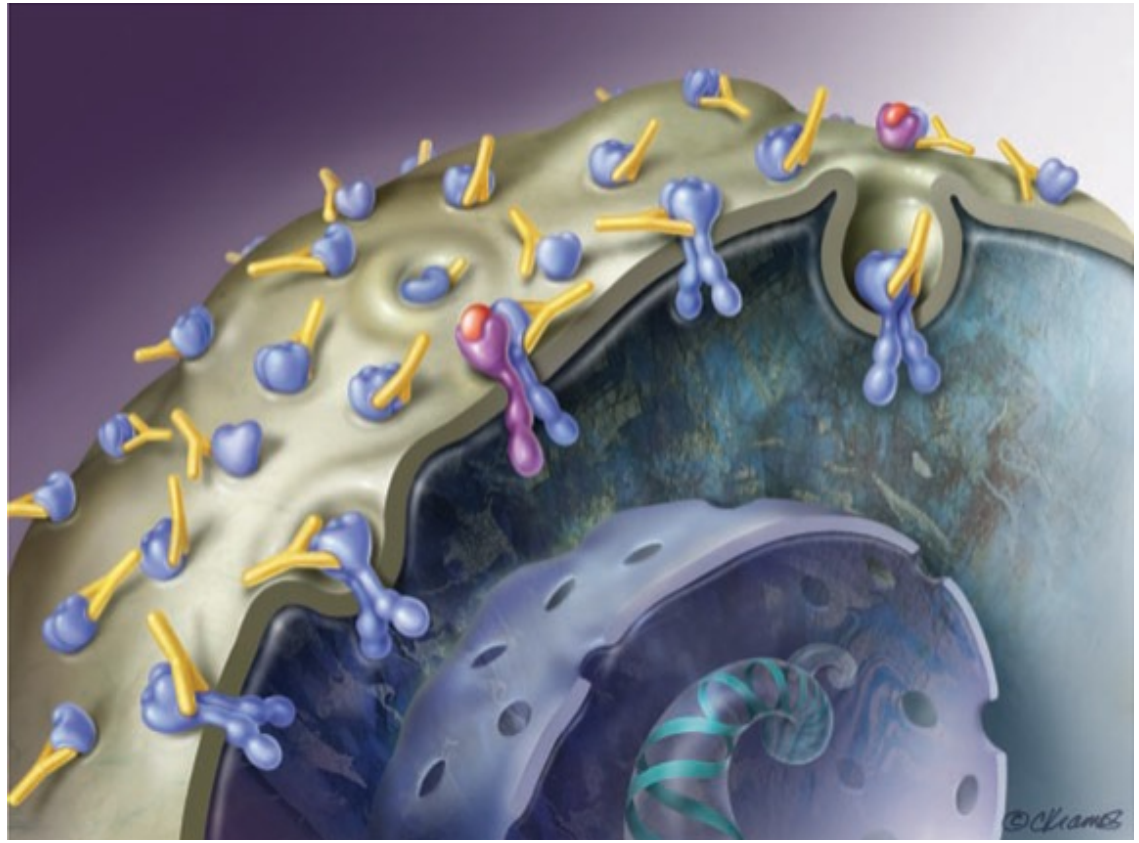
HER2 Amplification

Binding of Trastuzumab to HER2 & mechanism of anti-tumor effec

- Enable immune cells to attack tumor target cells (ADCC)

- Accelerate internalization & Degradation of HER2 protein receptor
- Antagonizing growth signal properties





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CURRENT ISSUE

Meeting Abstract: 2023 ASCO Annual Meeting I
FREE ACCESS | Symptoms and Survivorship | May 31, 2023

Trastuzumab-induced cardiotoxicity in breast cancer patients: A meta-analysis and review of the literature (2012-2022).

Authors: Fnu Anamika, Akshit Chitkara, Komal Saharan, Tushar Choudhary, Ujjwal Soni, Gabriella Angelina Harmon, and Anwaar Saeed | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 41, Number 16_suppl
https://doi.org/10.1200/JCO.2023.41.16_suppl.e24101

After a full literature review, selecting four studies that included 1481 patients with cardiotoxicity data in the treatment and control groups.

Cardiotoxicity (specifically LVEF reduction) in patients treated with Trastuzumab were about **seven times higher** than the control group (OR 6.78, 95% CI 2.85-16.09, p-value < 0.0001).

Targeted Therapy ….Which cells are we killing?

Signal Transduction and Targeted Therapy

www.nature.com/sigtrans

REVIEW ARTICLE OPEN

Advantages of targeting the tumor immune microenvironment over blocking immune checkpoint in cancer immunotherapy

Tianyu Tang[1,2,3,4], Xing Huang[1,2,3,4], Gang Zhang[1,2,3,4], Zhengtao Hong[1,2,3,4], Xueli Bai[1,2,3,4] and Tingbo Liang[1,2,3,4]

- The incidence of all grades of irAE is reported to range from 15 to 90%, and the frequency of severe irAEs requiring immunosuppression and withdrawal from immunotherapy is estimated to be between 0.5 and 13%.
- Disordered infiltration of immune cells in normal skin, gastrointestinal, hepatic, thyroid, renal, pulmonary, musculo-skeletal, and pituitary tissues has been reported in cancer patients receiving ICP-targeted therapies.
- These irAEs can lead to treatment interruption and even multiple organ failure.

Advantages of targeting the tumor immune microenvironment over blocking immune checkpoint in cancer immunotherapy. Sig Transduct Target Ther 6, 72 (2021)

Targeted Therapy

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01655-5

Check for updates

Intestinal *Akkermansia muciniphila* predicts clinical response to PD-1 blockade in patients with advanced non-small-cell lung cancer

potential biomarkers to refine patient stratification

Baseline **stool Akk** was associated with increased objective response rates and overall survival in multivariate analyses, independent of PD-L1 expression, antibiotics, and performance status.

However, antibiotic use (20% of cases) coincided with a relative dominance of Akk above 4.8% accompanied with the genus *Clostridium*, both associated with **resistance to ICI**.

Derosa, et al (2022). Intestinal Akkermansia muciniphila predicts clinical response to PD-1 blockade in patients with advanced non-small-cell lung cancer. Nature Medicine, 28(2), 315-324.

Targeted Therapy

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 25 October 2022
DOI 10.3389/fonc.2022.887383

The gut microbiota modulates responses to anti–PD-1 and chemotherapy combination therapy and related adverse events in patients with advanced solid tumors

Zhaozhen Wu[1,2,3], Sujie Zhang[1], Lingling Li[1,3], Ziwei Huang[1], Di Huang[1] and Yi Hu[1,3*]

[1]Department of Medical Oncology, the Fifth Medicine Center of Chinese People's Liberation Army (PLA) General Hospital, Beijing, China, [2]Beijing Chest Hospital, Beijing, China, [3]School of Medicine, Nankai University, Tianjin, China

Conclusion: Beta diversity and differences in the gut microbiota modulated AEs and the response to anti–PD-1 blockade combined with chemotherapy Dynamic changes in the intestinal microbiome may predict the efficacy of PD-1 inhibitor–based therapy.

Wu Z, et al (2022) The gut microbiota modulates responses to anti–PD-1 and chemotherapy combination therapy and related adverse events in patients with advanced solid tumors. Front. Oncol. 12:887383.

"Boss is coming! Discover something!"

Optimizing Tumor Microenvironment

GUT MICROBES
2024, VOL. 16, NO. 1, 2341717
https://doi.org/10.1080/19490976.2024.2341717

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

An emerging strategy: probiotics enhance the effectiveness of tumor immunotherapy via mediating the gut microbiome

Shuaiming Jiang[a], Wenyao Ma[a], Chenchen Ma[b], Zeng Zhang[a], Wanli Zhang[a], and Jiachao Zhang[a]

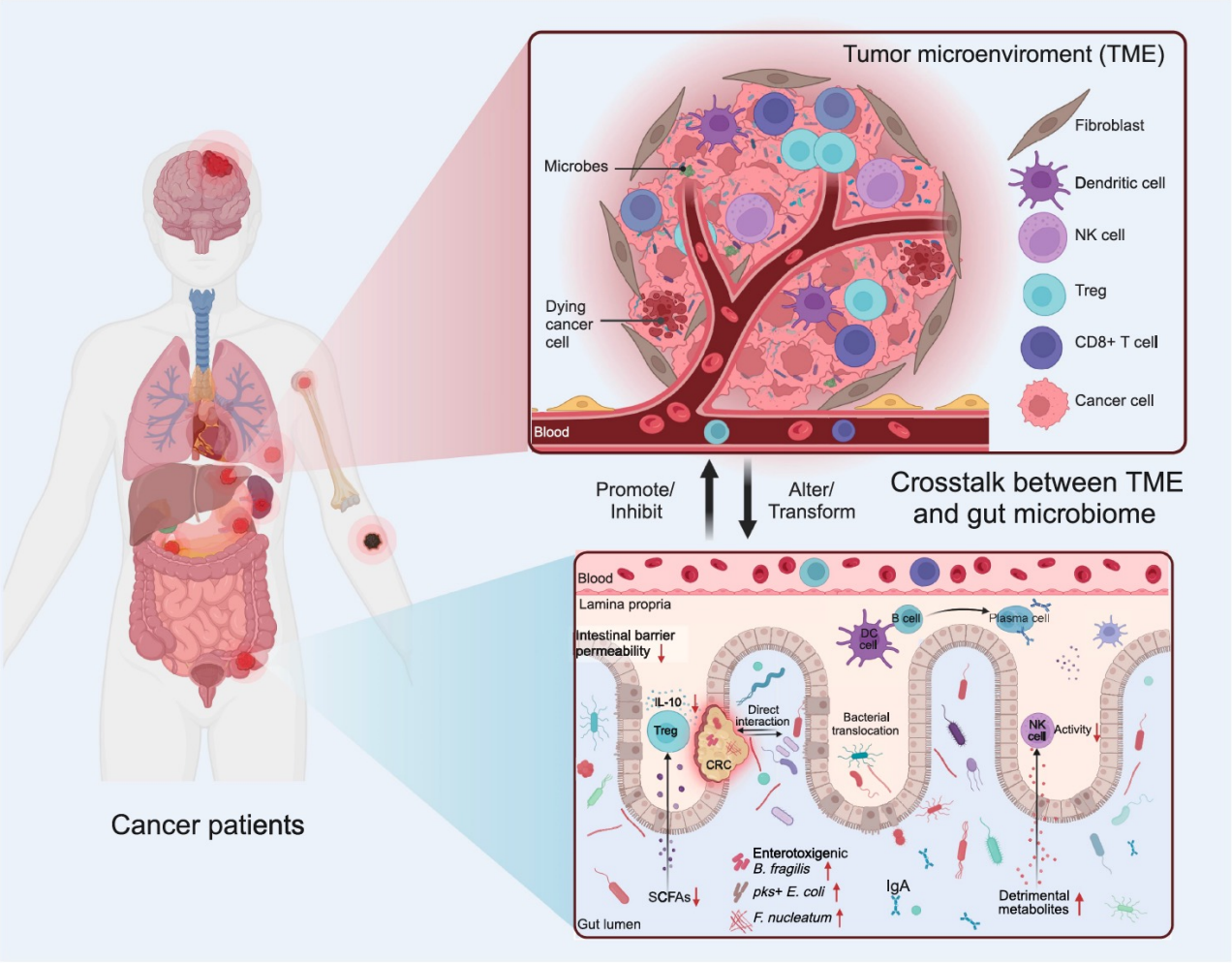


Figure 2. The crosstalk between gut microbiome and TME.

Optimizing Tumor Microenvironment

Table 1. Human-Based Studies Reporting on the Gut Microbiome and Anti-Tumor Effect of ICIs

Study (year)	Microbiota positively correlated with ICI efficacy (a)	Microbiota negatively correlated with ICI efficacy (b)	Target of ICI	Inter-vention	Included malignancy	No. of patients	Significant outcome
Chaput et al. (2017)[14]	*Faecalibacterium* *Firmicutes*	*Bacteroides*	CTLA-4	-	Metastatic melanoma	26	Group with enriched (a) showed longer PFS and OS than group with enriched (b)
Gopalakrishnan et al. (2018)[15]	*Ruminococcaceae* family	-	PD-1	-	Metastatic melanoma	43	Responders showed higher alpha-diversity and abundance of (a)
Matson et al. (2018)[16]	*Bifidobacterium longum* *Collinsella aerofaciens* *Enterococcus faecium*	-	PD-1	-	Metastatic melanoma	42	Responders showed commensal bacteria composition was more abundant in (a) compared to non-responders
Routy et al. (2018)[17]	*Akkermansia muciniphila*	-	PD-1	-	NSCLC+ RCC	100	(a) was correlated with clinical response of PD-1 Ab
Routy et al. (2018)[17]	*Ruminococcus* *Alistipes* *Eubacterium*	*Bifidobacterium adolescentis* *B. longum* *Parabacteroides distasonis*	PD-1	-	NSCLC	60	Responders showed commensal bacteria composition was more abundant in (a) compared to non-responders Responders showed commensal bacteria composition was less abundant in (b) compared to non-responders
Baruch et al. (2021)[18]	*Enterococcaceae* *Enterococcus* *Streptococcus australis*	*Veillonella atypica*	PD-1	FMT	PD-1 refractory metastatic melanoma	10	Clinical response to PD-1 Ab in 3 out of 10 patients who underwent FMT Higher abundance of (a) and lower abundance of (b) in responders to PD-1 Ab after FMT
Davar et al. (2021)[19]	phylum *Firmicutes* (*Lachnospiraceae*, *Ruminococcaceae* families) phylum *Actinobacteria* (*Bifidobacteriaceae*, *Coriobacteriaceae* families)	phylum *Bacteroidetes*	PD-1	FMT	PD-1 refractory metastatic melanoma	15	Clinical response to PD-1 Ab in 6 out of 15 patients who underwent FMT (a) enriched in responders, and (b) decreased in responders
Spencer et al. (2021)[20]	*Ruminococcaceae* family *Faecalibacterium*	-	PD-1	-	Metastatic melanoma	132	Responders showed higher abundance of (a)
Spencer et al. (2021)[20]	-	-	PD-1 / CTLA-4	Probiotics	Metastatic melanoma	158	No difference in survival probability between probiotics intake group and control group
Dizman et al. (2022)[21]	*Bifidobacterium*	-	PD-1 + CTLA-4	Probiotics	RCC	30	Longer PFS in probiotics supplement group

ICI, immune checkpoint inhibitor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PFS, progression-free survival; OS, overall survival; PD-1, programmed cell death protein 1; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; FMT, fecal microbiota transplantation; Ab, antibody.

Intest Res 2023;21(4):433-442

Optimizing Tumor Microenvironment

nature cell biology

Review Article

https://doi.org/10.1038/s41556-022-01002-x

Metabolic communication in the tumour–immune microenvironment

Received: 12 July 2021

Accepted: 29 August 2022

Published online: 13 October 2022

Check for updates

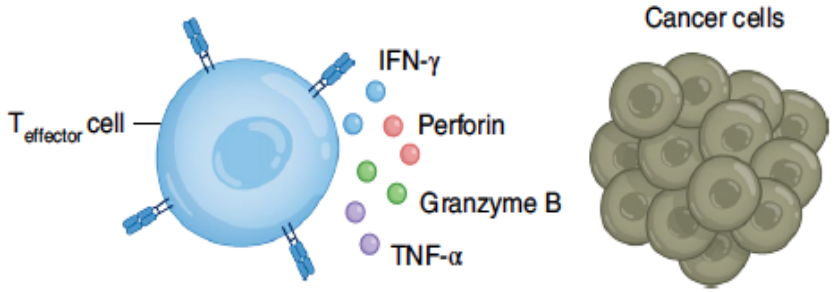
Kung-Chi Kao[1,2], Stefania Vilbois[1,2], Chin-Hsien Tsai[3] and Ping-Chih Ho[1,2]

The metabolically hostile tumour microenvironment imposes barriers to tumour-infiltrating immune cells and impedes durable clinical remission following immunotherapy. Metabolic communication between cancer cells and their neighbouring immune cells could determine the amplitude and type of immune responses, highlighting a potential involvement of metabolic crosstalk in immune surveillance and escape. In this Review, we explore tumour–immune metabolic crosstalk and discuss potential nutrient-limiting strategies that favour anti-tumour immune responses.

Metabolic communication in the tumour–immune microenvironment. Nat Cell Biol 24, 1574–1583 (2022)

Optimizing Tumor Microenvironment

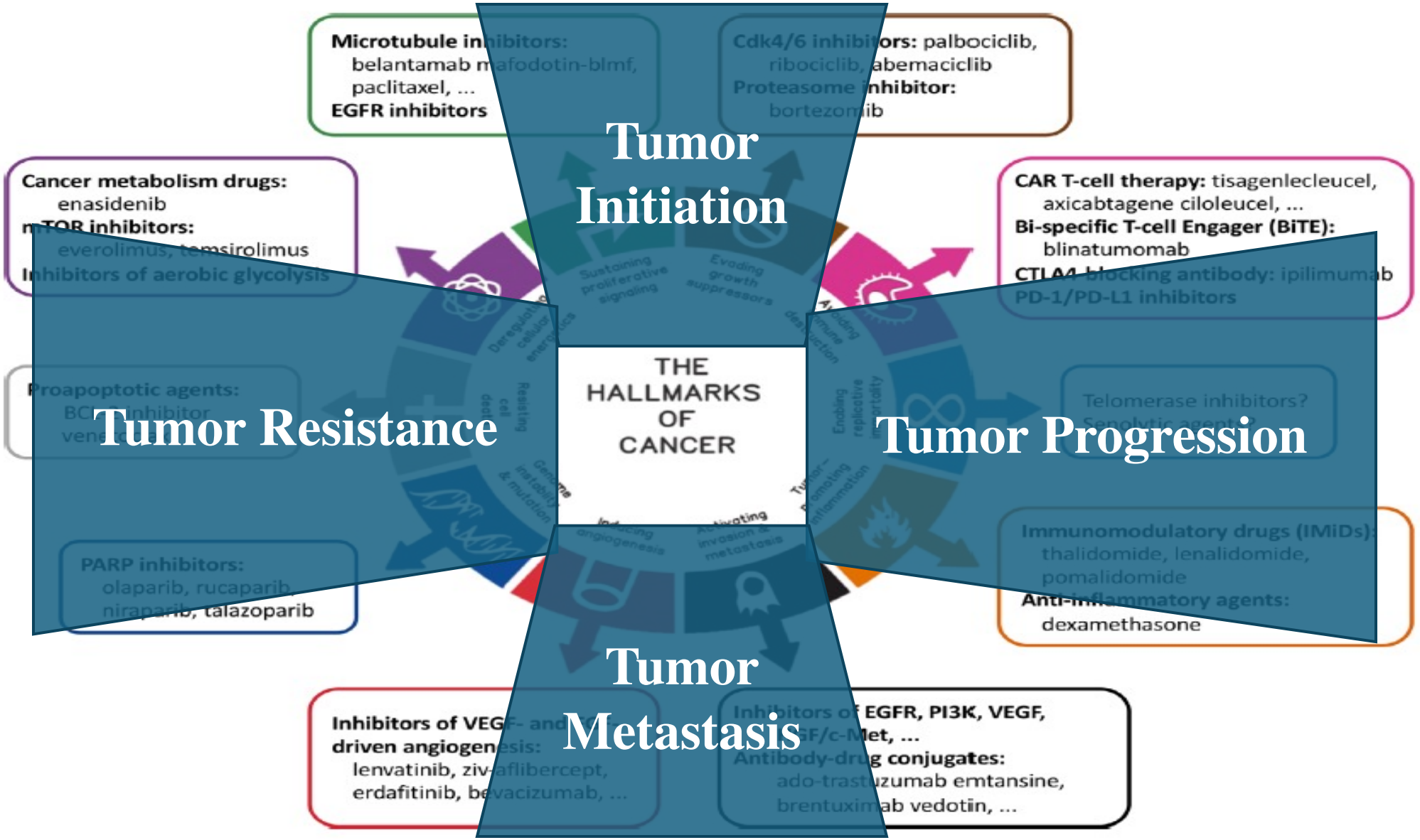
Influence of Nutritional interventions on the TME



Ketogenic diet	↑ OXPHOS pathway IFN-γ, perforin, granzyme B and TNF-α	↓ Warburg effect
Caloric restriction	Expands $CD8^+$ TIL population Immune signature linked with anti-tumour immunity ↑ Protection from chemotherapy toxic effects via caloric restriction-induced autophagy Stem cell-like property via caloric restriction-induced autophagy	↑ Senescence and cell death (in combination with chemotherapy) ↓ Survival signal
Intermittent fasting	↑ $CD8^+$ TIL recuitment to tumour site	↓ Glycolytic pathway Proliferation (in combination with rapamycin
Amino acids	L-arginine supplementation (switches T cell metabolism from glycolysis to OXPHOS) ↑ Improves T cell survival, proliferation and anti-tumoral activity Methionine supplementation (causes the secretion of IL-2, TNF-α and IFN-γ from T cells and enhances survival)	Methionine supplementation (inhibits tumour growth) ↓ Methionine restriction in cancers using methionine as fuel (inhibits tumour growth)

Metabolic communication in the tumour–immune microenvironment. Nat Cell Biol 24, 1574–1583 (2022)

Targeted Therapy ….do we have to rethink?



Druggable genome and precision medicine in cancer: current challenges. FEBS J. 2021 Nov;288(21):6142-6158

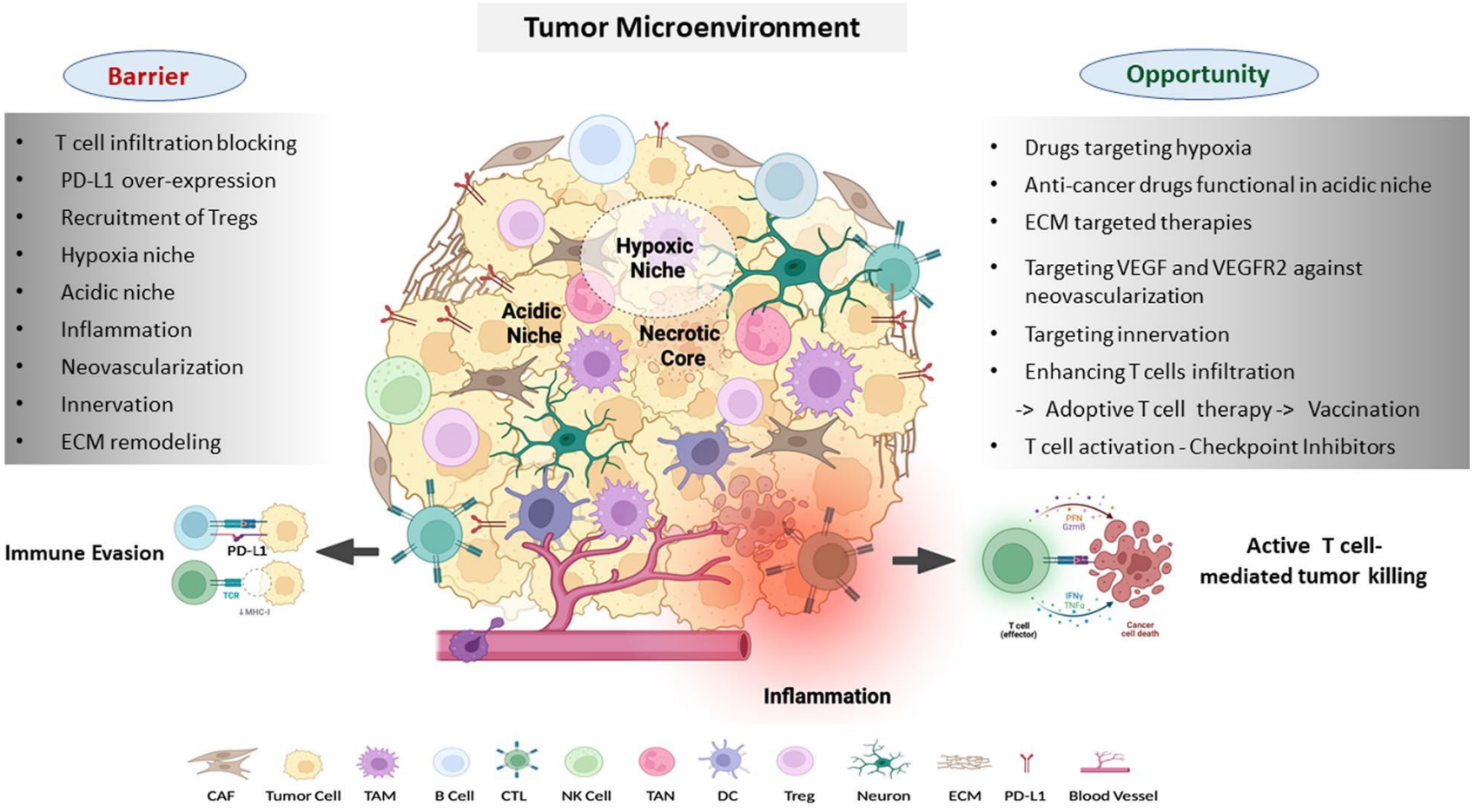
Understanding TIME .. Barrier or Opportunity?

Tiwari *et al.*
Journal of Biomedical Science (2022) 29:83
https://doi.org/10.1186/s12929-022-00866-3

NSTC 國家科學及技術委員會 National Science and Technology Council
The cost of publication in *Journal of Biomedical Science* is borne by the National Science and Technology Council (NSTC), Taiwan.

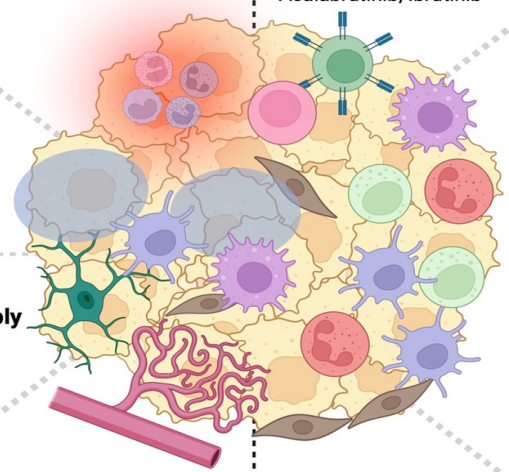
Journal of Biomedical Science

REVIEW **Open Access**



Tiwari, A., et al. Tumor microenvironment: barrier or opportunity towards effective cancer therapy. J Biomed Sci 29, 83 (2022).

Targeting different TME components for cancer therapy



Inflammation

A) Targeting inflammation

NSAIDs- Aspirin, Ibuprofen, Naproxen
NF-κB inhibition- Curcumin, Resveratrol, Ursolic acid, Capsaicin, Silibinin, Silymarin, Guggulsterone, plumbagin
STAT3 inhibition- AG- 490, Static, S3I-M2001
COX-2 inhibition- Celecoxib
Corticosteroids- Dexamethasone
Antiinflammatory effect- Statins, Metformin
Blocking monocytes infiltration- CNTO 88, Trabectedin
JAK inhibition- Ruxolitinib, Tofacitinib
Blocking IL-6 signaling-Siltuximab
Blocking IL-8 signaling-Reparixin

Hypoxia

B) Targeting hypoxic TME

HIF-1 inhibition- Topotecan, EZN-2968, Digoxin,Glufosfamide
GLUT1- 2-GLU-SNAP, Fasentin,
EGFR targeting - Gefitinib, erlotinib, Cetuximab
RAS–MAPK signalling- Sorafenib
Targeting mTOR- Rapamycin, Everolimus
Autophagy- Chloroquine,
UPR pathway-Geldanamycin, Salicaldehydes, Bortezomib

Innervation

C) Targeting TME nerve supply

Surgical ablation of nerve
Blocking of parasympathetic cholinergic nerve signals

Blocking neural input- 6- hydroxydopamine (6HODA),
Electrical stimulation
Chemical denervation- For cancer associated pain
Antipsychotic drugs- Fluoxetine
Antineurotrophic therapies
NGF inhibition- Tanezumab
TRK inhibition- Entrectinib
Larotrectinib (impact nerve recruitment in TME
Beta-blockers

Angiogenesis

D)Targeting TME vasularization

Antiangiogenic agents
VEGF inhibition - Bevacizumab, Ramucirumab, Vanucizumab
Vandetanib, Cediranib
anti- EGFR- Cetuximab, Panitumumab
MMPs Inhibition- Marimastat

FGFR inhibition- Futibatinib, Infigratinib
Combine targeting TGF-β & PD-L1 - Bintrafusp alfa, SHR1701

Tyrosine kinase inhibition- Gefitinib, Erlotinib, Sorafenib,
Sunitinib, Axitinib, Pazopanib
Pericyte targeting,
Targeting miRNAs and extracellular vesicles
Inhibition of Adesion molecule JAM-A

CAFs

E) Targeting fibroblast

FAP Inhibition- SynCon DNA vaccine, FAP-specific CAR T cell, Oncolytic adenovirus
Vitamin A analog - ATAR
Vitamin D analog - Calcipotriol

CXCL12-CXCR4 blocking - AMD3100,
JAK inhibition - Ruxolitinib

Blocking TGF-β - NIS793 ABBV151, HA-PTX/MATT HNPs,

Killing CAF - 5-Fluorouracil, sTRAIL LPD, Imatinib,
Targeting TGF-β- Artemisinin derivatives

Adaptive Immune system

K) Activation of CTLs

Immune Checkpoint Inhibition-
PD-1- PEMBROLIZUMAB, NIVOLUMAB,
PD-L1- DURVALUMAB ,ATEZOLIZUMAB, CA-170,
CTLA-4- TIPILIMUMAB,
Tim3- TSR-022 (phase I),
OX40- MOR0916, **ICOS-** JTX-2011 (phase I),
VISTA- JNJ-61610588, CA-170 (phase I)

CAR-T based Therapy (Engineered T-cells)
Cancer vaccines (tumor neo-antigen)

L) Targeting B cells

Cancer vaccines- CD40B cells
Adoptive B-cell therapy
BCR signalling inhibitors
Acalabrutinib, Ibrutinib

Innate Immune system

F) Inducing M1 Polarization

IFNγ, CD40 agonists,
Inhibition of PI3K, mTOR,

DICER, TLR agonists,
Methionine sulfoximine, Tasquinimod,**HDAC inhibition,**
MARCO antibody

G) Inhibiting M2 Polarization:

CSF1R inhibition- Pexidartinib (phase IIb).
Corosolic acid, Omeprazole, ARRY-382,
Gpr132 inhibition, MEK/STAT3 inhibitors,
Antibodies againstf IL-4, IL-4Ra, IL-13

H) Targeting Neutrophils

Neutrophils activation- FcγR targeting, β-glucan, EGFR antibodies- zalutumumab (IgG1), panitumumab, cetuximab (IgG1)
Depleting Neutrophils - anti-Ly-6 G antibodies

I) Targeting Natural Killer cells

Antibody-Based NK Cell Therapy- Expressing high-affinity CD16 FcγRIII in NK cells
Potentiation of NK Cell Activity - IL-15, ALT-803, BiKEs or TriKEs
CAR-NK Therapy

J) Targeting Dendritic cells

TLR agonists- Imiquimod, R848, IMO-2125, Poly-ICLC,
VEGF inhibition- Regorafenib, Bevacizumab
Blocking IL-10,
DC *in vivo* expansion by Flt3L
DC Vaccines - Sipuleucel-T
Targeting TGFß - M7824, Galunisertib,
STING agonism - MK-1454
CD40 agonism- APX005M, ABBV-927

Sum up- Optimizing Tumor Microenvironment

IT ALL STARTS IN THE GUT!

- Gut Microbiome optimization
- Applying Nutrigenomics is essential
- Applying targeted Nutraceuticals – right dose- no side effects
- Replenishing Nutritional Deficiencies
- Addressing Vitamin D levels
- Optimizing Methylation - compare with symptoms
- Optimizing detoxification & elimination

Do not forget Gut-Brain-Immune Axis !

Then choose the right Conventional treatment for your patient ☺

Applying targeted Nutraceuticals, why?

Biomedicine & Pharmacotherapy 150 (2022) 113054

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

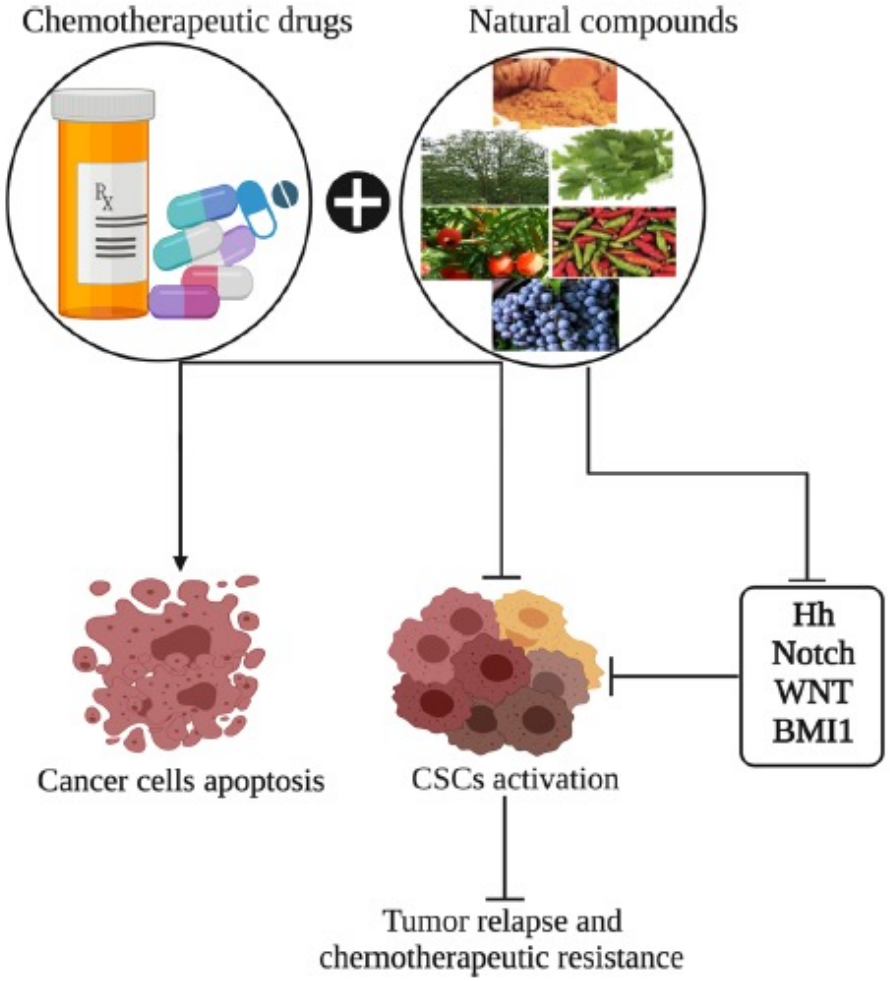
journal homepage: www.elsevier.com/locate/biopha

Review

Targeting cancer signaling pathways by natural products: Exploring promising anti-cancer agents

Sheema Hashem [a,1], Tayyiba Akbar Ali [a,1], Sabah Akhtar [a,1], Sabah Nisar [a], Geetanjali Sageena [b], Shahid Ali [c], Sharefa Al-Mannai [d], Lubna Therachiyil [e,f], Rashid Mir [g], Imadeldin Elfaki [h], Mohammad Muzaffar Mir [i], Farrukh Jamal [j], Tariq Masoodi [a], Shahab Uddin [e], Mayank Singh [k], Mohammad Haris [a,l,m], Muzafar Macha [n,*], Ajaz A. Bhat [a,**]

[a] Laboratory of Molecular and Metabolic Imaging, Sidra Medicine, Doha, Qatar
[b] Keshav Mahavidyalaya, University of Delhi, New Delhi 110034, India
[c] International Potato Center (CIP), Shillong, Meghalaya, India
[d] Division of Translational Medicine, Research Branch, Sidra Medicine, Doha 26999, Qatar



Targeting cancer signaling pathways by natural products: Exploring promising anti-cancer agents. Biomed Pharmacother. 2022 Jun;150:113054.

Applying targeted Nutraceuticals & Food:

Seminars in Cancer Biology 73 (2021) 45–57

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Effects of caloric restriction on immunosurveillance, microbiota and cancer cell phenotype: Possible implications for cancer treatment

Francesca Pistollato [a,1], Tamara Yuliett Forbes-Hernandez [b,1], Ruben Calderón Iglesias [a], Roberto Ruiz [a], Maria Elexpuru Zabaleta [a], Irma Dominguez [c,d], Danila Cianciosi [e], Josè L. Quiles [f], Francesca Giampieri [e,g,h,*], Maurizio Battino [e,i,*]

[a] Centre for Nutrition and Health, Universidad Europea del Atlántico (UEA), Santander, Spain
[b] Nutrition and Food Science Group, Department of Analytical and Food Chemistry, CITACA, CACTI, University of Vigo, Vigo, Spain
[c] Universidad Internacional Iberoamericana (UNINI), Campheee, Mexico
[d] Universidade Internacional do Cuanza, Cuito, Angola

F. Pistollato et al. Effects of caloric restriction on immunosurveillance, microbiota and cancer cell phenotype: Possible implications for cancer treatment. Seminars in Cancer Biology 73 (2021) 45–57

Applying targeted Nutraceuticals & Food:

Caloric Restriction Mimetics (CRMs) and their possible effects

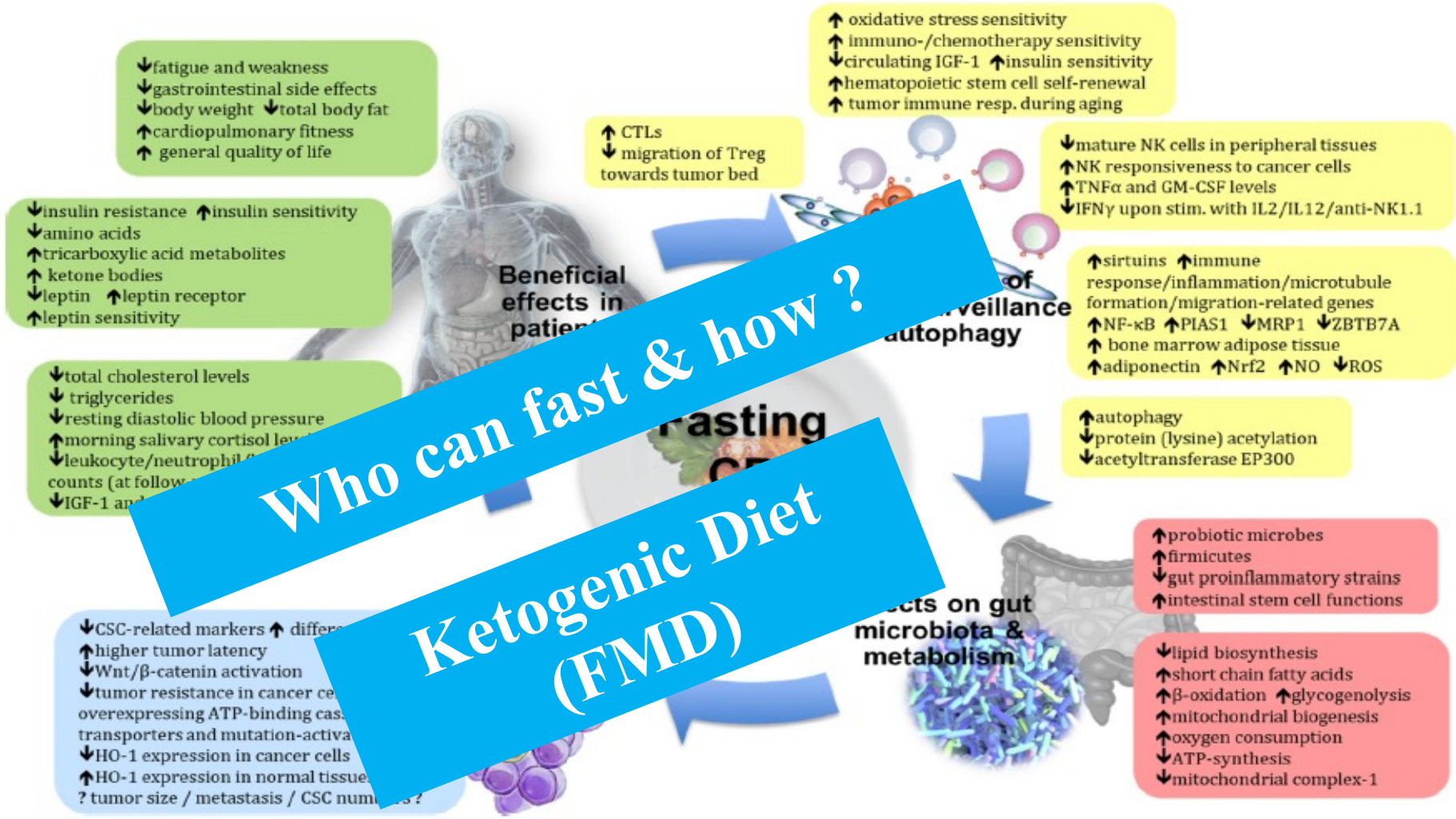
- hydroxycitrate
- nicotinamide
- resveratrol
- epigallocatechin-3-gallate
- garcinol
- anacardic acid
- curcumin
- spermidine
- 3,4-dimethoxychalcone
- aspirin, salicylate
- gamma/delta-tocopherols/ tocotrienols
- carotenoids (e.g., lycopene)
- isothiocyanates (from cruciferae)
- sulfur compounds (from allieae, terpenoids)
- quercetin

- ✓ induction of autophagy (via reduction of lysine acetylation)
- ✓ improvement of chemotherapy efficacy (via stimulation of cellular immune response)
- ✓ decrease of tumor resistance
- ✓ possible cardio-protective effects
- ✓ upregulation of sirtuins
- ✓ cytoprotection (via activation of Nrf2 pathway)
- ✓ antioxidant effects
- ✓ anti-inflammatory response
- ✓ mitochondrial biogenesis
- ✓ detoxification and excretion of toxic metals and organic xenobiotics
- ✓ depending on cancer cell type: increase of mitochondrial respiration and oxygen consumption; inhibition of mitochondrial complex I in a SIRT1-dependent mechanism
- ✓ increased ROS production and apoptosis in cancer cells
- ✓ reduction of CSC-related markers

Fig. 1. Summary of the possible effects elicited by caloric restriction mimetics (CRMs).

F. Pistollato et al. Effects of caloric restriction on immunosurveillance, microbiota and cancer cell phenotype: Possible implications for cancer treatment. Seminars in Cancer Biology 73 (2021) 45–57

Applying targeted Nutraceuticals & Food:



F. Pistollato et al. Effects of caloric restriction on immunosurveillance, microbiota and cancer cell phenotype: Possible implications for cancer treatment. Seminars in Cancer Biology 73 (2021) 45–57

Applying targeted Nutraceuticals & Food:

Biotechnology Advances 38 (2020) 107385

Contents lists available at ScienceDirect

Biotechnology Advances

journal homepage: www.elsevier.com/locate/biotechadv

Research review paper

Anti-cancer effects of polyphenols via targeting p53 signaling pathway: updates and future directions

- Stabilize p53 protein
- Overcome chemoresistance of cancer cells by increasing p53 expression.
- Resveratrol can drive cancer cell death in p53-dependent way
- Derivatives of of gallic acid;Berries, sea buckthorn, pomegranate in CRC→ Caspase 3 ↑, caspase 9 ↑, p53 ↑

Anti-cancer effects of polyphenols via targeting p53 signaling pathway: updates and future directions. Biotechnol Adv. 2020 Jan-Feb;38:107385.

Applying targeted Nutraceuticals & Food:

molecules

MDPI

Review

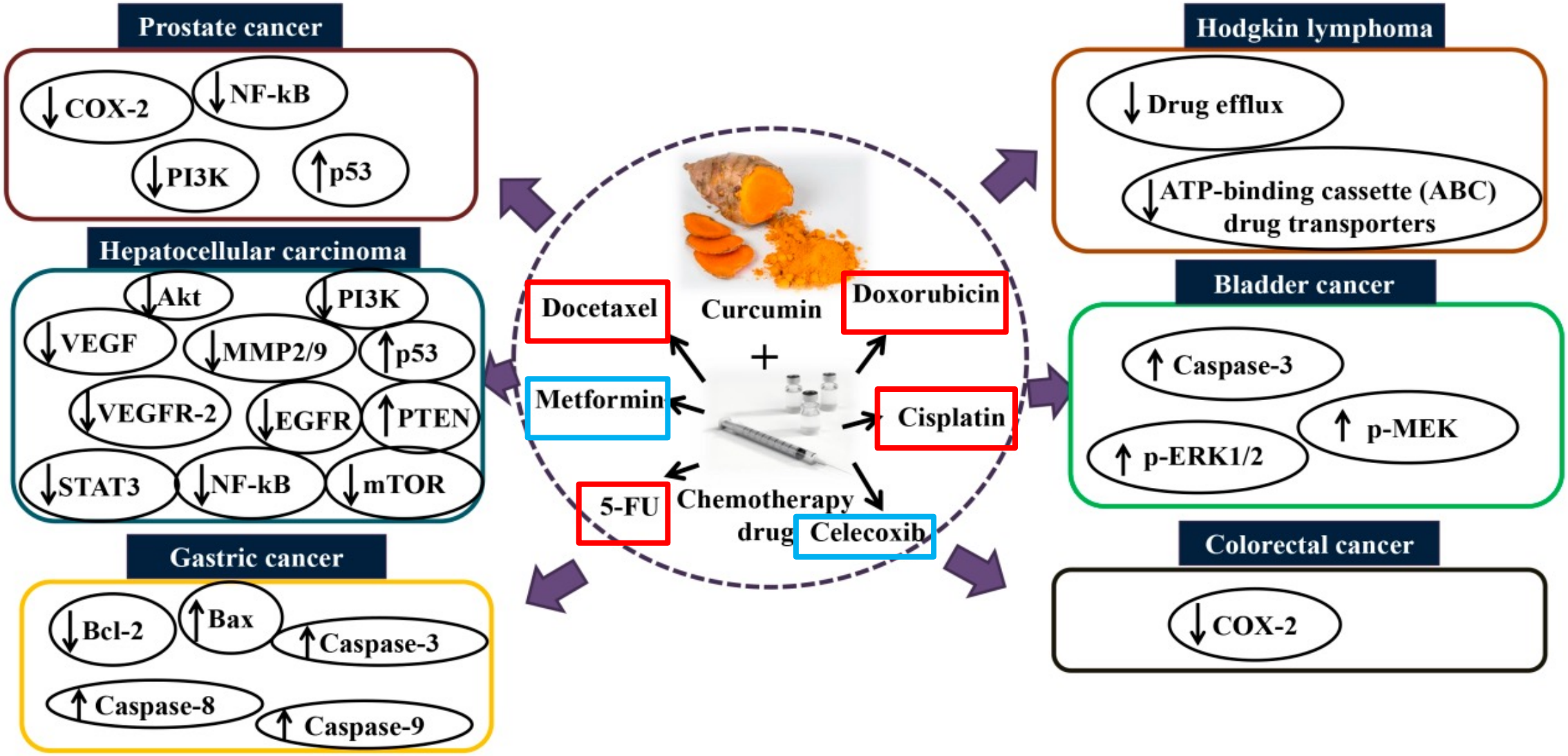
Curcumin Combination Chemotherapy: The Implication and Efficacy in Cancer

Bee Ling Tan [1] and Mohd Esa Norhaizan [1,2,3,*]

1 Department of Nutrition and Dietetics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang 43400, Selangor, Malaysia
2 Laboratory of Molecular Biomedicine, Institute of Bioscience, Universiti Putra Malaysia, Serdang 43400, Selangor, Malaysia
3 Research Centre of Excellent, Nutrition and Non-Communicable Diseases (NNCD), Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang 43400, Selangor, Malaysia
* Correspondence: nhaizan@upm.edu.my; Tel.: +603-89472427

Curcumin Combination Chemotherapy: The Implication and Efficacy in Cancer. Molecules. 2019 Jul 10;24(14):2527

Applying targeted Nutraceuticals & Food:



Curcumin Combination Chemotherapy: The Implication and Efficacy in Cancer. Molecules. 2019 Jul 10;24(14):2527

Applying targeted Nutraceuticals & Food:

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Biotechnology Advances

journal homepage: www.elsevier.com/locate/biotechadv

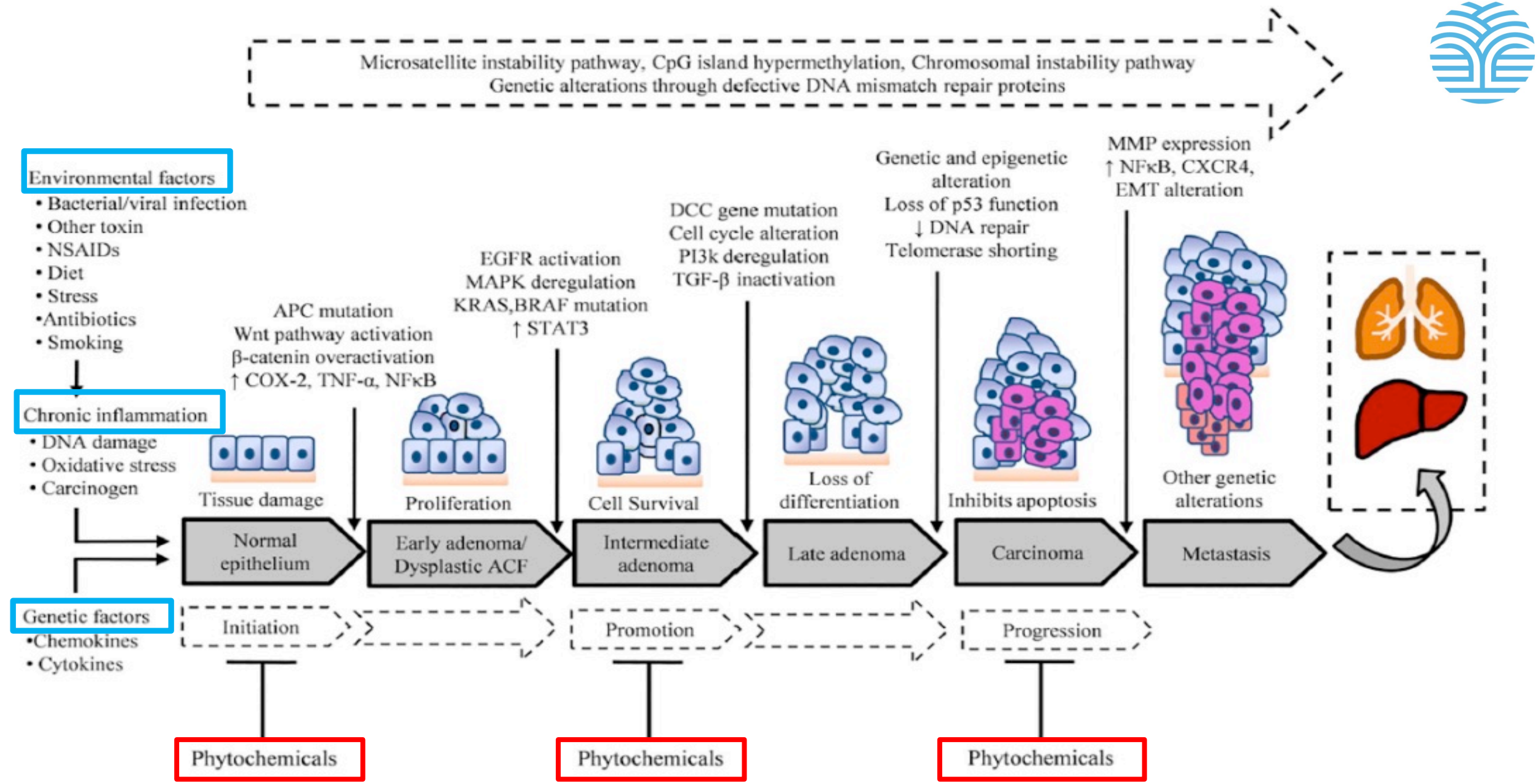
Research review paper

Dietary phytochemicals in colorectal cancer prevention and treatment: A focus on the molecular mechanisms involved

- Modulate carcinogenic processes through alteration of different molecular targets, such as:

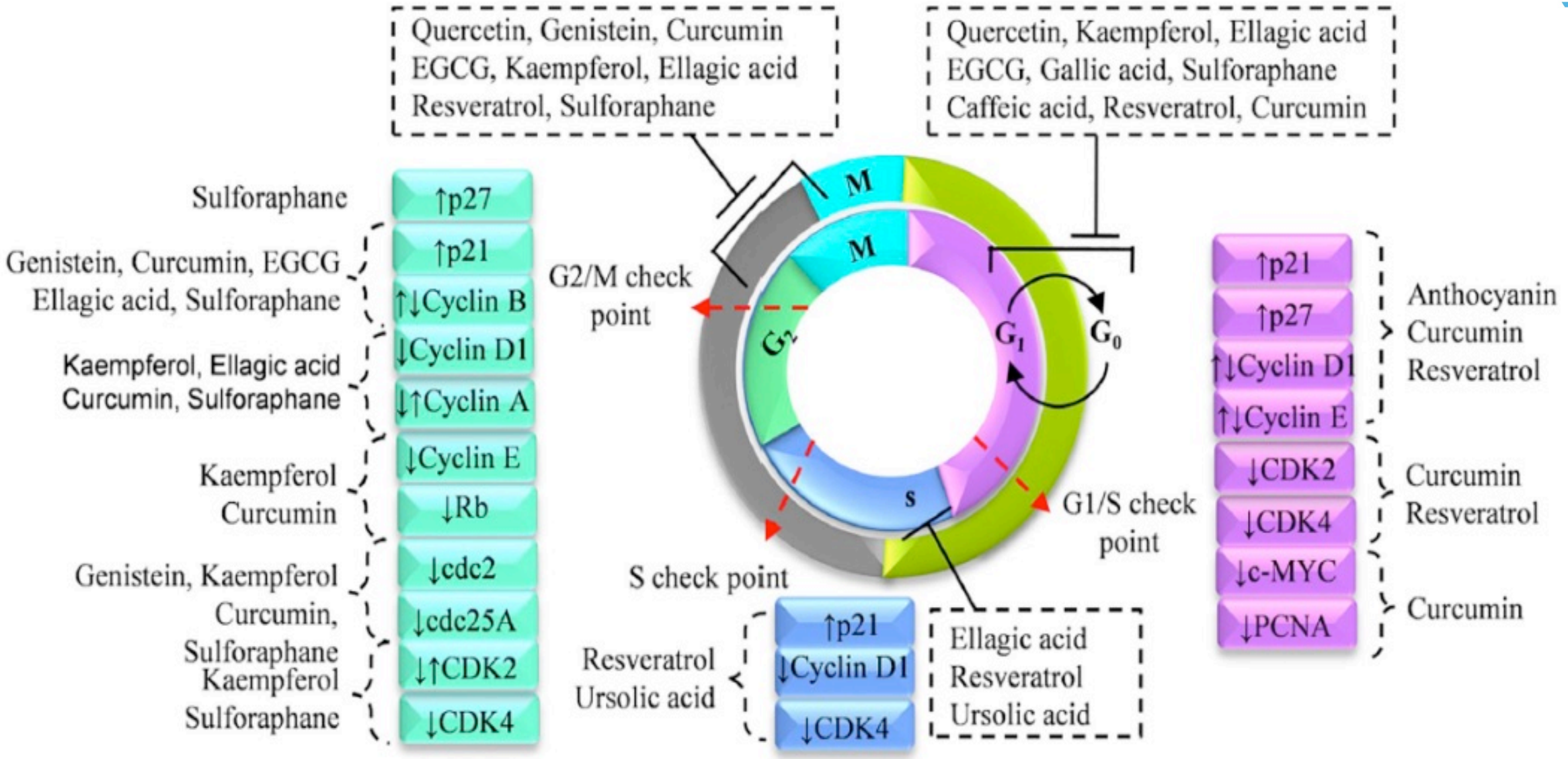
- **Wnt/β-catenin,**
- **MAPK (p38, JNK and Erk1/2),**
- **TGF-β/Smad2/3,**
- **STAT1-STAT3, NF-κB, Nrf2**
- **PI3K/Akt/mTOR,**
- **EGFR/Kras/Braf,**
- **Cyclin-CDK complexes**

Dietary phytochemicals in colorectal cancer prevention and treatment: A focus on the molecular mechanisms involved. Biotechnol Adv. 2020 Jan-Feb;38:10732?



Dietary phytochemicals in colorectal cancer prevention and treatment: A focus on the molecular mechanisms involved. Biotechnol Adv. 2020 Jan-Feb;38:107322

Applying targeted Nutraceuticals & Food:



Dietary phytochemicals in colorectal cancer prevention and treatment: A focus on the molecular mechanisms involved. Biotechnol Adv. 2020 Jan-Feb;38:107322

Applying targeted Nutraceuticals & Food:

Nutrition 79–80 (2020) 110964

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review

Role of vitamin D_3 in selected malignant neoplasms

Anna Markowska Prof. [a], Michał Antoszczak Ph.D. [b], Zbigniew Kojs Prof. [c], Wiesława Bednarek Prof. [d], Janina Markowska Prof. [e], Adam Huczyński Prof. [b,*]

[a] Department of Perinatology and Women's Health, Poznań University of Medical Sciences, Poznań, Poland
[b] Department of Medical Chemistry, Faculty of Chemistry, Adam Mickiewicz University, Poznań, Poland
[c] Department of Gynecology Oncology, Center of Oncology M. Skłodowska-Curie Institute, Cracow, Poland
[d] Clinic of Gynecological Oncology, Medical University of Lublin, Lublin, Poland
[e] Department of Oncology, Gynecological Oncology, Poznań University of Medical Sciences, Poznań, Poland

Role of vitamin D_3 in selected malignant neoplasms. Nutrition. 2020 Nov-Dec;79-80:110964

Applying targeted Nutraceuticals & Food:

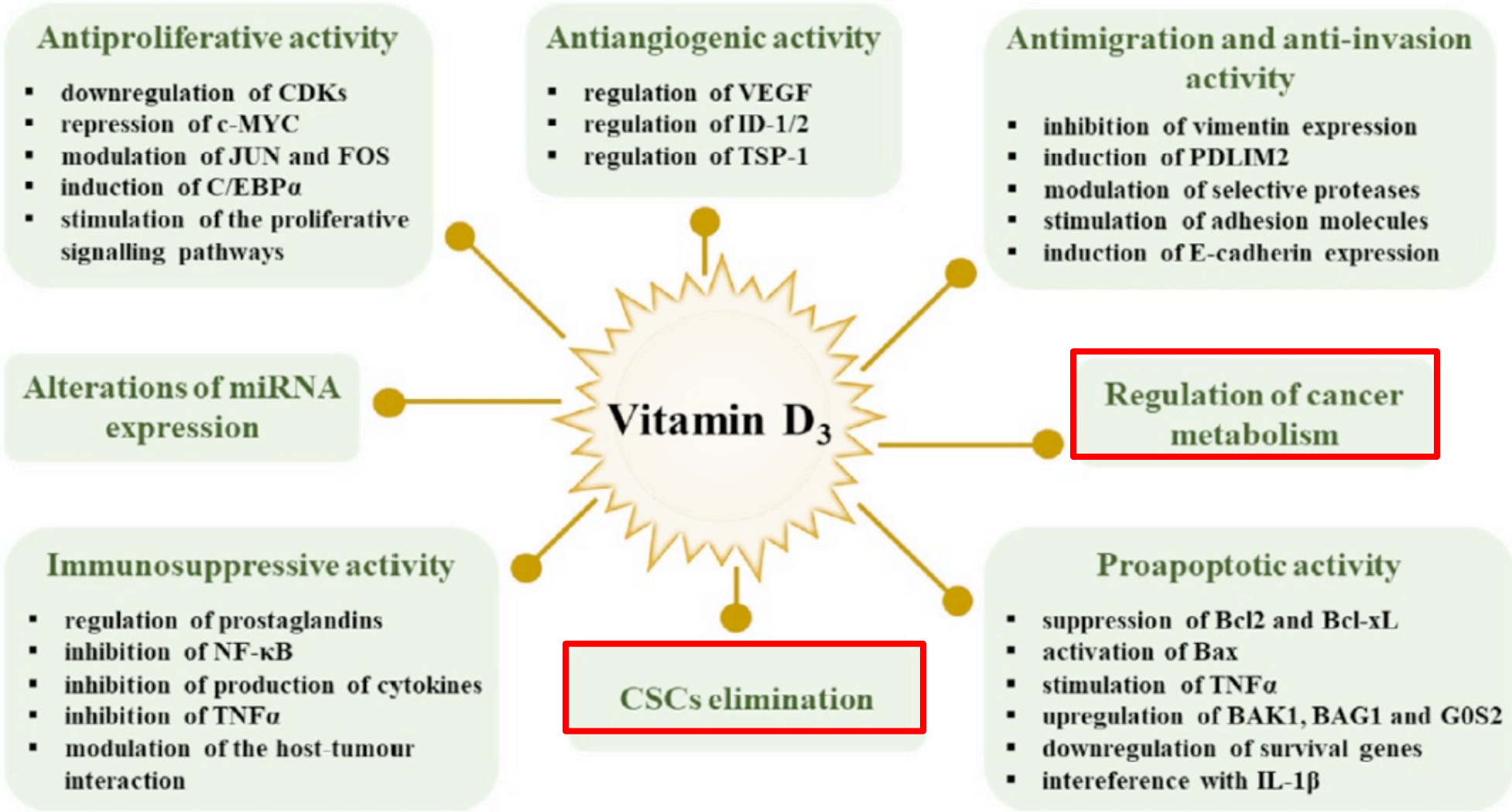
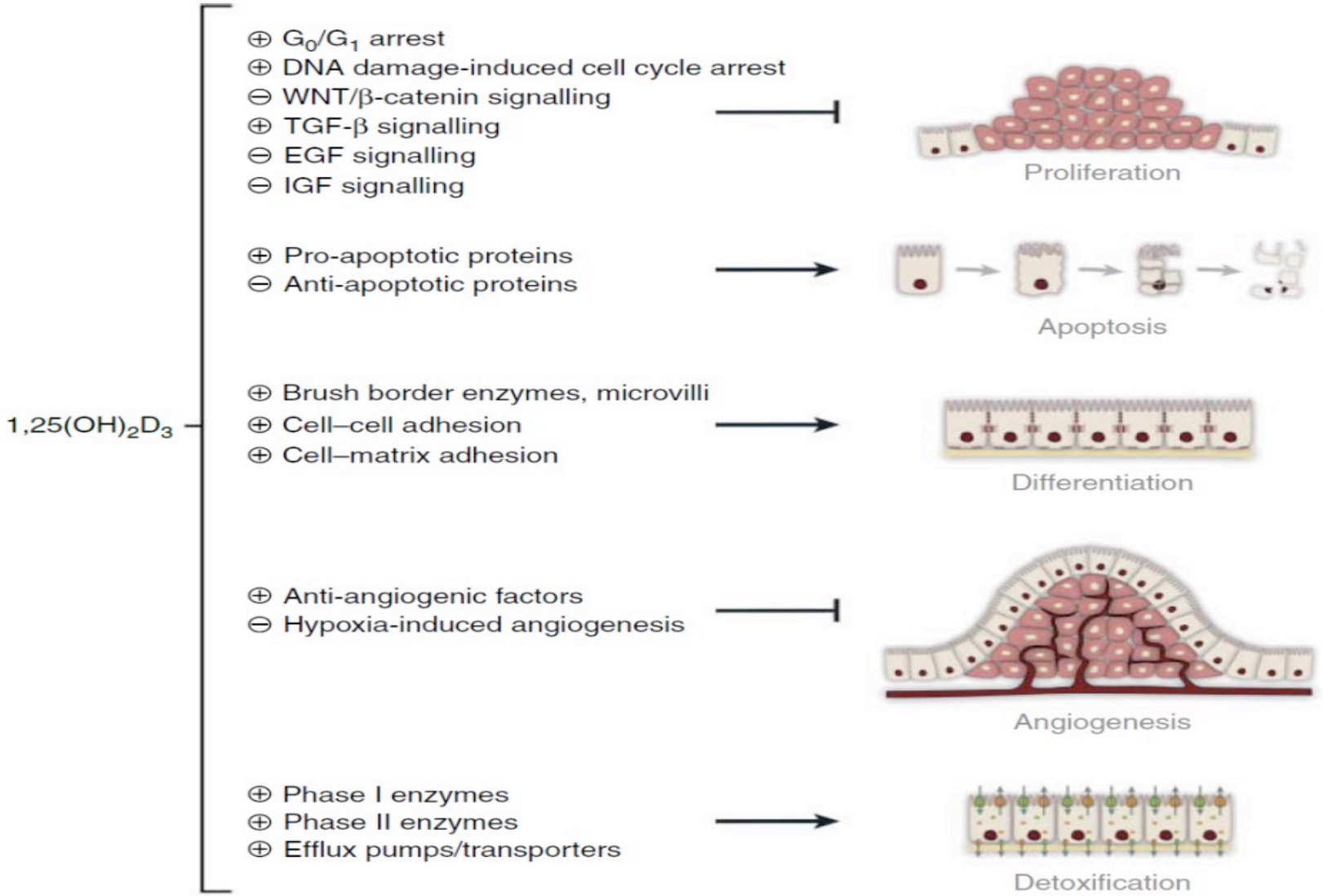


Fig. 1. Anticancer activity of vitamin D_3 in solid tumors.

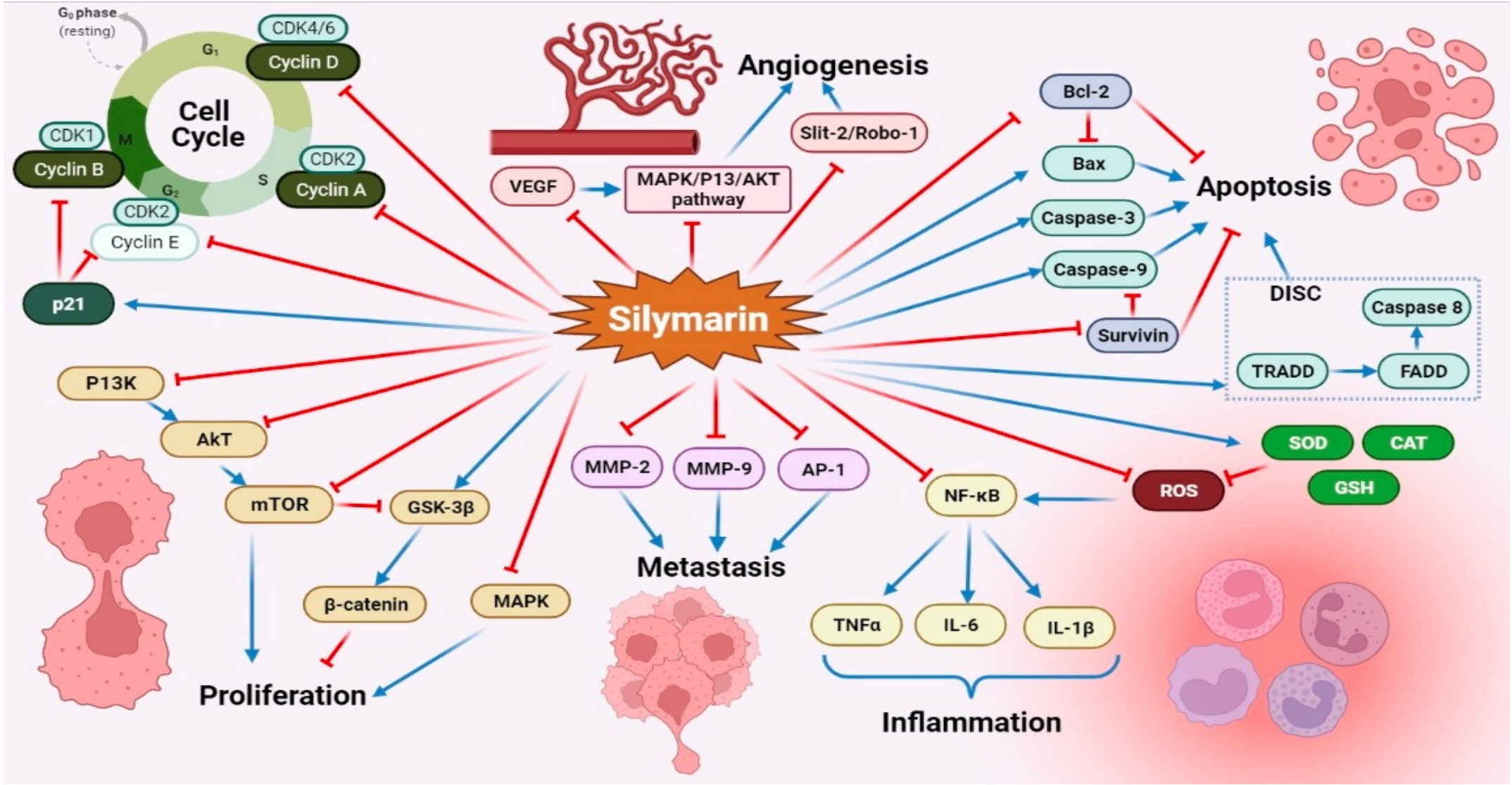
Role of vitamin D_3 in selected malignant neoplasms. Nutrition. 2020 Nov-Dec;79-80:110964

Applying targeted Nutraceuticals & Food:



Endocrine-Related Cancer (2012) **19** R51–R71

Applying targeted Nutraceuticals & Food:



Mechanistic Insights into the Pharmacological Significance of Silymarin. Molecules. 2022 Aug 21;27(16):5327

Applying targeted Nutraceuticals & Food:

Research Article

Intravenous Mistletoe Treatment in Integrative Cancer Care: A Qualitative Study Exploring the Procedures, Concepts, and Observations of Expert Doctors

Gunver S. Kienle,[1,2] Milena Mussler,[1] Dieter Fuchs,[3] and Helmut Kiene[1]

[1]*Institute for Applied Epistemology and Medical Methodology, University of Witten/Herdecke, Zechenweg 6, 79111 Freiburg, Germany*
[2]*Center for Complementary Medicine, Institute for Environmental Health Sciences and Hospital Infection Control, University Medical Center Freiburg, Breisacher Strasse 115B, 79106 Freiburg, Germany*
[3]*Department of Theology, Caritas Sciences, University of Freiburg, Werthmannplatz 3, 79098 Freiburg, Germany*

Intravenous Mistletoe Treatment in Integrative Cancer Care: A Qualitative Study Exploring the Procedures, Concepts, and Observations of Expert Doctors. Evid Based Complement Alternat Med. 2016;2016:4628287

Applying targeted Nutraceuticals & Food:

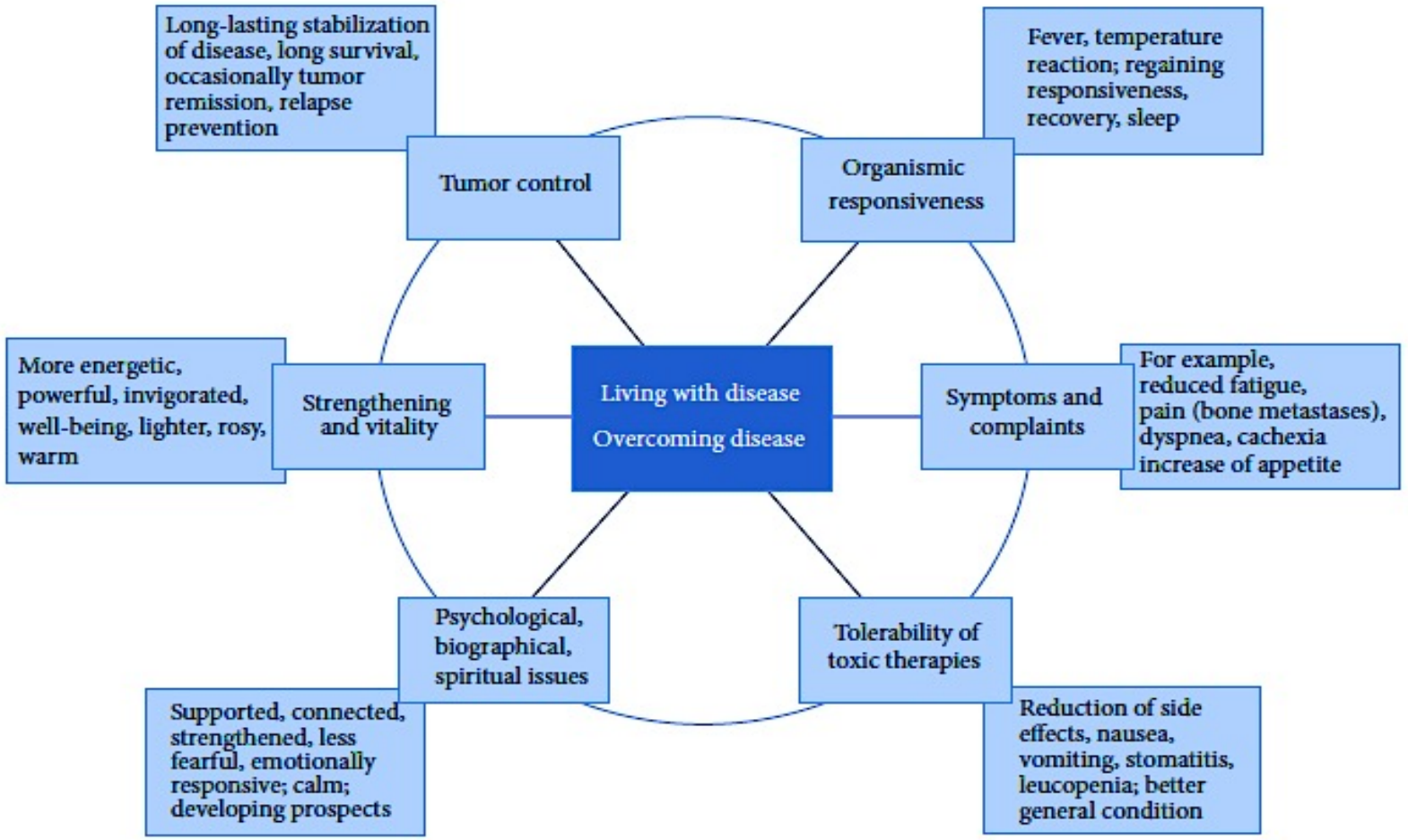
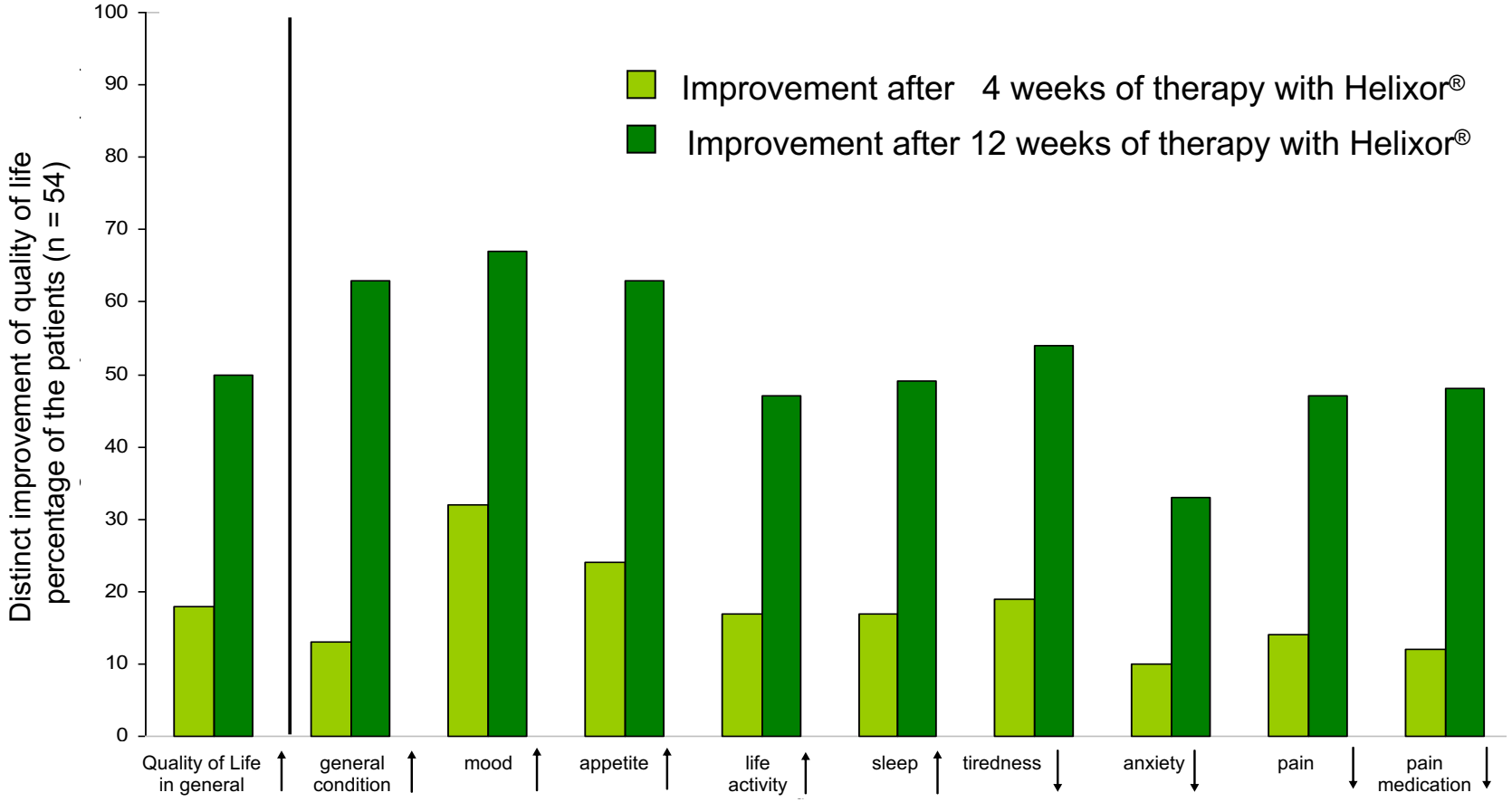


FIGURE 2: Concepts, goals, and observations associated with intravenous MT.

Intravenous Mistletoe Treatment in Integrative Cancer Care: A Qualitative Study Exploring the Procedures, Concepts, and Observations of Expert Doctors. Evid Based Complement Alternat Med. 2016;2016:4628287

Applying targeted Nutraceuticals & Food:

Benefit for Patients with Advanced Tumors Receiving Mistletoe Therapy



Quality of life during palliative therapy with Helixor®, survey of 54 tumor patients

Liedtke. S.: Ärztezeitschrift für Naturheilverfahren 12/2002, 806

Sum up- Optimizing Tumor Microenvironment

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Do not forget the Gut-Brain-Immune Axis !

Then choose the right Conventional treatment for your patient ☺

AWARE CLINIC

Thank you ☺ !

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