TUMOR-HOST INTERACTION-1: THE MICROBIOME

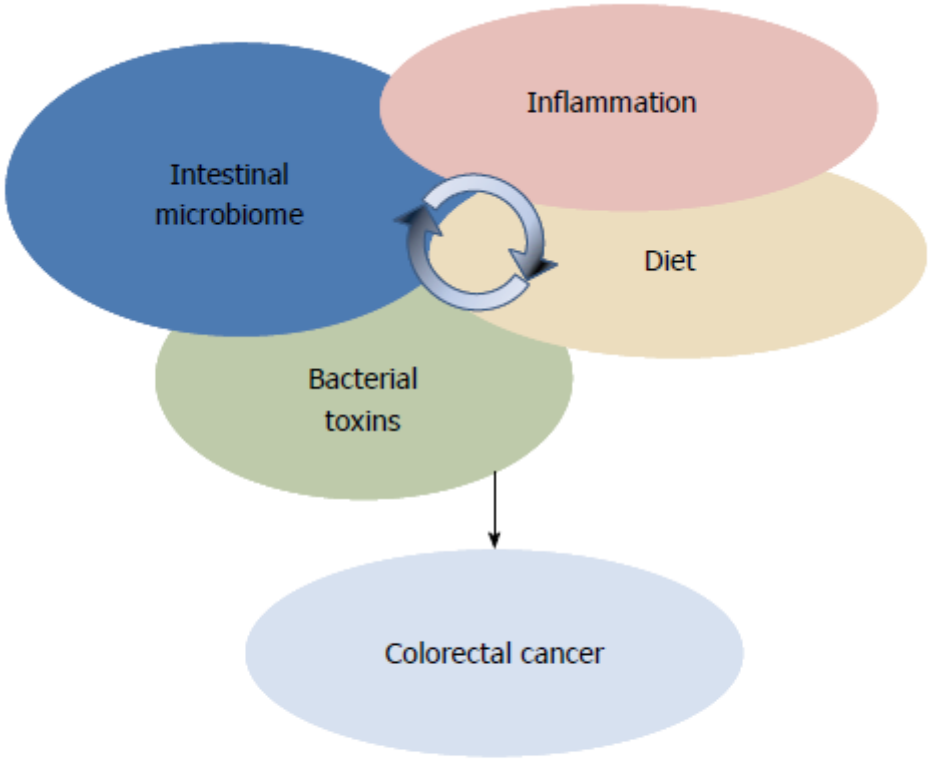


Figure 2 Colorectal cancer arises from the interplay between endogenous and exogenous factors, such as inflammation, diet, intestinal microbiome structure, and transcription and activity of bacterial genotoxins.

Candela et al., 2014

Candela M *et al*. Inflammation, gut microbiome and colorectal cancer
2014

Table 1 Microorganisms involved in colorectal cancer

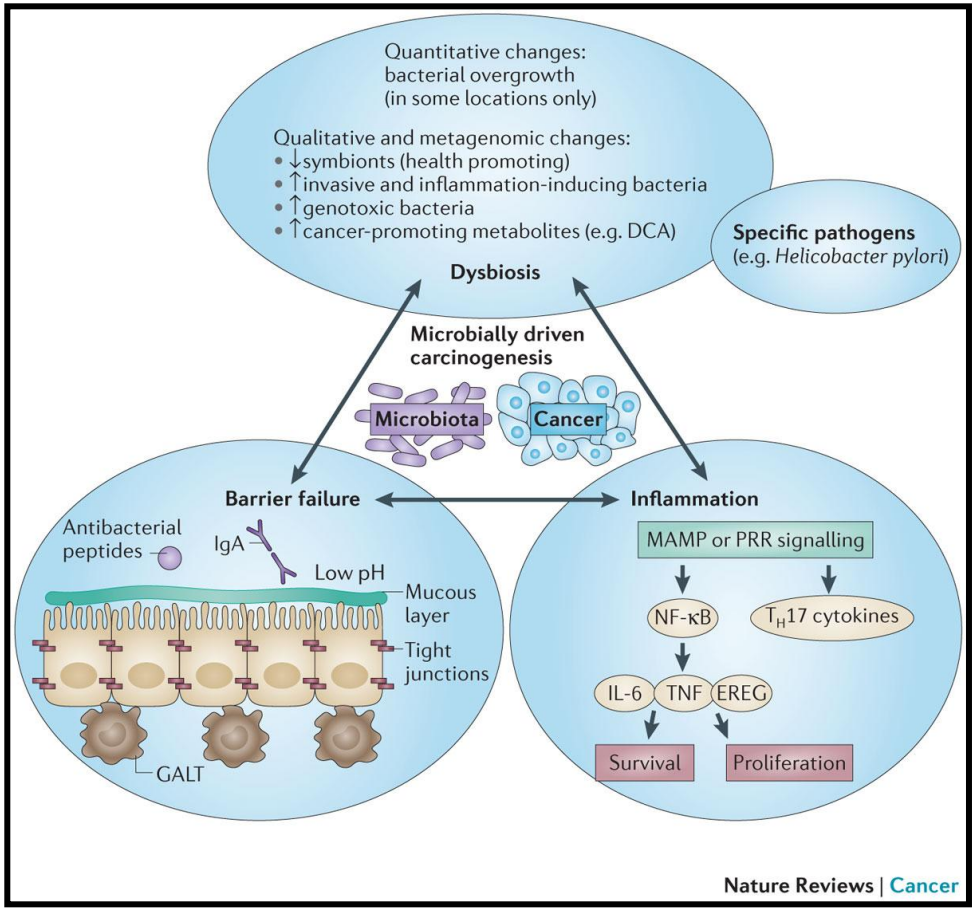
Microorganism	Role in CRC	Mechanism	Ref.
E. faecalis	Driver	Production of superoxide	[92]
*E. coli NC*101	Driver	Genotoxin production (colibactin)	[122]
B. fragilis	Driver	Genotoxin production (fragilisin)	[94]
Shigella	Driver	Induction of inflammation	[73]
Citrobacter	Driver	Induction of inflammation	[73]
Salmonella	Driver	Induction of inflammation	[73]
Enterobacteriaceae	Helper	Induction of inflammation	[73]
Fusobacterium	Passenger	Induction of inflammation	[84]
S. gallolyticus	Passenger	Induction of inflammation	[98]
C. septicum	Passenger	Induction of inflammation	[99]
F. prausnitzii	Protective	Butyrate production; anti-inflammatory properties	[78]
Roseburia	Protective	Butyrate production; anti-inflammatory properties	[78]
Bifidobacterium	Protective	Protection from pathogens; anti-inflammatory properties	[71]
Corynebacteriaceae	Protective	Anti-inflammatory properties	[78]

Cancer	Mechanism	Evidence	Refs
Cancers promoted or inhibited by specific bacterial pathogens			
Gastric cancer	Chronic infection with *Helicobacter pylori*	• Epidemiology • Reduction by *H. pylori* eradication	39,40, 46,47
• Gastric MALT lymphoma • IPSID • Skin MALT lymphoma • Ocular adnexal lymphoma	Uncontrolled adaptive immune responses in patients with chronic infection with *H. pylori*, *Campylobacter jejuni*, *Borellia burgdorferi* or *Chlamydia psittaci*	• Epidemiology • Antibiotic treatment	52–54
Gallbladder cancer	Chronic infection with *Salmonella enterica* subsp. *enterica* serovar Typhi	Epidemiology	49,50
Oesophageal cancer	Reduced risk in patients with *H. pylori* infection	Epidemiology	46,48
Cancers promoted by specific pathogens (in mice only)			
Breast cancer	Increased inflammation, mediated by T regulatory cells	Cancer promoted in *Helicobacter hepaticus*-infected $Apc^{Min/+}$ mice	94
Liver cancer	Chronic hepatitis	Cancer promoted in *H. hepaticus*-infected mice	89
Colorectal cancer	TNF-mediated and NO-mediated	Cancer promoted in *H. hepaticus*-infected $Rag2^{-/-}$ mice	90
Cancers suspected to be promoted by commensal bacteria or dysbiotic microbiomes			
Colorectal cancer	• Dysbiosis • Barrier failure • Chronic inflammation • Bacterial genotoxicity	Cancer reduction by antibiotics and in germ-free mice; transmission of dysbiotic microbiota triggers cancer development	25,27, 32–34,36
Liver cancer	• Increased hepatic exposure to TLR-activating MAMPs • Increased exposure to the secondary bile acid DCA	• Cancer reduction by treatment with antibiotics and in germ-free mice • Cancer increased by treatment with LPS and DCA	21,22,35
Lung cancer	Increased bacterial infection in COPD?	• Decreased cancer in germ-free animals • Promotion of cancer by LPS and infections	24,59–62
Pancreatic cancer	LPS–TLR4-mediated increase of pancreatic cancer	LPS treatment increases cancer development	56–58

Apc, adenomatous polyposis coli; COPD, chronic obstructive pulmonary disease; DCA, deoxycholic acid; IPSID, immunoproliferative small intestinal disease; LPS, lipopolysaccharide; MALT, mucosa-associated lymphoid tissue; MAMPs, microorganism-associated molecular patterns; NO, nitric oxide; *Rag2*, recombination activating gene 2; TLR, Toll-like receptor; TNF, tumour necrosis factor.

Schwabe and Jobin, 2013

Figure 1 | Mechanisms controlling host–microbiota interactions and associated failures implicated in cancer development.
A state of homeostasis and symbiotic relationships is maintained by the separation of microbial entities from the host through a multi-level barrier, by a eubiotic microbiome that actively suppresses pathobionts and that maintains a symbiotic relationship with the host, and by a state of low inflammation in the host. Perturbation of this balance leads to chain reactions that ultimately result in a cancer-promoting state with a failing barrier, inflammation and dysbiosis. This state includes qualitative and sometimes quantitative changes in the microbiota; failure of the barrier either physically (for example, at the level of tight junctions or at the mucous layer), or at the level of antibacterial defence systems — either those of epithelial cells or those of cells from the gut-associated lymphoid tissue (GALT); and increased inflammatory responses, which are often mediated by pattern recognition receptors (PRRs) and downstream cytokines that promote epithelial cell proliferation and survival. DCA, deoxycholic acid; EREG, epiregulin; IgA, immunoglobulin A; IL-6, interleukin-6; MAMP, microorganism-associated molecular pattern; NF-κB, nuclear factor-κB; TH17, T helper 17; TNF, tumour necrosis factor.



Schwabe and Jobin, 2013

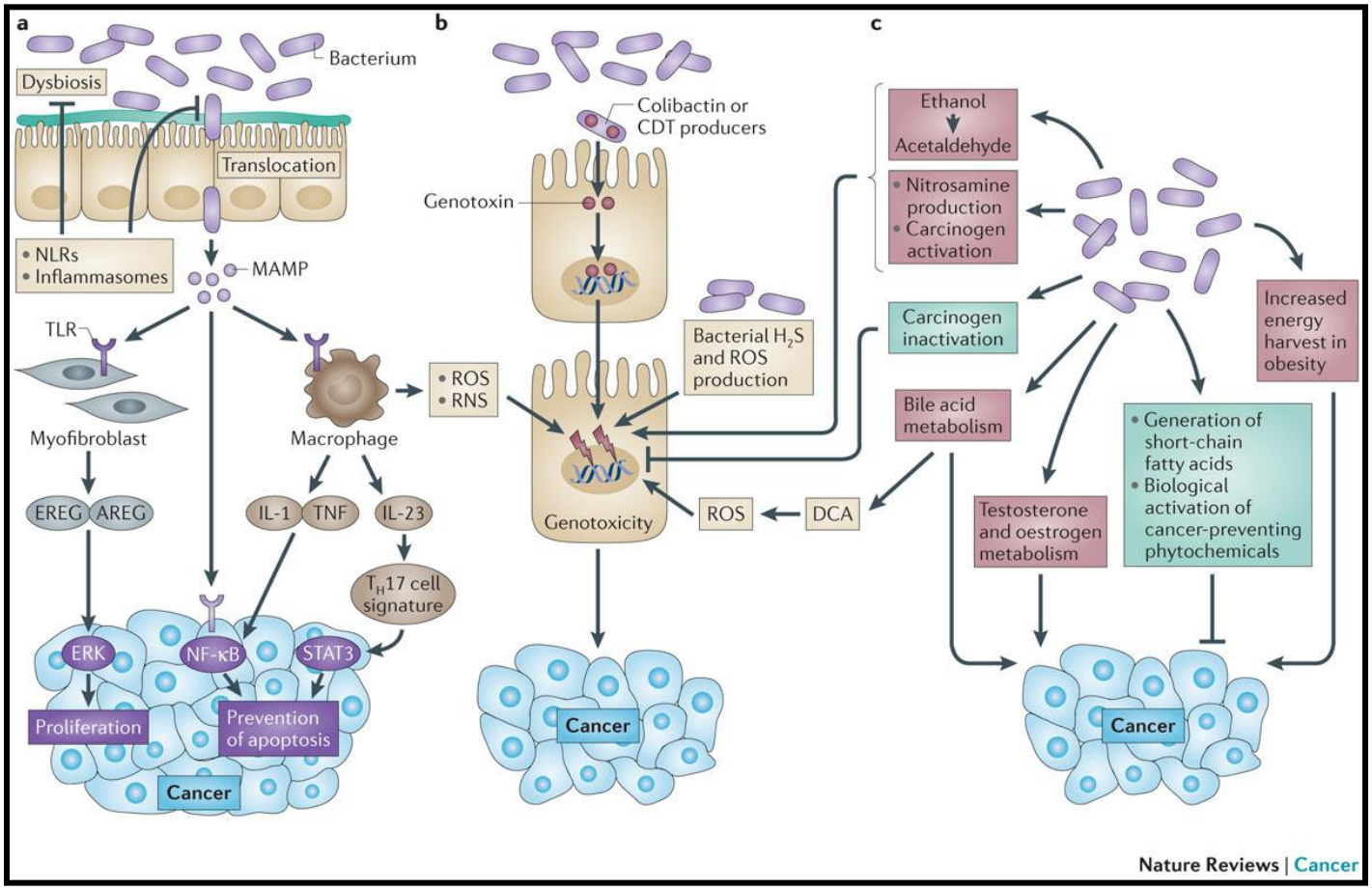


Figure 2 | Mechanisms by which the bacterial microbiome modulates carcinogenesis. The bacterial microbiome promotes carcinogenesis through several mechanisms. a | Changes in the microbiome and host defences may favour increased bacterial translocation, leading to increased inflammation, which is mediated by microorganism-associated molecular patterns (MAMPs) that activate Toll-like receptors (TLRs) in several cell types, including macrophages, myofibroblasts, epithelial cells and tumour cells. These effects may occur locally or through long-distance effects in other organs. b | Genotoxic effects are mediated by bacterial genotoxins — such as colibactin and cytolethal distending toxin (CDT) — that, after being delivered to the nucleus of host cells, actively induce DNA damage in organs that are in direct contact with the microbiome, such as the gastrointestinal tract. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) released from inflammatory cells such as macrophages, as well as hydrogen sulphide (H2S) from the bacterial microbiota, may also be genotoxic. c | Metabolic actions of the microbiome may result in the activation of genotoxins such as acetaldehyde, dietary nitrosamine and other carcinogens, in the metabolism of hormones such as oestrogen and testosterone, in the metabolism of bile acids and in alterations of energy harvest. The microbiota also mediates tumour suppressive effects (shown in green) through inactivation of carcinogens, through the generation of short-chain fatty acids such as butyrate and through the biological activation of cancer-preventing phytochemicals. Many of these tumorigenic and tumour-suppressive mediators exert both local and long-distance effects. AREG, amphiregulin; DCA, deoxycholic acid; EREG, epiregulin; IL, interleukin; NF-κB, nuclear factor-κB; NLR, NOD-like receptor; STAT3, signal transducer and activator of transcription 3; TH17, T helper 17; TNF, tumour necrosis factor.

Schwabe and Jobin, 2013

TABLE 1. Microbes Designated as Class 1 (Carcinogens) by the International Agency for Research on Cancer (IARC)[a]

MICROBE	SITE OF CANCER
Helicobacter pylori	Stomach
Hepatitis B virus (HBV) Hepatitis C virus (HCV) *Opisthorchis viverrini* *Clonorchis sinensis*	Liver
Human papillomavirus (HPV)	Cervix Vagina Vulva Anus Penis Oropharynx
Epstein-Barr virus (EBV)	Nasopharynx Non-Hodgkin lymphoma Hodgkin lymphoma
Kaposi sarcoma-associated herpesvirus (KSHV or HHV8)	Kaposi sarcoma Primary effusion lymphoma
Human T-cell lymphotropic virus type 1 (HTLV-1)	Adult T-cell lymphoma
Schistosoma haematobium	Bladder

[a]IARC 2012.[6]

Bhatt et al., 2017

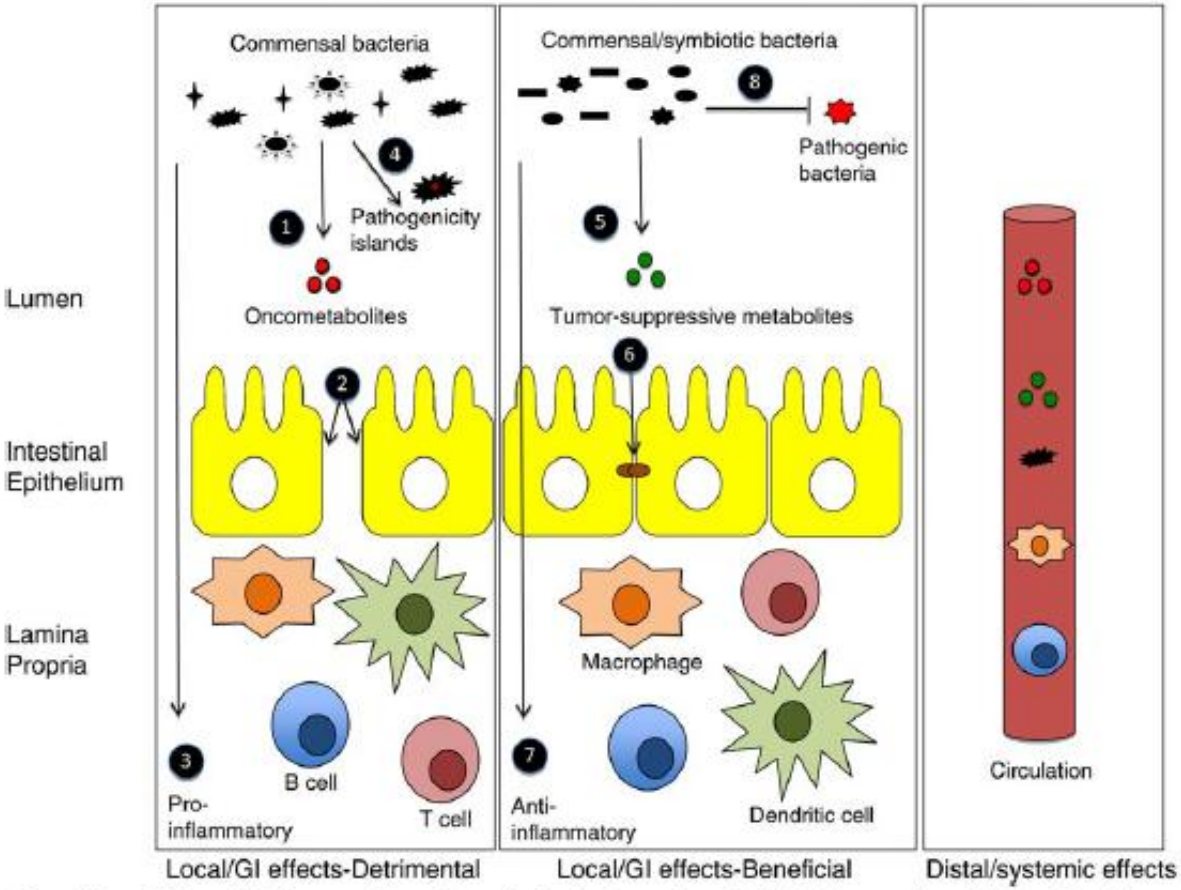
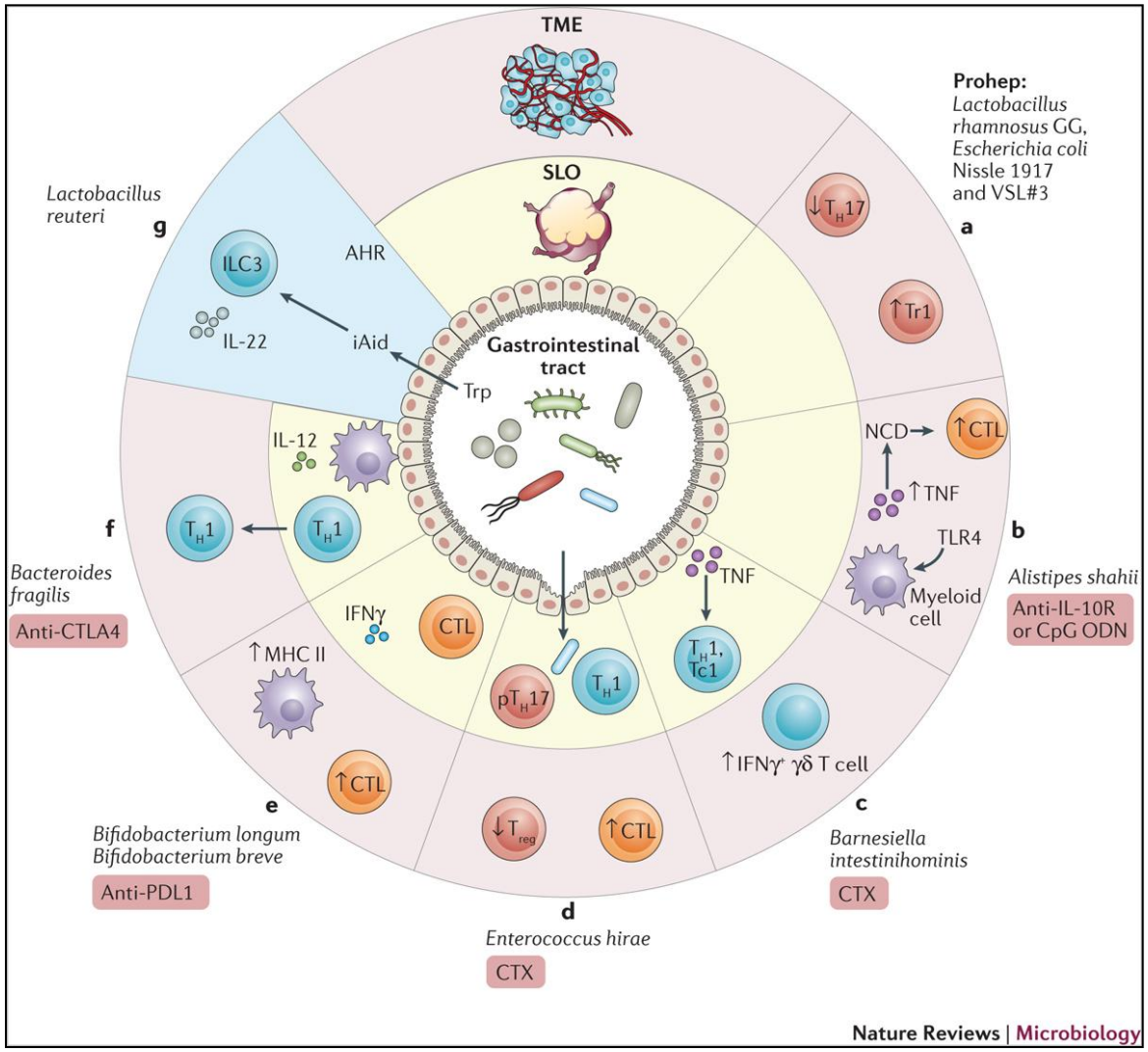


FIGURE 2. Gut Microbiota Have Differential Effects on Tumorigenesis in the Gastrointestinal (GI) Tract and at Distant Sites. The colon is depicted with a single layer of intestinal epithelial cells (yellow) separating commensal bacteria (black shapes) in the lumen above from immune cells (4 different colors) in the underlying lamina propria. The bacteria can have local effects that are either (*Left box*) oncogenic or (*Center box*) tumor suppressive for colorectal cancer, or (*Right box*) they can have distal effects mediated by the circulation that are oncogenic or tumor suppressive for cancer at other anatomical sites. Some of the general effects that gut microbiota can have on tumorigenesis are numbered, including (*Left box*): 1) production of putative oncometabolites, such as hydrogen sulfide; 2) impairment of barrier function, which increases the exposure of immune cells to bacterial endotoxins (eg, lipopolysaccharides) and antigens; 3) direct effects of bacterial metabolites and antigens on immune cells to stimulate inflammation by altering immune cell subsets (eg, the effect of segmented filamentous bacteria or segmented filamentous bacteria on T-helper 17 [TH_{17}] cells) and hyperactivating immune cell responses via proinflammatory cytokines (eg, interleukin 6 [IL-6]); 4) the presence of virulence factors, including pathogenicity islands, which distinguish pathogens from commensals, such as *Escherichia coli* polyketide synthase, can exert multiple effects, including the induction of DNA damage and aberrant Wnt signaling; and (*Center box*) 5) the production of putative tumor-suppressive metabolites, such as butyrate, which functions via multiple mechanisms; 6) maintenance of barrier function; 7) direct effects on immune cells to prevent inflammation by altering immune cells subsets (eg, the ability of butyrate to induce regulatory T-cells) and dampening the immune cell response via immunosuppressive cytokines (eg, IL-10); and 8) competitive exclusion of pathogenic bacteria similar to the prevention of lethal *Clostridium difficile* infections. *Right box:* Gut microbiota can also have oncogenic or tumor-suppressive effects at distal sites in the body via circulation of microbiota, microbial metabolites, activated or suppressed immune cells, and cytokines.

Bhatt et al., 2017



Probiotic microorganisms may shape the tumour microenvironment by inducing several effects described here. **a** | Prohep may induce a reduction of pro-inflammatory T helper 17 cells (T_H17 cells) and the differentiation of regulatory T cells (T_{reg} cells) to T regulatory type 1 cells (Tr1 cells). **b** | In antibiotic-pretreated mice, *Alistipes shahii* increases the number of infiltrating innate immune cells against colorectal cancer by triggering tumour necrosis factor (TNF)-mediated necrotic cell death (NCD). **c,d** | Alternatively, microorganisms may act in secondary lymphoid organs, inducing splenic polyfunctional $CD4^+$, $CD8^+$ or γδ T cells, and bacteria-specific $CD4^+$ T_H1 or pathogenic T_H17 (pT_H17) cells[23]. Consequently, they modulate innate and adaptive immune responses in the tumour beds[88]. **e,f** | Following immune checkpoint blockades, *Bifidobacterium* spp. and *Bacteroides fragilis* promote maturing intratumoural dendritic cells and the production of interleukin-12 (IL-12) by bone marrow-derived dendritic cells, respectively, that allow the expansion of anticancer T cells. **g** | *Lactobacillus reuteri* also influences the expression of IL-22 by group 3 innate lymphoid cells (ILC3s) by the immunosuppressive tryptophan catabolite indole-3-aldehyde (iAid)[122]. Globally, these mechanisms enhance cancer antigen-specific cytotoxic T lymphocyte (CTL) responses and cancer immunosurveillance[27]. In this figure, cancer treatments are highlighted in red and cytokines are represented by coloured spheres. The green fields represent secondary lymphoid organs (SLO) and the red fields represent tumour microenvironments (TME). AHR, aryl hydrocarbon receptor; anti-IL-10R, anti-IL-10 receptor; CTLA4, cytotoxic T lymphocyte protein 4; CTX, cyclophosphamide; IFN, interferon; MHC II, major histocompatibility complex class II; ODN, oligodeoxynucleotides; PDL1, programmed cell death 1 ligand 1; Tc1, type 1 $CD8^+$ T; TLR4, Toll-like receptor 4; Trp, tryptophan (Zitvogel et al., 2017).

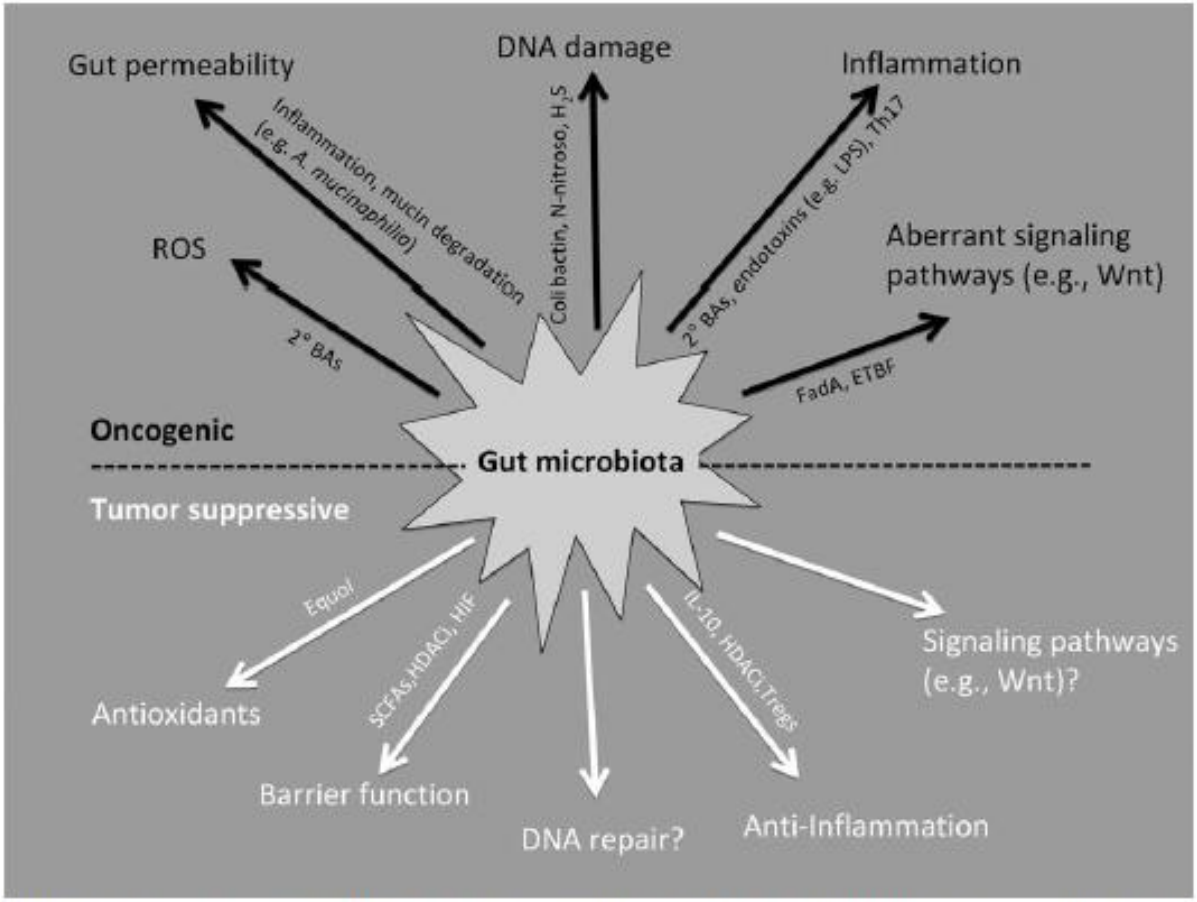
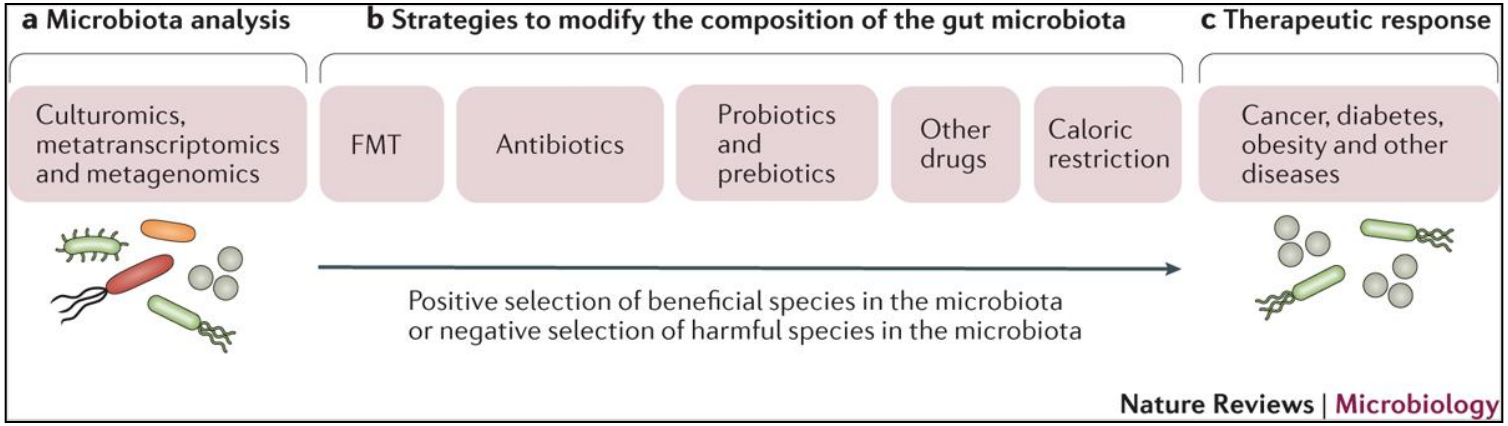


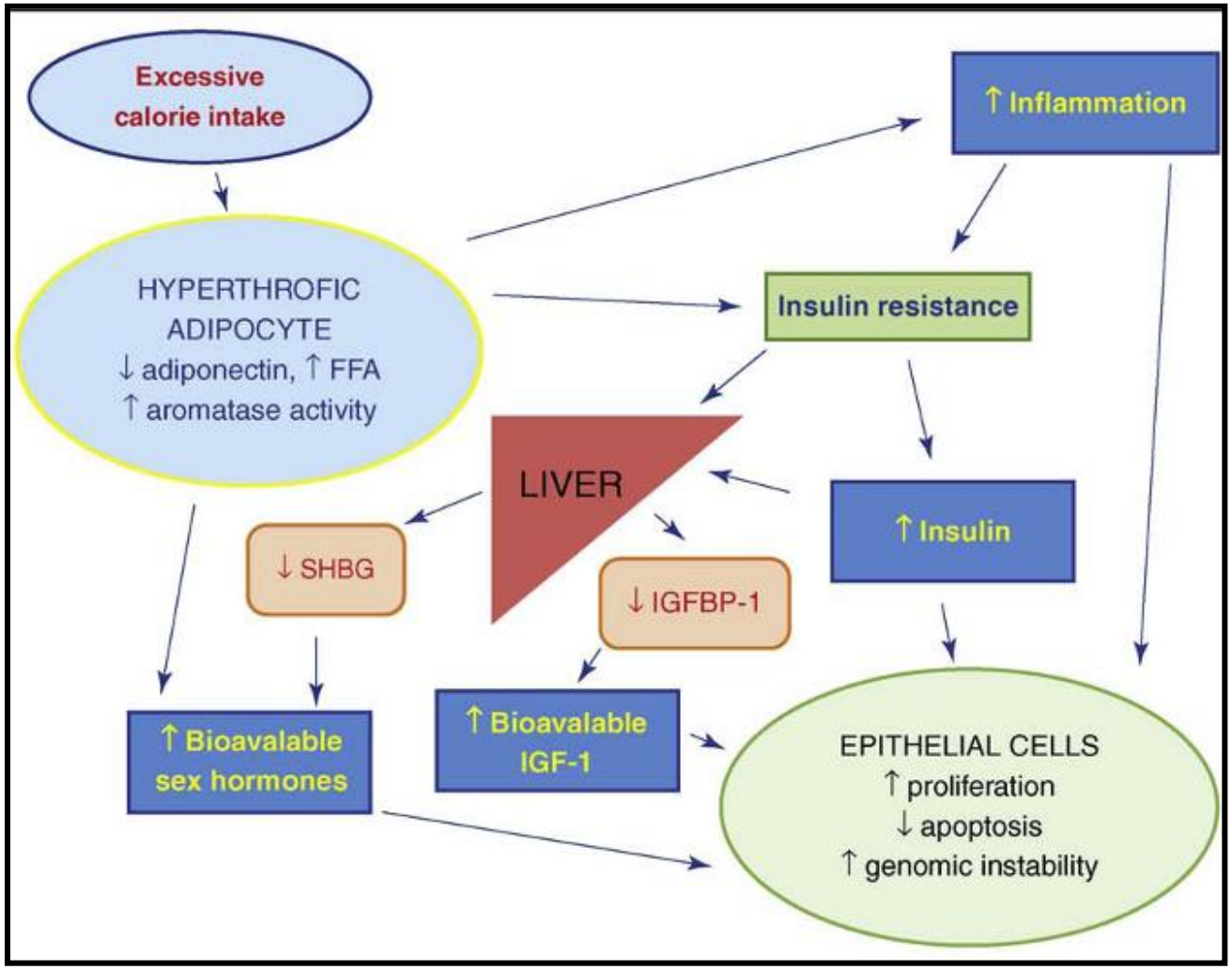
FIGURE 3. Microbial Mechanisms of Oncogenesis and Tumor Suppression. Microbiota can contribute to oncogenesis (*Top*, black arrows) or tumor suppression (*Bottom*, white arrows) by a variety of molecular mechanisms, which are listed at the end of each line. The mechanisms are listed from left to right in a symmetrical manner (from top to bottom) to make it easier to appreciate that some are diametrically opposed. The mechanisms are carried out by a variety of microbial gene products, metabolites, and immune modulators, some of which are indicated in smaller font along each arrow. See text for details. Question marks indicate speculative mechanisms that have not yet been characterized. BF indicates *Bacteroides fragilis*; ETBF, enterotoxigenic *Bacteroides fragilis*; FadA, fusobacterium adhesion A; HDAC, histone deacetylase; IL, interleukin; LPS, lipopolysaccharides.

Bhatt et al., 2017



a | Determining the composition of the microbiota in patients with cancer compared with healthy volunteers is becoming feasible with the development of metagenomics, metatranscriptomics and culturomics platforms. Data from these analyses can together build a picture of the microbiota in health and disease, and indicate which bacterial genera or species could be beneficial to patients. **b** | Interventional approaches that could modulate the microbiota in cancer include faecal microbiota transplantation (FMT), antibiotic regimens, prebiotic and/or probiotic formulations, other types of drug (such as the diabetes drug metformin) and dietary-based interventions, such as caloric restriction. **c** | The outcome of microbiota interventions can be evaluated by monitoring the response to standard cancer therapeutics. In addition, microbiota interventions may influence the outcome of other diseases, such as diabetes or obesity (Zitvogel et al., 2017).

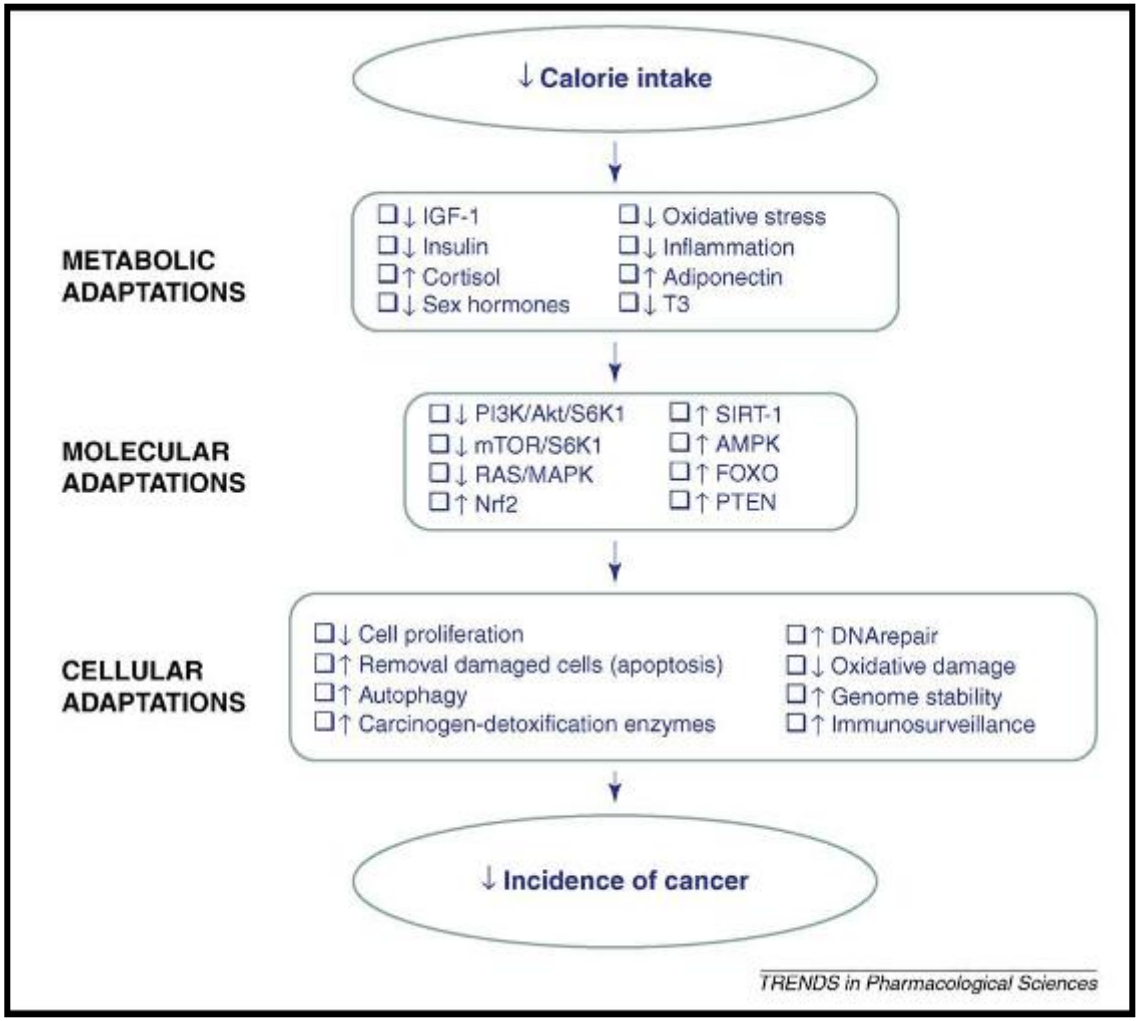
TUMOR-HOST INTERACTION-2: NUTRITION



Effects of excessive calorie intake and adiposity on hormones and growth factor production and cell proliferation. Excessive calorie intake and a sedentary lifestyle promote hypertrophy of adipose tissue, reduce adiponectin production and increase circulating free fatty acids (FFAs) and inflammation, leading to insulin resistance and compensatory hyperinsulinemia. Increased serum insulin concentration causes a reduction in hepatic synthesis of IGFBP1 and SHBG that leads to increased bioavailability of IGF-1 and sex hormones. Adipose tissue is also a major source of extraglandular estrogens. Chronically elevated circulating levels of insulin, IGF-1, sex hormones and inflammatory cytokines promote cellular proliferation, genomic instability and inhibit apoptosis in many cell types (Longo and Fontana, 2010).

CALORIC RESTRICTION

Moreschi, 1909:
inhibition of experimental tumor growth by caloric restriction



Mechanisms for cancer prevention by CR. CR causes several key metabolic/hormonal adaptations that alter the expression of several genes and signaling pathways (upregulation of certain genes/signaling pathways and downregulation of others as indicated by the arrows), which produce major cellular adaptations (e.g. a reduction in cell proliferation, increased removal of damaged organelles or cells via autophagy or apoptosis, upregulation of DNA repair systems and genomic stability) that result in a reduced cancer incidence (see the text). T3 = triiodothyronine; PI3K = phosphatidylinositol-3 kinase; AKT = kinase AKT, also known as protein kinase B; S6K1 = ribosomal S6 protein kinase 1; mTOR = mammalian target of rapamycin; MAPK = mitogen-activated protein kinase; NRF2 = transcription factors NF-E2-related factor 2; SIRT-1 = silent mating type information regulation 2 homolog 1; AMPK = adenosine monophosphate (AMP)-activated protein kinase; FOXO = Forkhead transcription factors; PTEN = phosphatase and tensin homolog (Longo and Fontana, 2010).

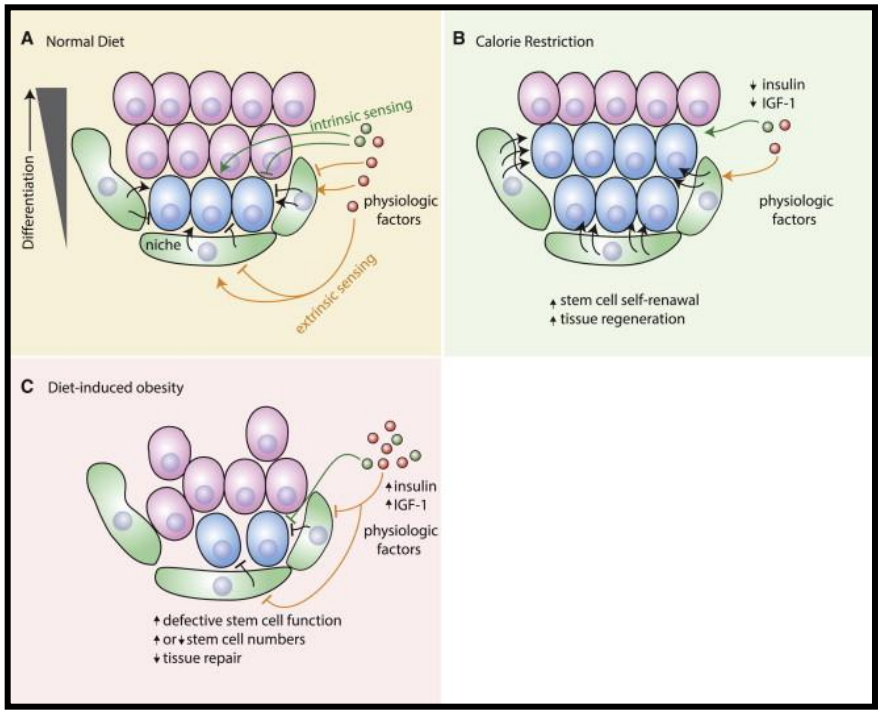


Figure 1. Dietary Regulation of Stem Cells in Tissue Homeostasis

(A) Intrinsic (dark green) and extrinsic (orange) diet-sensing mechanisms integrate diet-induced physiology with tissue homeostasis. Stem cells (blue) and their niche (green) sense physiologic cues such as hormones, growth factors, and nutrients to dynamically alter the production of differentiated cells (pink).

(B) Calorie restriction boosts regeneration in diverse tissues by increasing stem cell numbers and function. Niche-derived signals mediate some of the response of calorie restriction on stem cells.

(C) Diet-induced obesity is associated with an abundance of nutrients, growth factors, and hormones that eventually leads to physiologic disequilibrium, including insulin resistance, diabetes, and metabolic syndrome. This state reduces tissue repair, in part due to dysfunction of stem cells, their niches, or both.

Maria M. Mihaylova , David M. Sabatini , Ömer H. Yilmaz

Dietary and Metabolic Control of Stem Cell Function in Physiology and Cancer

Cell Stem Cell, Volume 14, Issue 3, 2014, 292 - 305

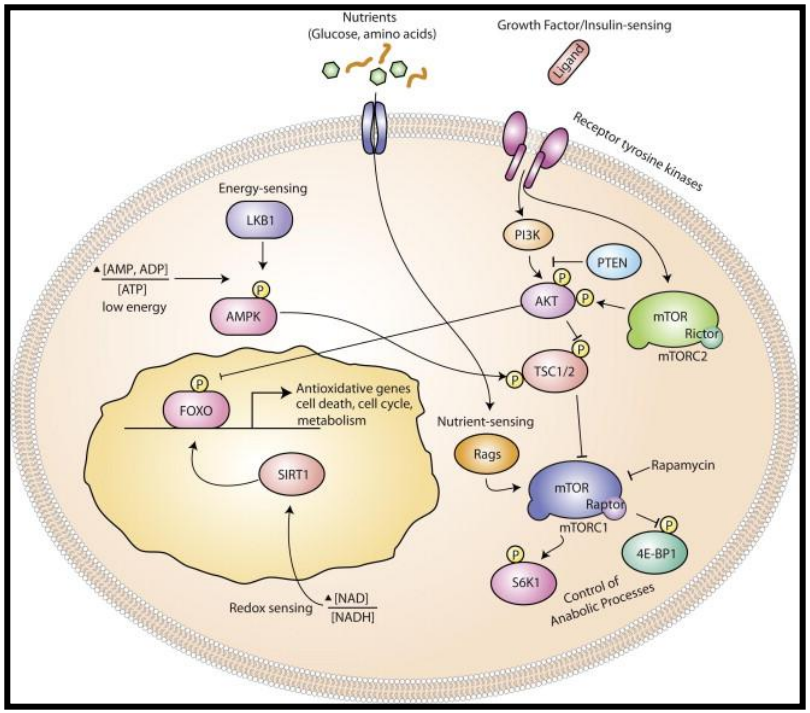


Figure 2. Diet-Sensing Pathways in Stem Cells

Growth factor binding to receptor tyrosine kinases activates phosphatidylinositol 3-kinase (PI3K) and PTEN suppresses signaling through this pathway. PI3K and mTORC2 activate AKT, which regulates mTORC1 activity by inhibition of the TSC1/TSC2 complex. Independently, the Rag-GTPases control mTORC1 activity in response to nutrients, such as amino acids and glucose, at the lysosome surface. Multiple pathways downstream of active mTORC1 control anabolic processes, including protein and lipid synthesis, and inhibit catabolic processes like autophagy. S6 kinase 1 (S6K1) regulates protein synthesis and ribosome biogenesis and 4E-BP1 regulates cap-dependent protein translation. Deletion of PTEN or TSC1 leads to the activation of mTORC1 and to stem cell depletion. Treatment with mTORC1 inhibitor rapamycin restores loss of stem cell function. The energy sensor AMPK becomes activated in response to glucose starvation and relative increases in the ratio of AMP and ADP to ATP levels. AMPK is phosphorylated and activated in an AMP-dependent manner by the upstream master kinase LKB1 and in turn negatively regulates mTORC1 to promote catabolic, energy producing processes such as autophagy and fatty acid oxidation. Another intracellular sensor, SIRT1, becomes activated in response to relative increases in the ratio of NAD+ to NADH to regulate the activity of FOXO transcription factors. FOXO family members control expression of genes involved in oxidative stress, cell death, cell-cycle control, and metabolism, which are important for stem cell maintenance.

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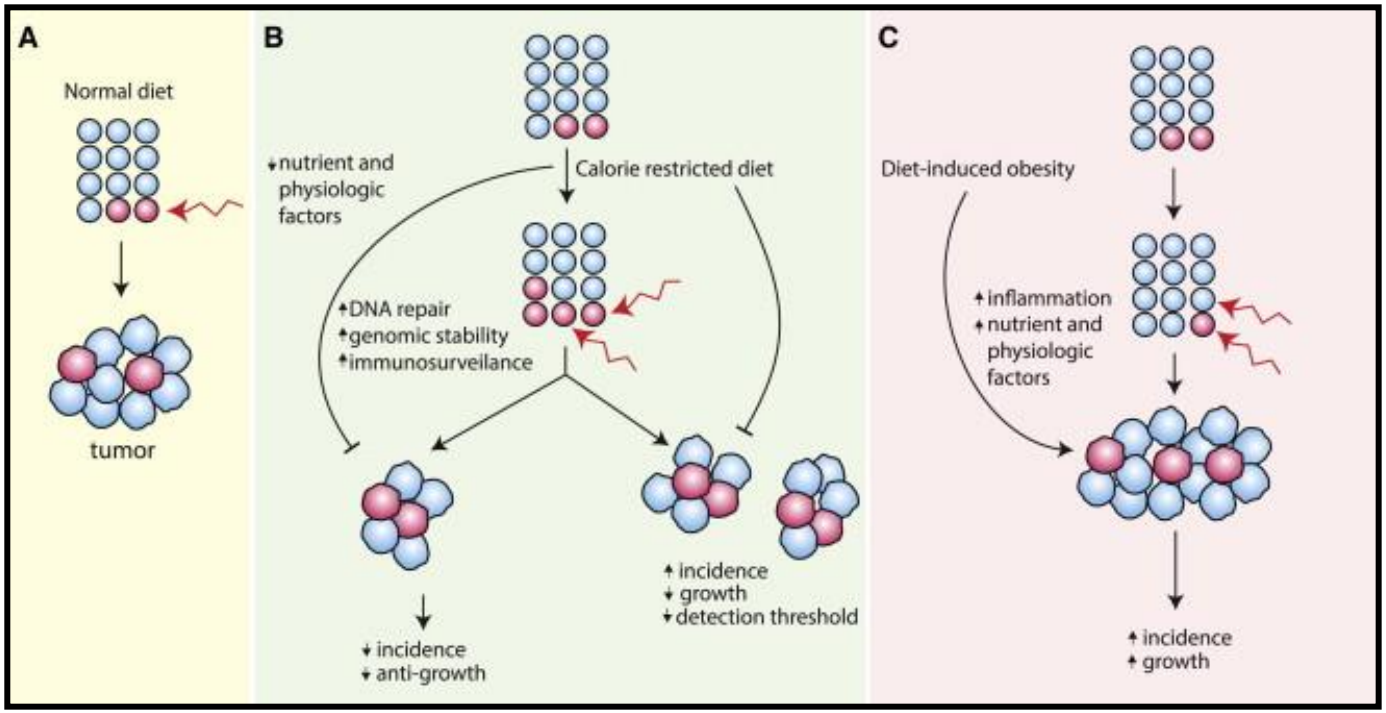

Figure 4. Diet and Cancer Initiation

(A) In tissues that follow a stem cell paradigm, stem cells (red) acquire early oncogenic events (red arrow) that lead to transformation and tumor formation.

(B) Calorie restriction augments stem cell numbers and function in diverse tissues and is proposed to have antitumor initiation and growth effects. If stem cell numbers increase with calorie restriction and they undergo some of the early changes that give rise to tumors, calorie restriction may potentially increase tumor incidence. It is possible that autonomous and nonautonomous protective mechanisms are activated in stem cells with calorie restriction, which neutralize the effects of a larger, more robust stem cell pool. Another possibility may be that the antigrowth effects of calorie restriction on tumor growth mask its effects on initiation. Tumors arising in calorie restriction may remain below detection threshold because they are small in size.

(C) Diet-induced obesity has untoward effects on tissue repair and cancer incidence. Although stem cell numbers can decrease with chronic obesity, the susceptibility of differentiated cells to undergo transformation can also increase as has been noted to occur with inflammation. In this case, early oncogenic events can occur in stem cells and differentiated cells, effectively increasing the pool of cells that can undergo early transformation. Surplus growth factors, nutrients, and hormones then drive tumor progression and growth.

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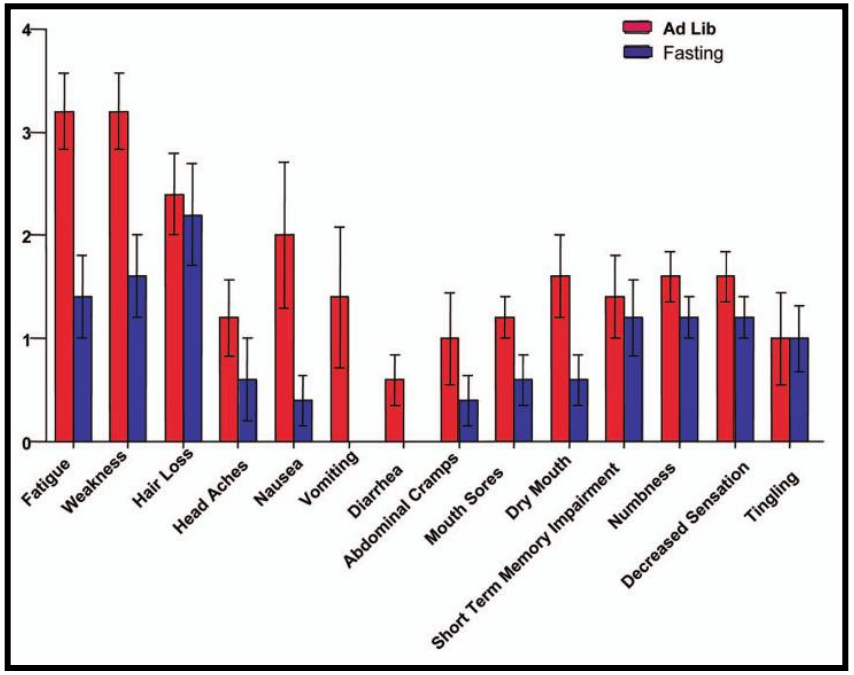
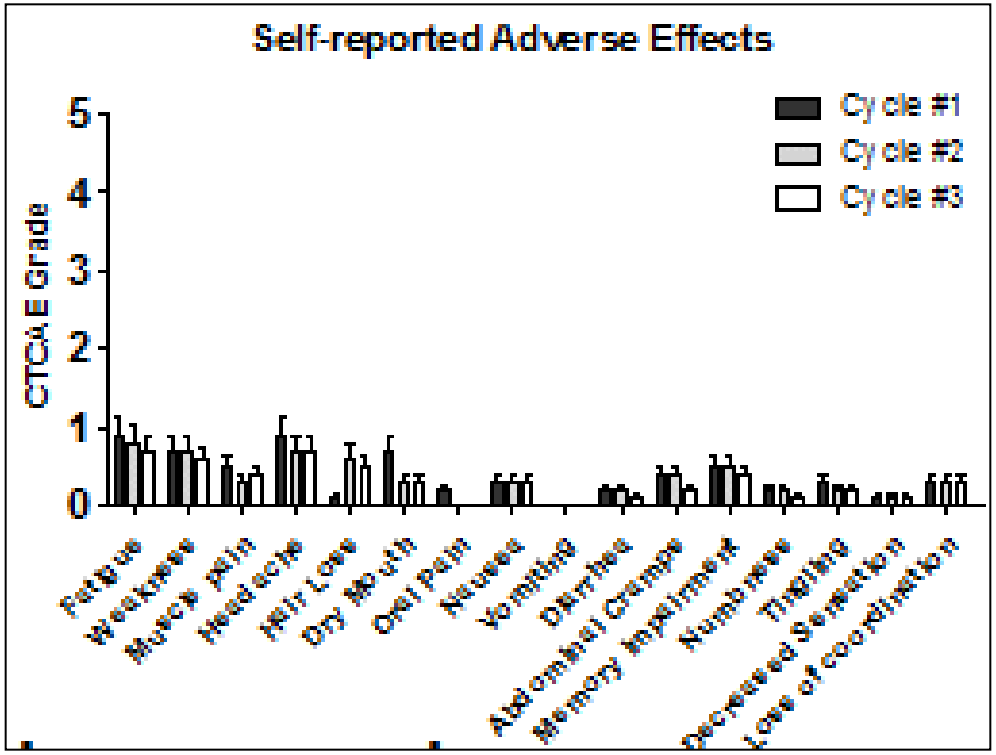
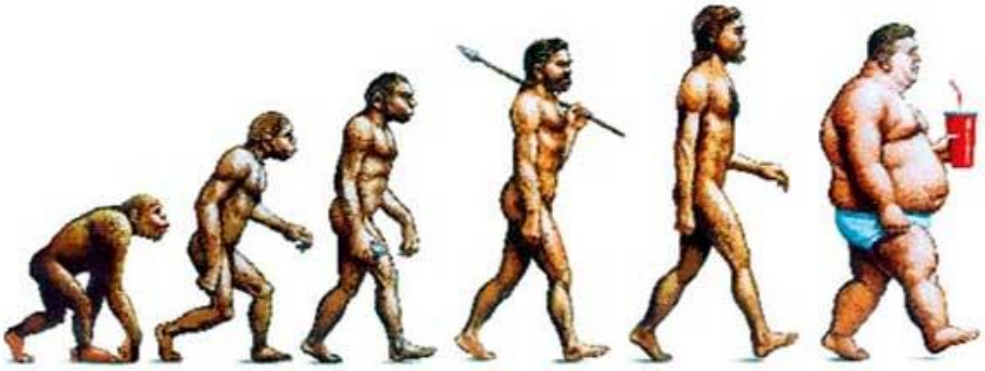


Average self-reported severity of symptoms in patients that have received chemotherapy with or without fasting (Raffaghello et al., 2010)



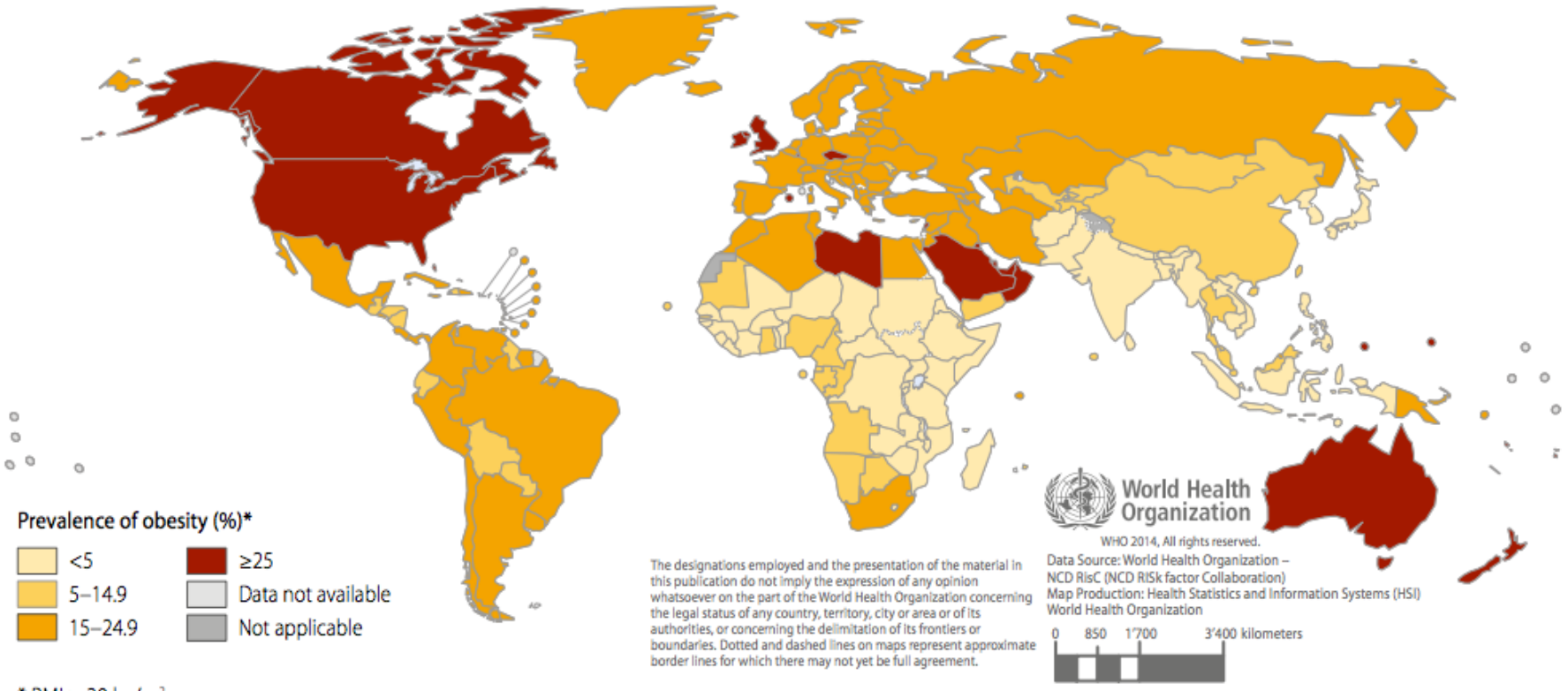
Brandhorst et al., 2015

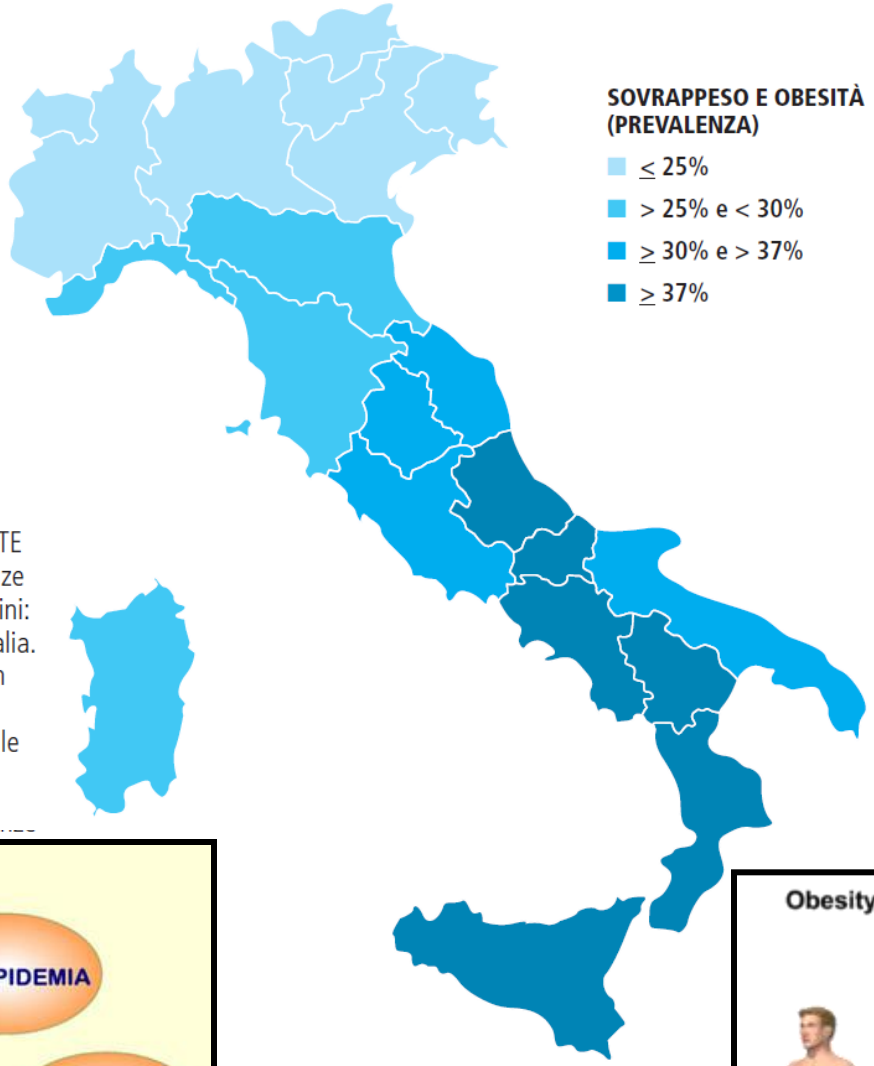
TUMOR-HOST INTERACTION-3: OBESITY AND METABOLIC SYNDROME



OBESITY

Fig. 7.1 Age-standardized prevalence of obesity in men aged 18 years and over (BMI ≥30 kg/m²), 2014

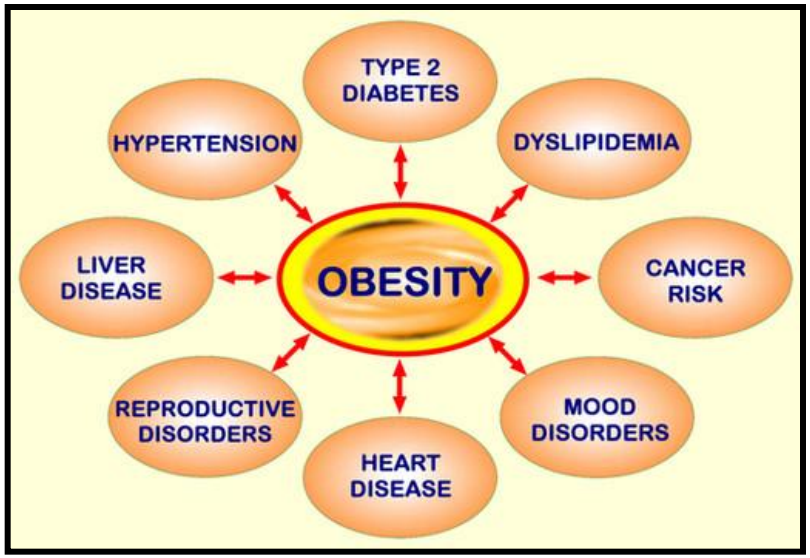


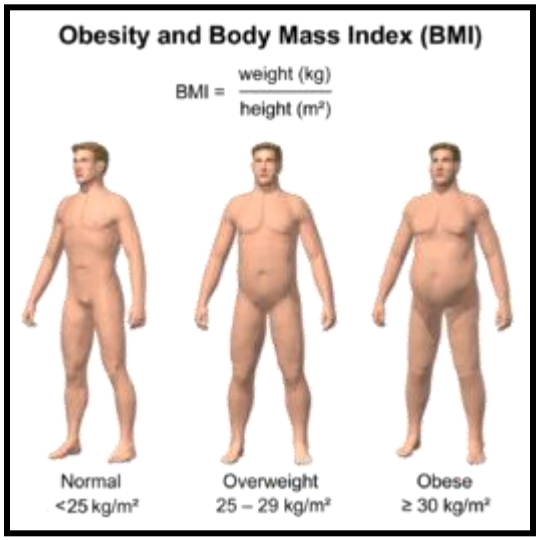


SOVRAPPESO E OBESITÀ NEI BAMBINI ITALIANI DI 8-9 ANNI PER REGIONE

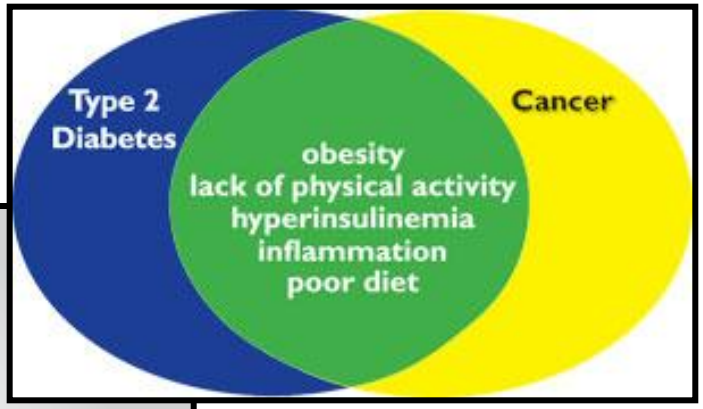
OKkio alla SALUTE, Italia 2014

MAPPA. La rilevazione del 2014 di OKkio alla SALUTE conferma la forte variabilità geografica nelle prevalenze di eccesso ponderale (sovrappeso+obesità) nei bambini: 23,8% al Nord, 29,4% al Centro e 38,0% nel Sud Italia. Valori più elevati si riscontrano nei figli di genitori con titolo di studio basso. Per ridurre il fenomeno delle disuguaglianze in salute, è necessario tener conto delle differenze socioeconomiche e culturali nella pianificazione di interventi.





METABOLIC SYNDROME



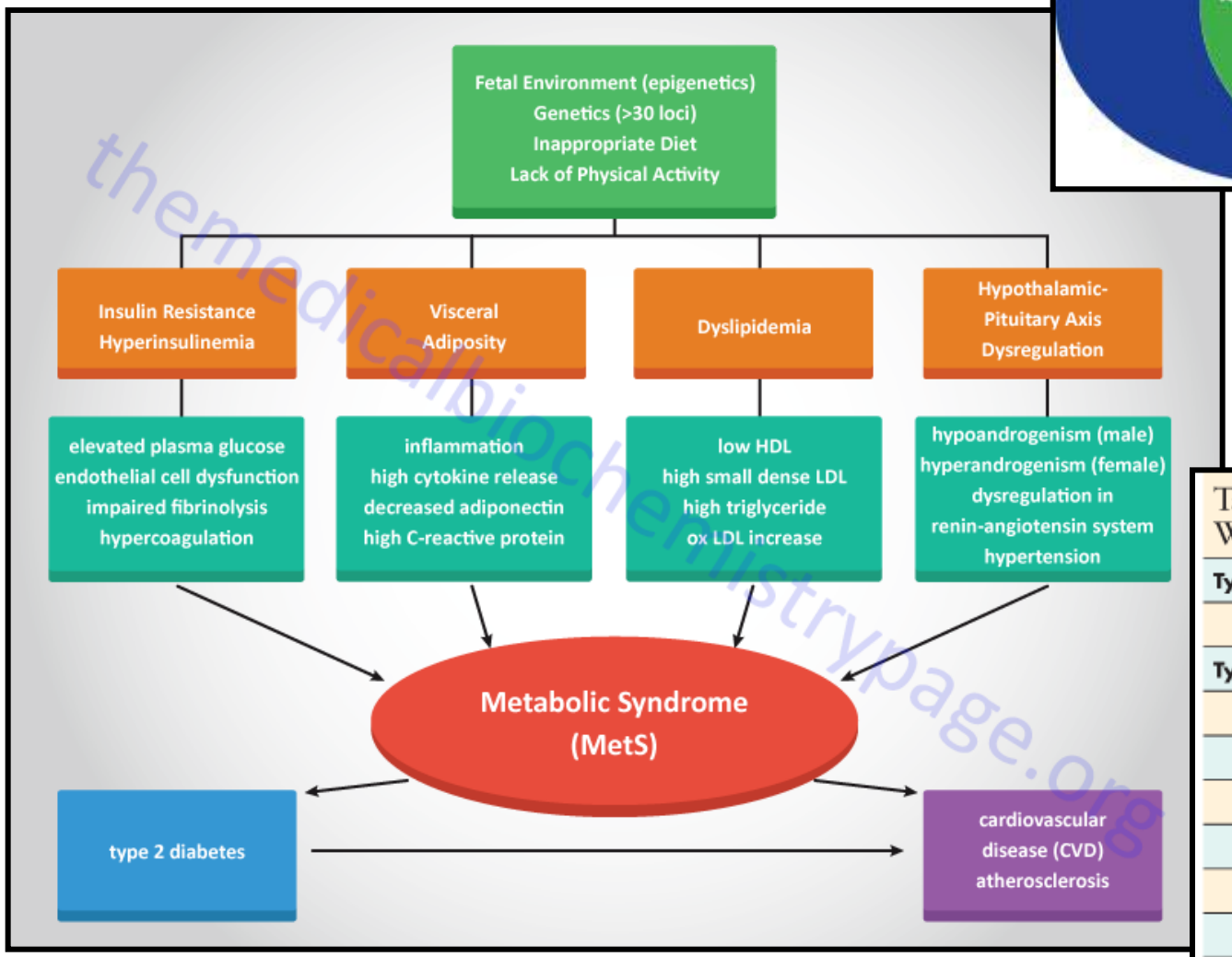
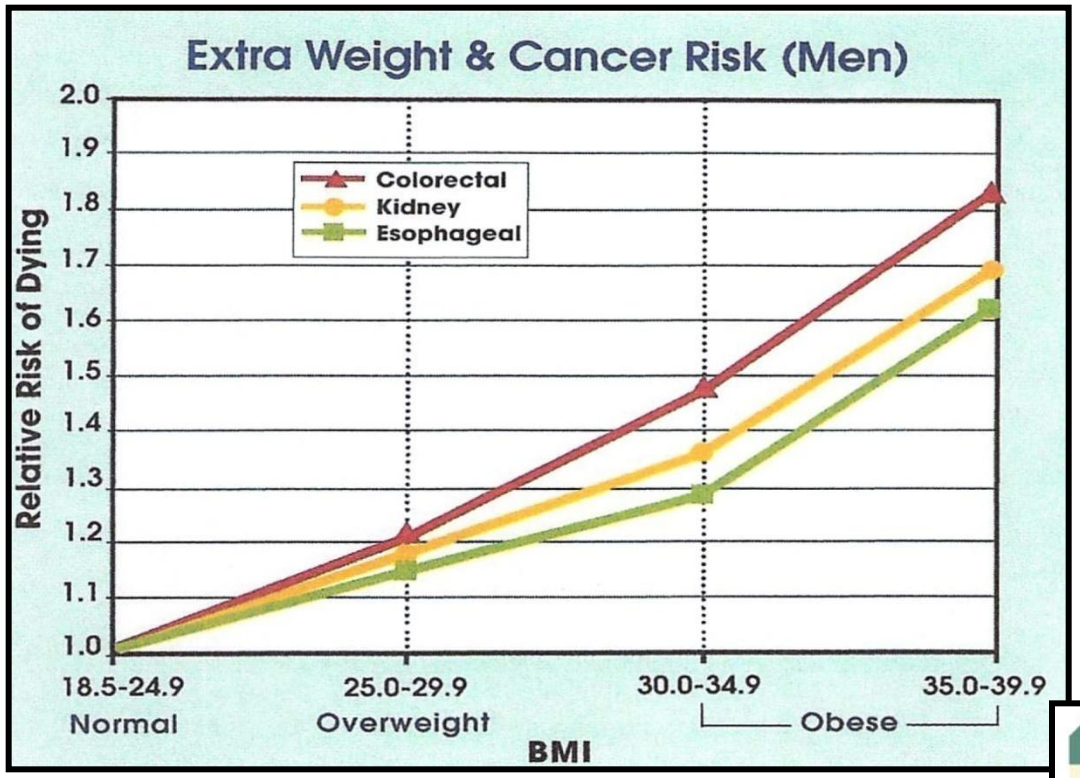
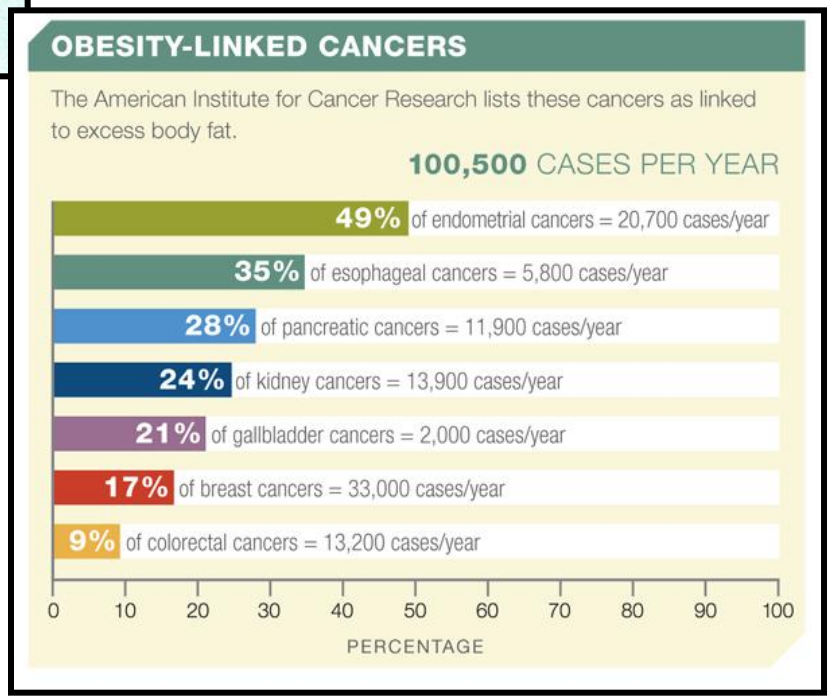


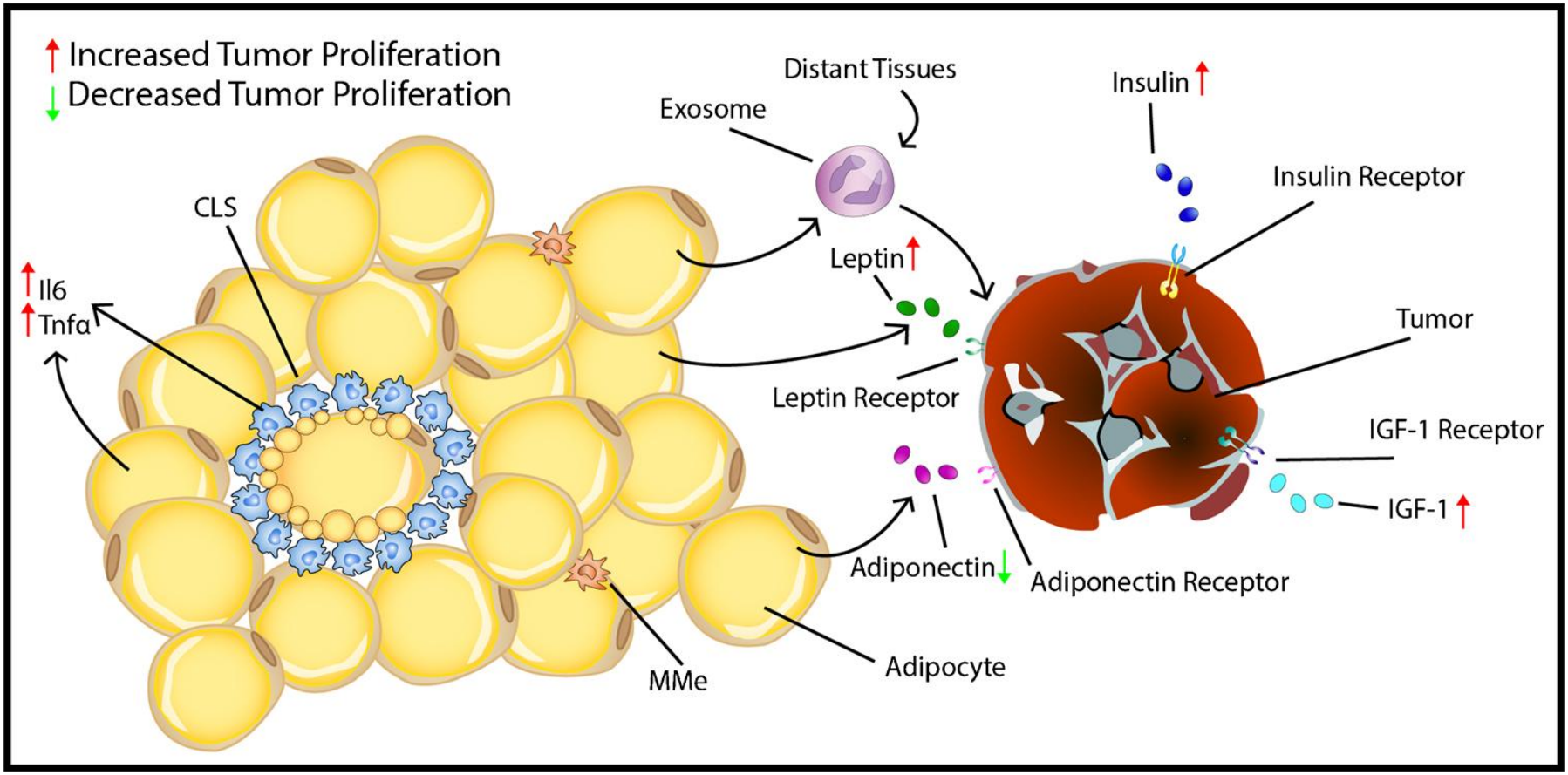
Table 2: Cancers Associated With Diabetes Mellitus

Type 1 DM	Cervix
	Stomach
Type 2 DM	Breast
	Colon
	Endometrial
	Pancreatic
	Liver
	Bladder cancer
	Non-Hodgkin's lymphoma
	Hodgkin's lymphoma

Information from References 6 and 7.

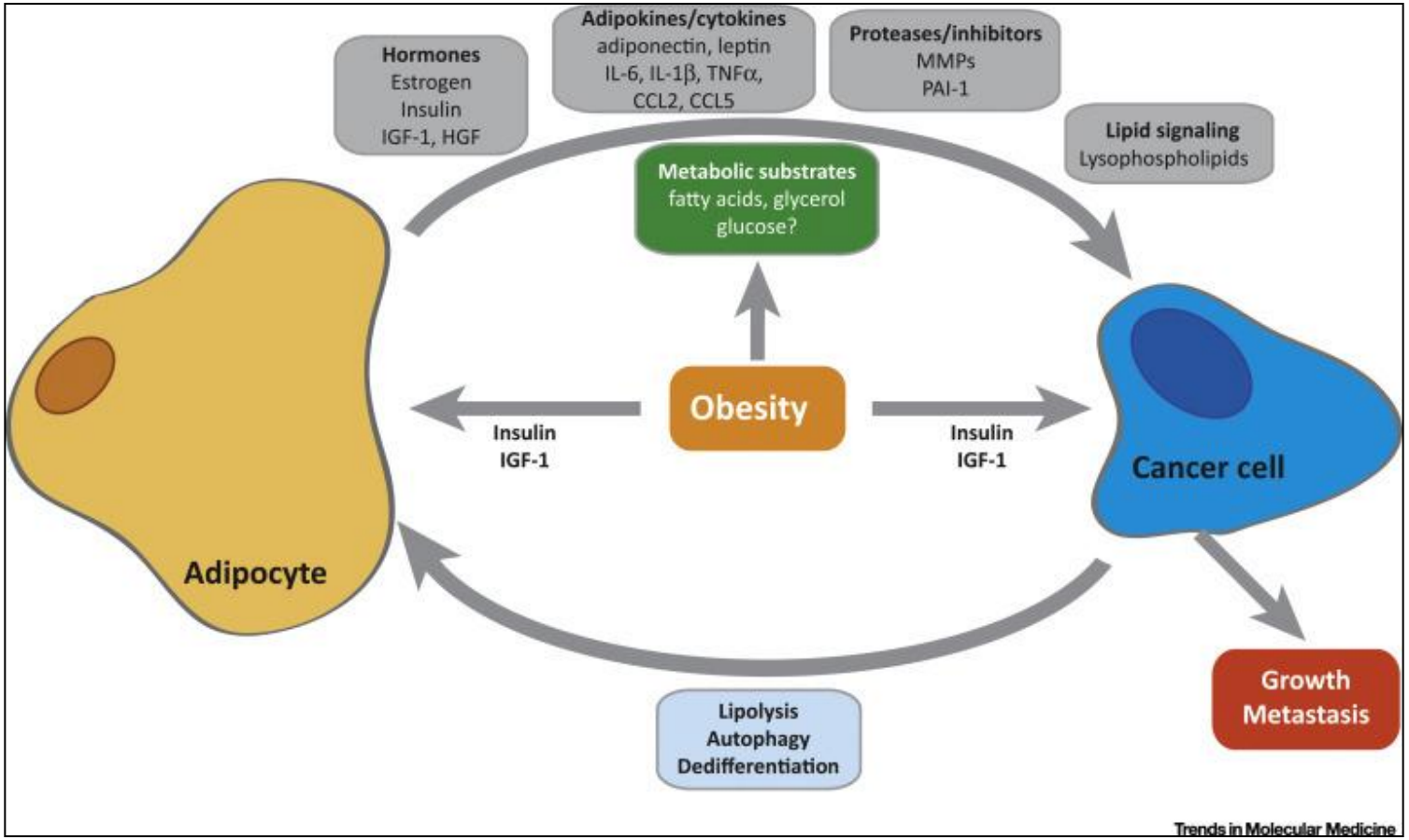

Extra Weight & Cancer Risk (Men)
Relative Risk of Dying
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
Colorectal
Kidney
Esophageal
18.5-24.9
Normal
25.0-29.9
Overweight
30.0-34.9
35.0-39.9
Obese
BMI


OBESITY-LINKED CANCERS
The American Institute for Cancer Research lists these cancers as linked to excess body fat.
100,500 CASES PER YEAR
49% of endometrial cancers = 20,700 cases/year
35% of esophageal cancers = 5,800 cases/year
28% of pancreatic cancers = 11,900 cases/year
24% of kidney cancers = 13,900 cases/year
21% of gallbladder cancers = 2,000 cases/year
17% of breast cancers = 33,000 cases/year
9% of colorectal cancers = 13,200 cases/year
0
10
20
30
40
50
60
70
80
90
100
PERCENTAGE



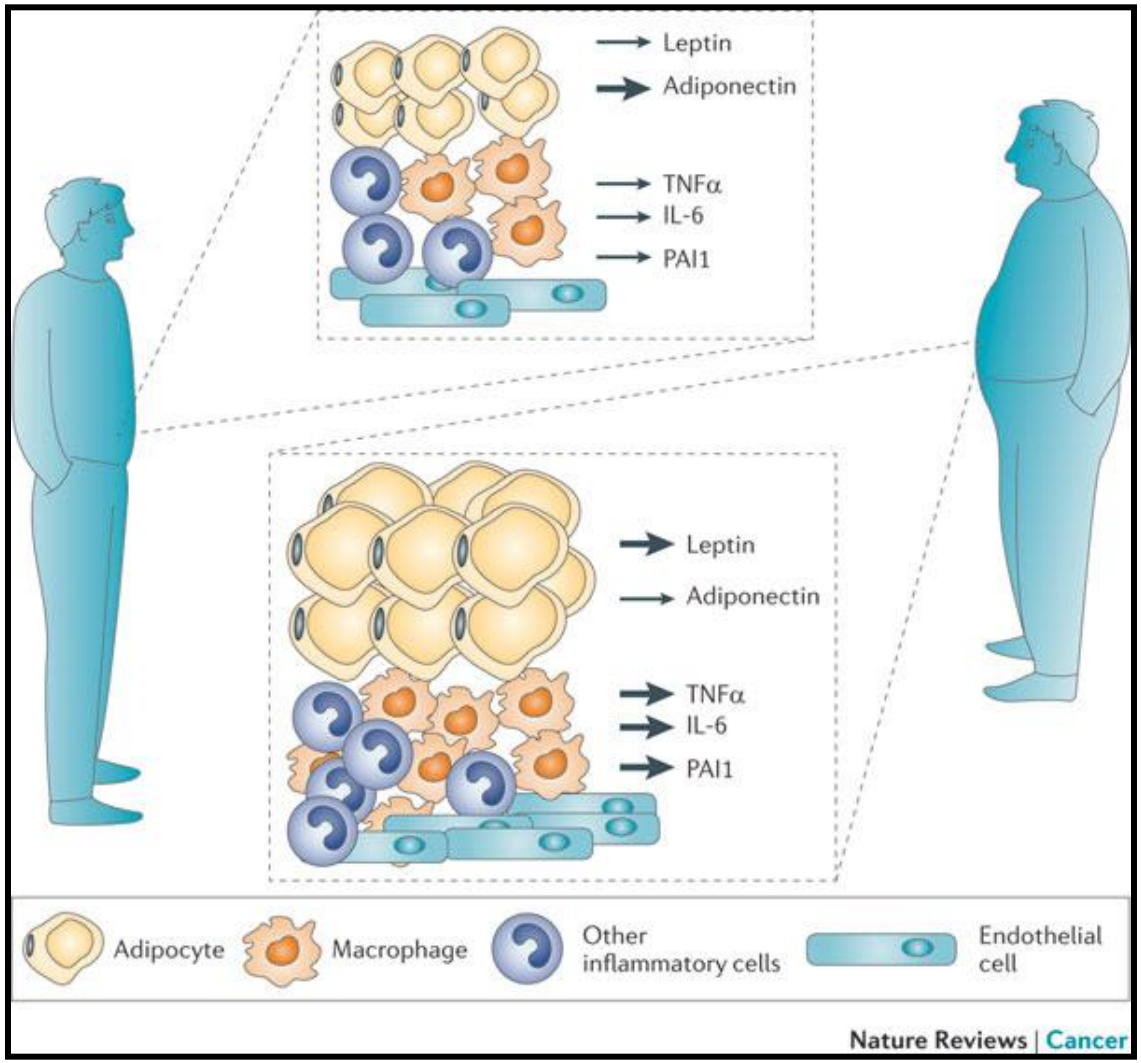
Mme = metabolically activated macrophages

Ackerman et al., 2017

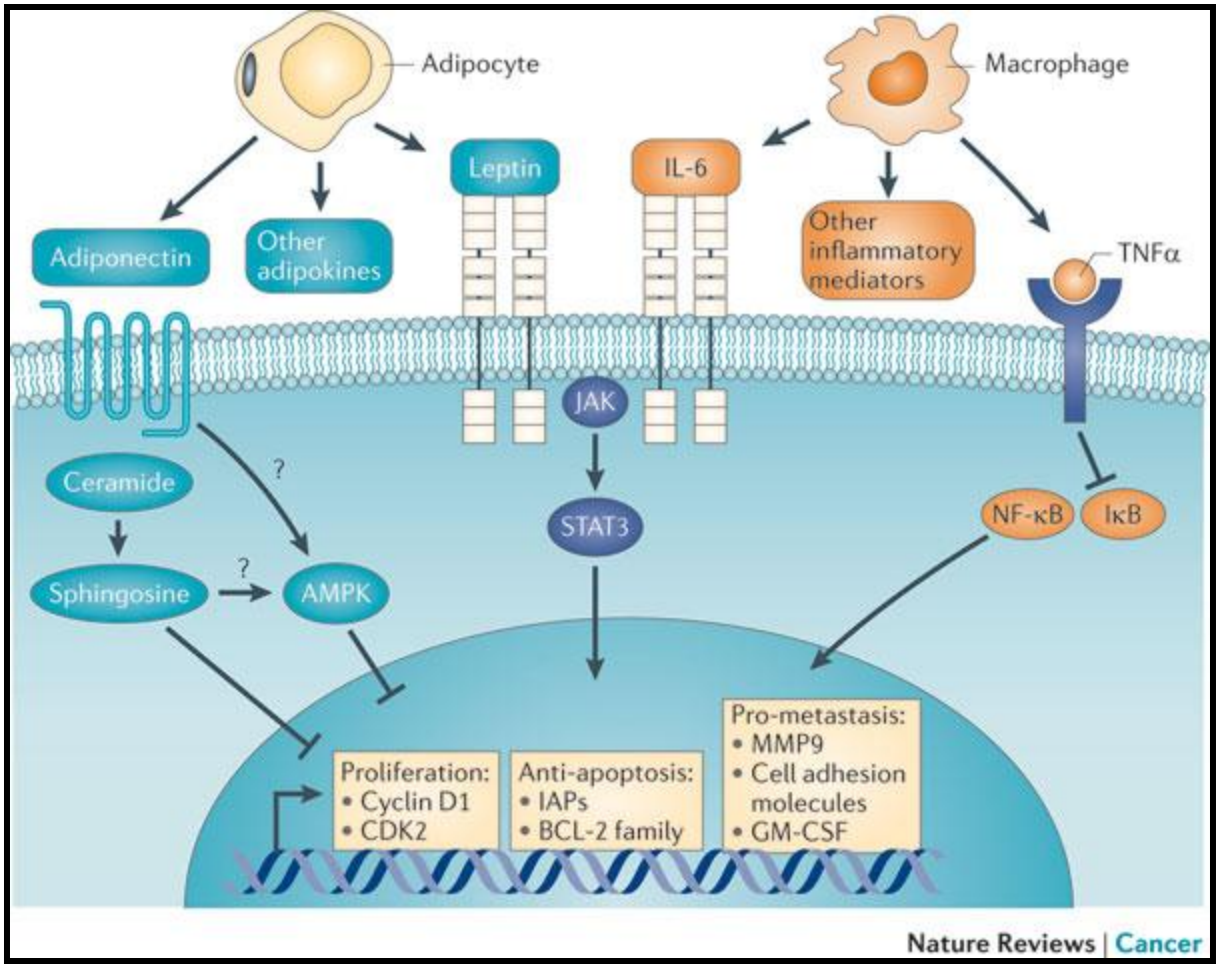


Reciprocal Interactions between Human Stromal Adipocytes and Breast Cancer Cells

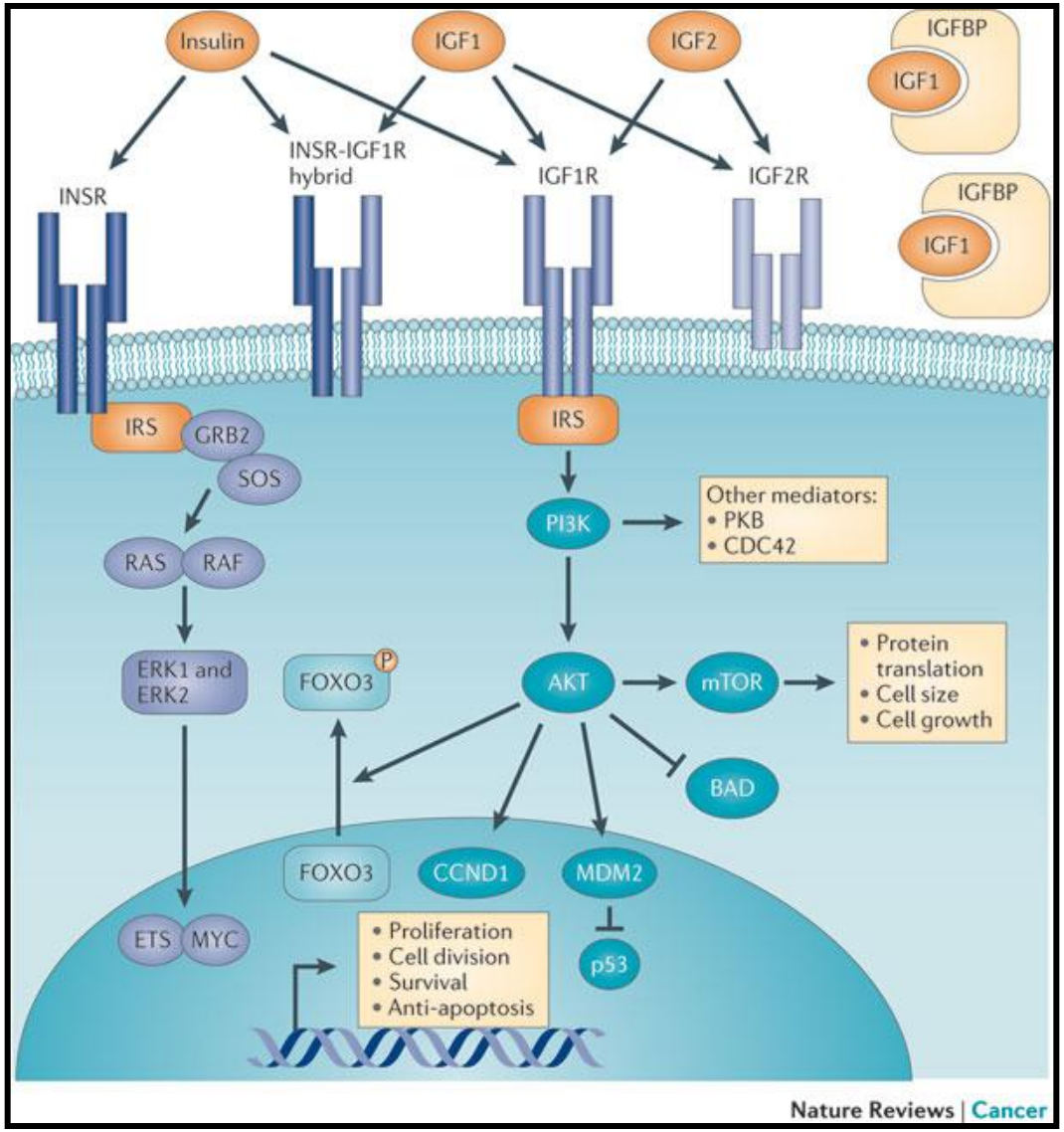
Within the breast cancer microenvironment, tumor cells and adipocytes are in close proximity and can exert a variety of reciprocal effects on each other. Breast cancer cells induce the production of endocrine and paracrine signaling mediators, proteolytic enzymes, and bioactive lipids, along with metabolic substrates by adipocytes. These in turn drive increased growth and invasion of tumor cells along with therapeutic resistance. Obesity leads to the increased production of some signaling factors, such as hormones and adipokines and/or cytokines, and increased availability of metabolic substrates, accentuating in turn, cancer cell growth and metastasis. Abbreviations: CCL2, C-C motif chemokine ligand 2; CCL5, C-C motif chemokine ligand 5; HGF, hepatocyte growth factor; IGF-1, insulin-like growth factor 1; IL-1β, interleukin 1β; IL-6, interleukin 6; MMP, matrix metalloproteinases; PAI-1, plasminogen activator inhibitor-1; TNFα, tumor necrosis factor α (Hoy et al., 2017).



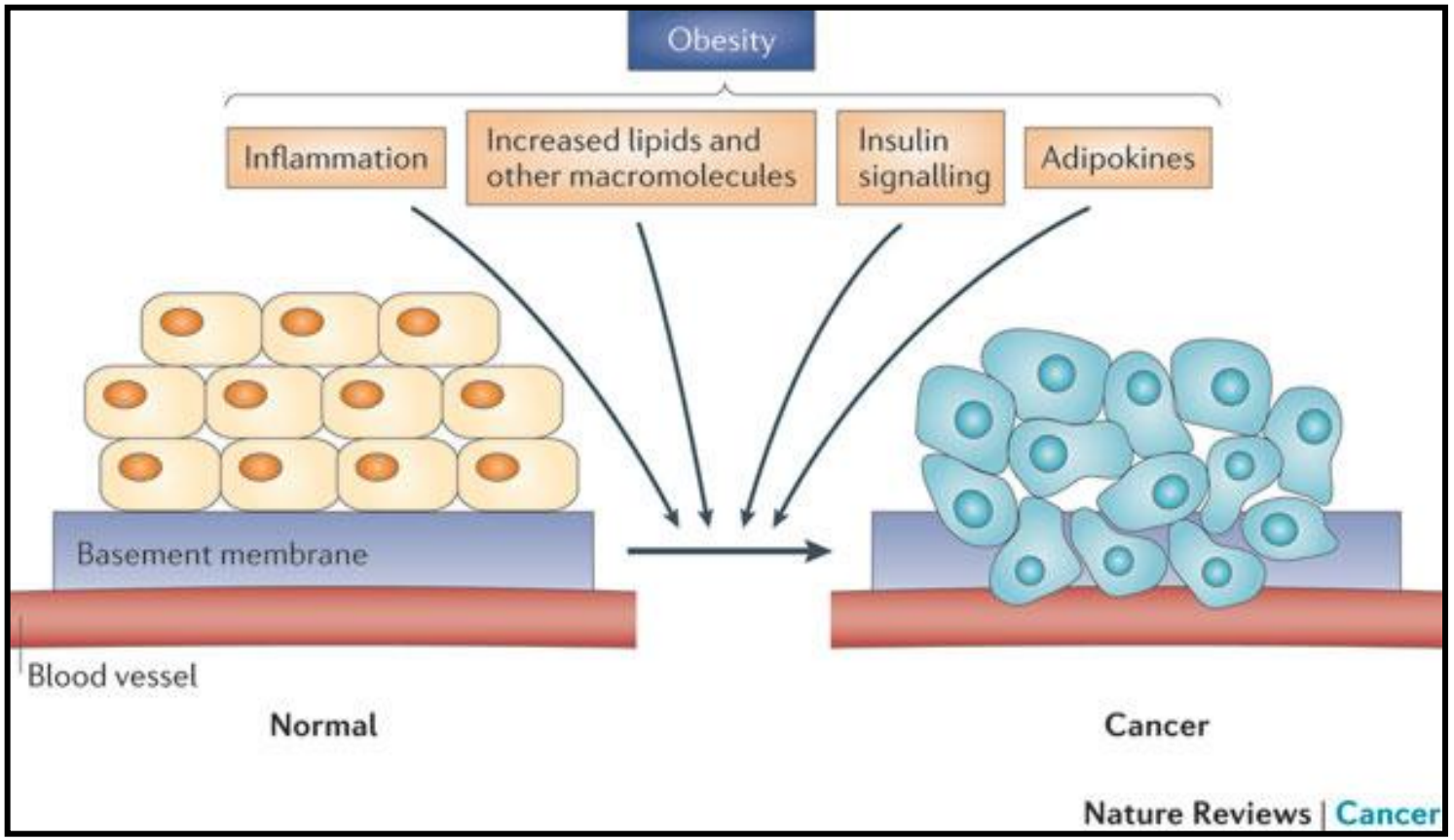
Khandekar et al., 2011



Khandekar et al., 2011

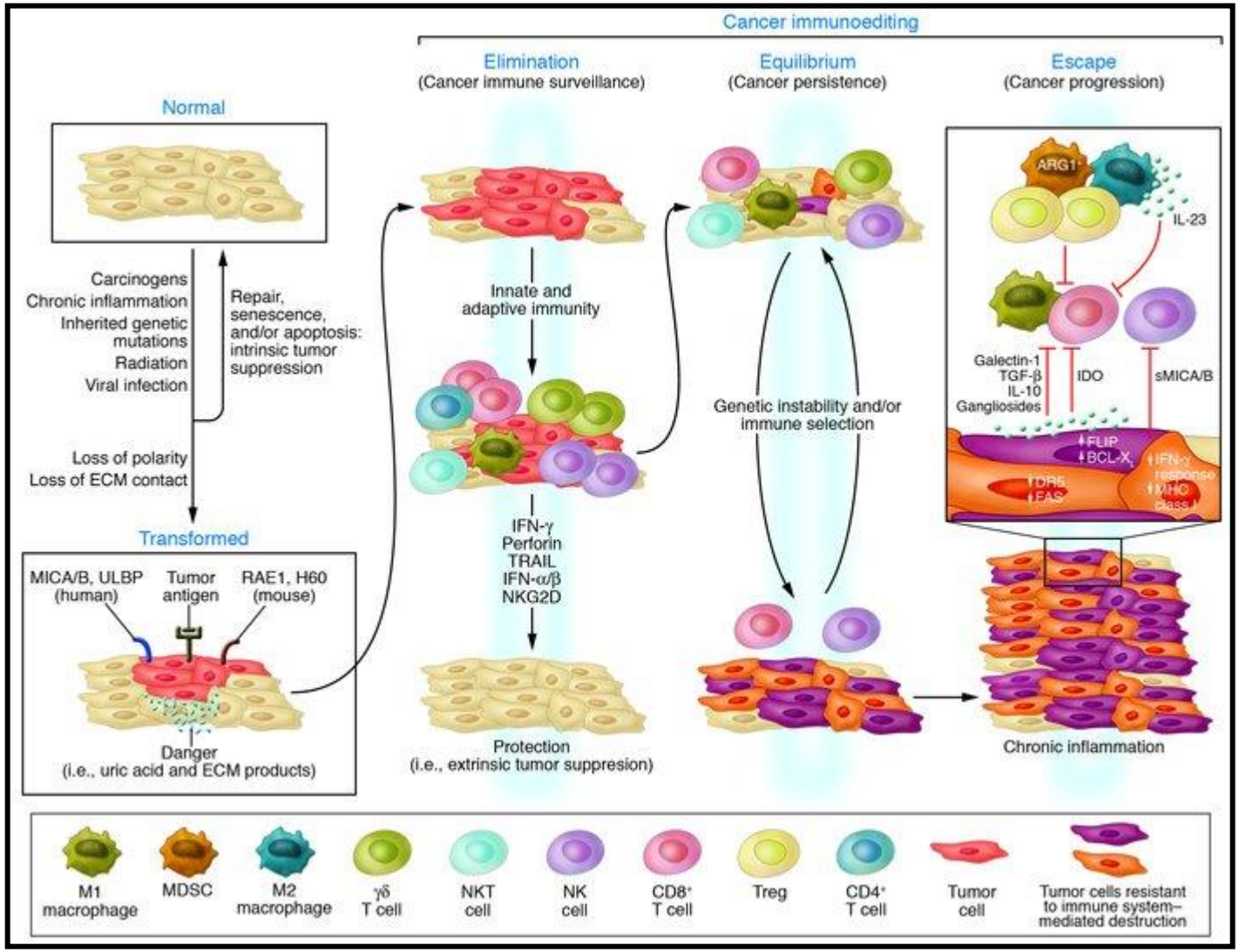


Khandekar et al., 2011

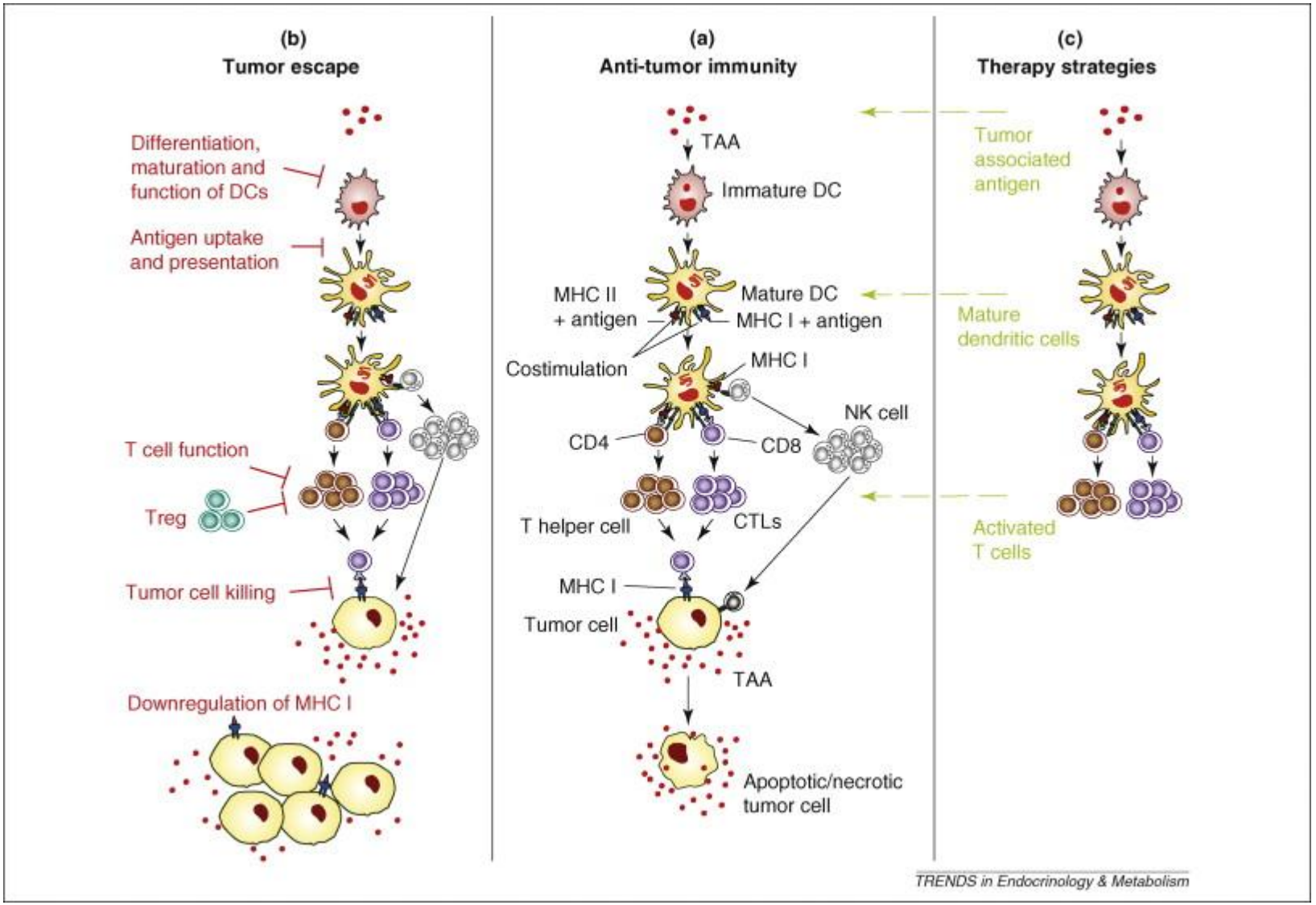


Khandekar et al., 2011

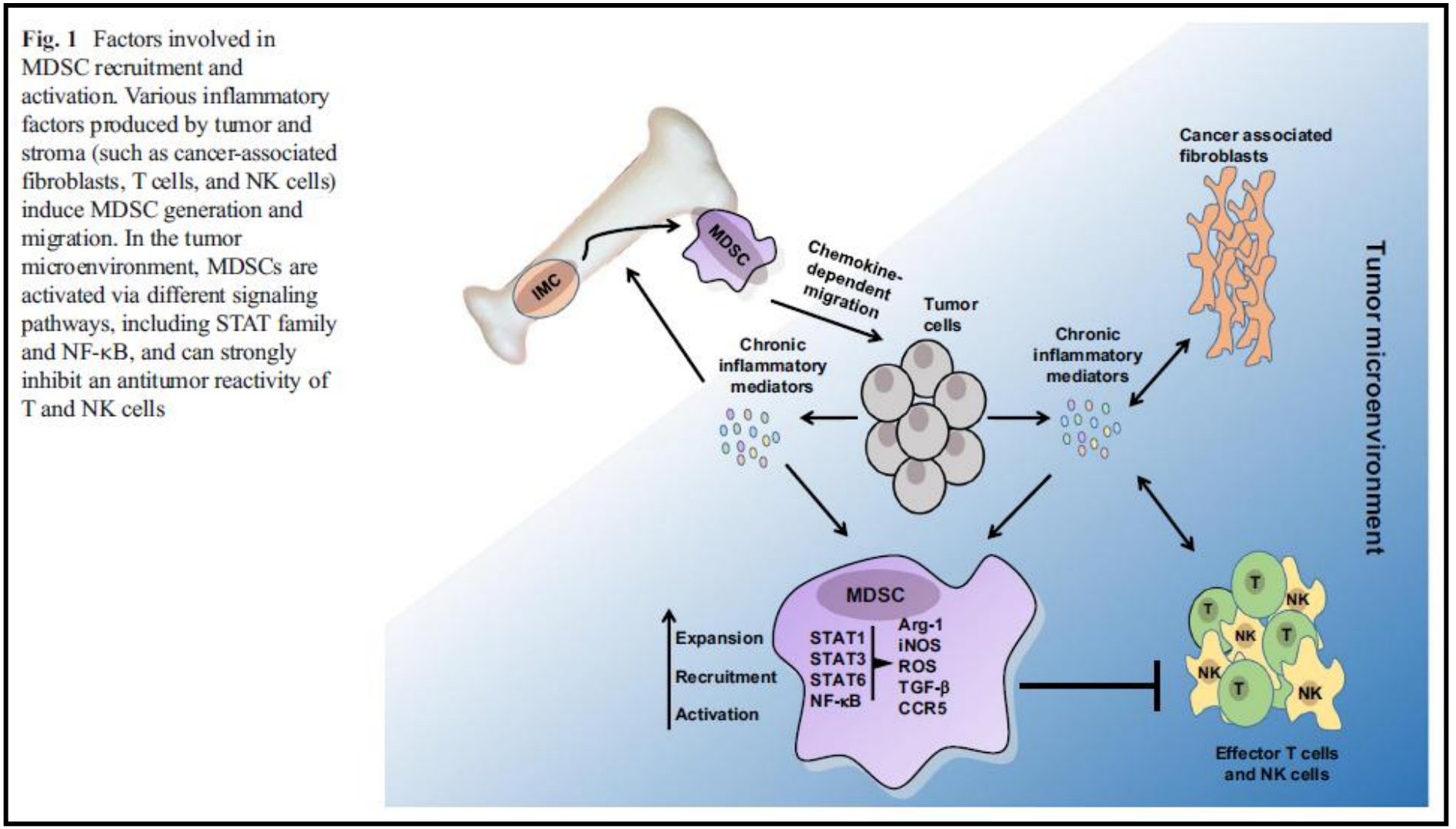
TUMOR-HOST INTERACTION-4: IMMUNE SURVEILLANCE



Swan & Smith, 2007



Wuttke et al., 2009



Umansky et al., 2016

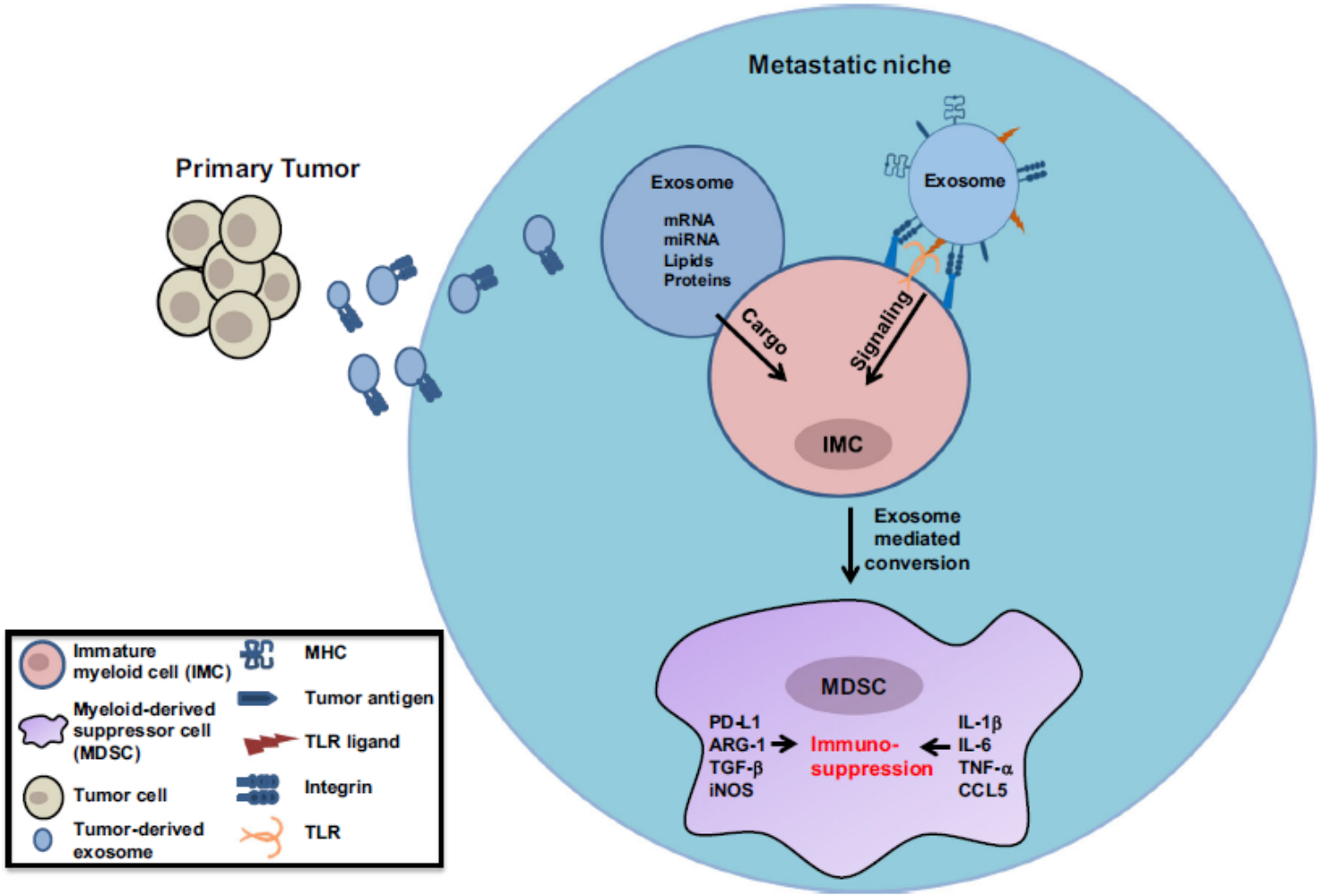
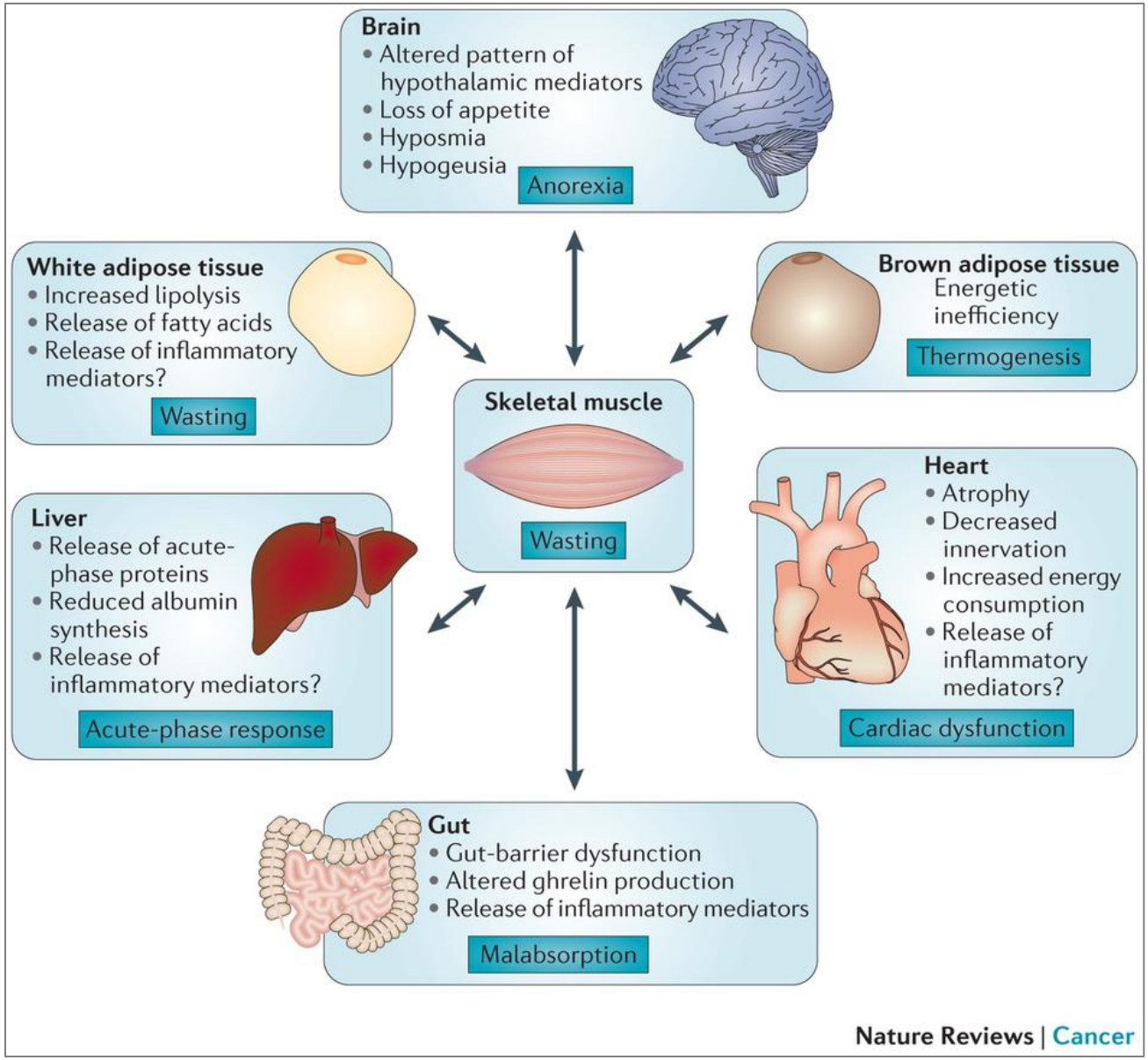


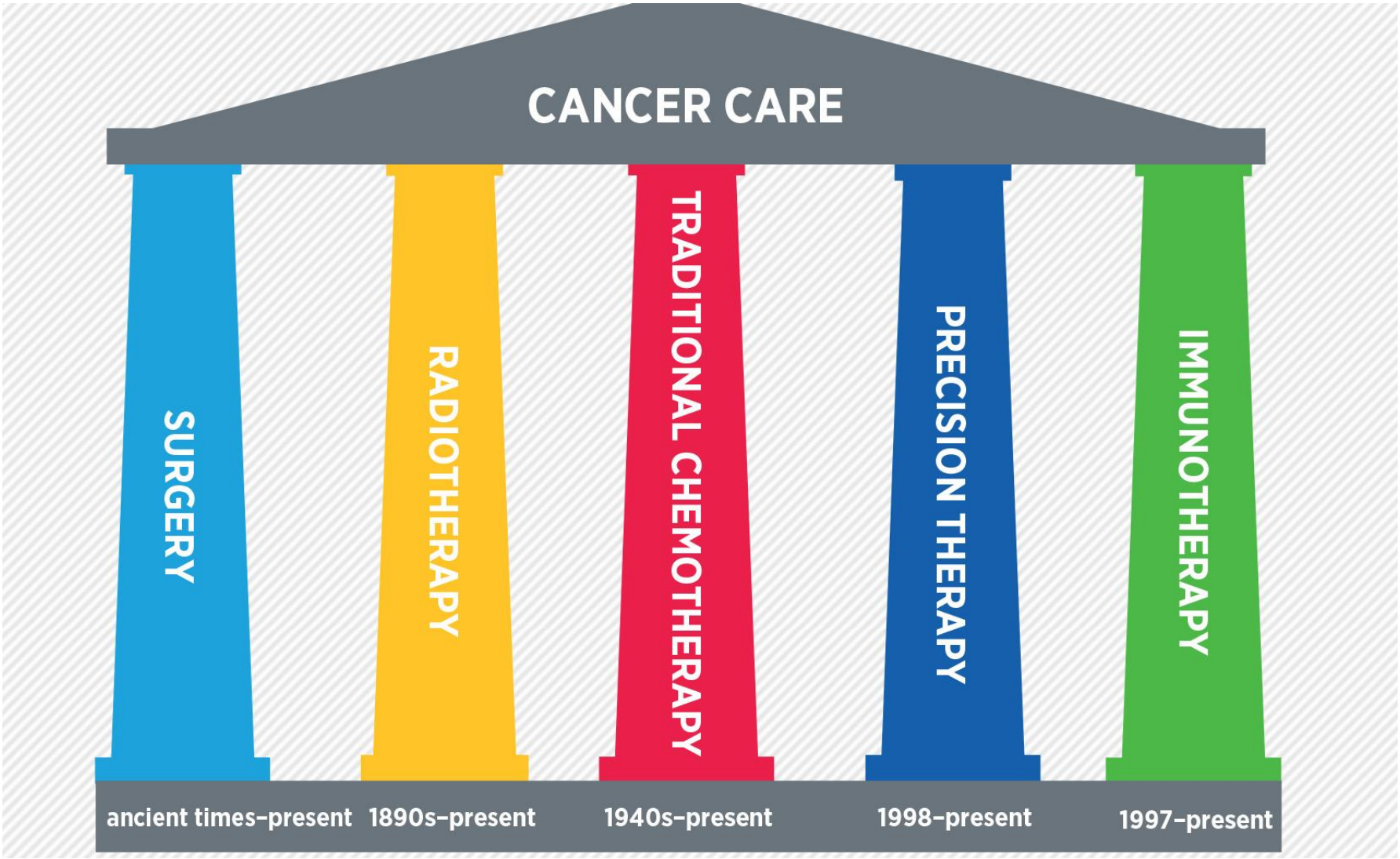
Fig. 2 Tumor-derived EVs support MDSC formation. EVs secreted by tumor cells convert immature myeloid cells (IMCs) into highly suppressive MDSCs serving as a cargo for miRNAs and proteins or by inducing signaling in the IMC. MDSCs can foster the formation of metastatic niche and the process of metastasis

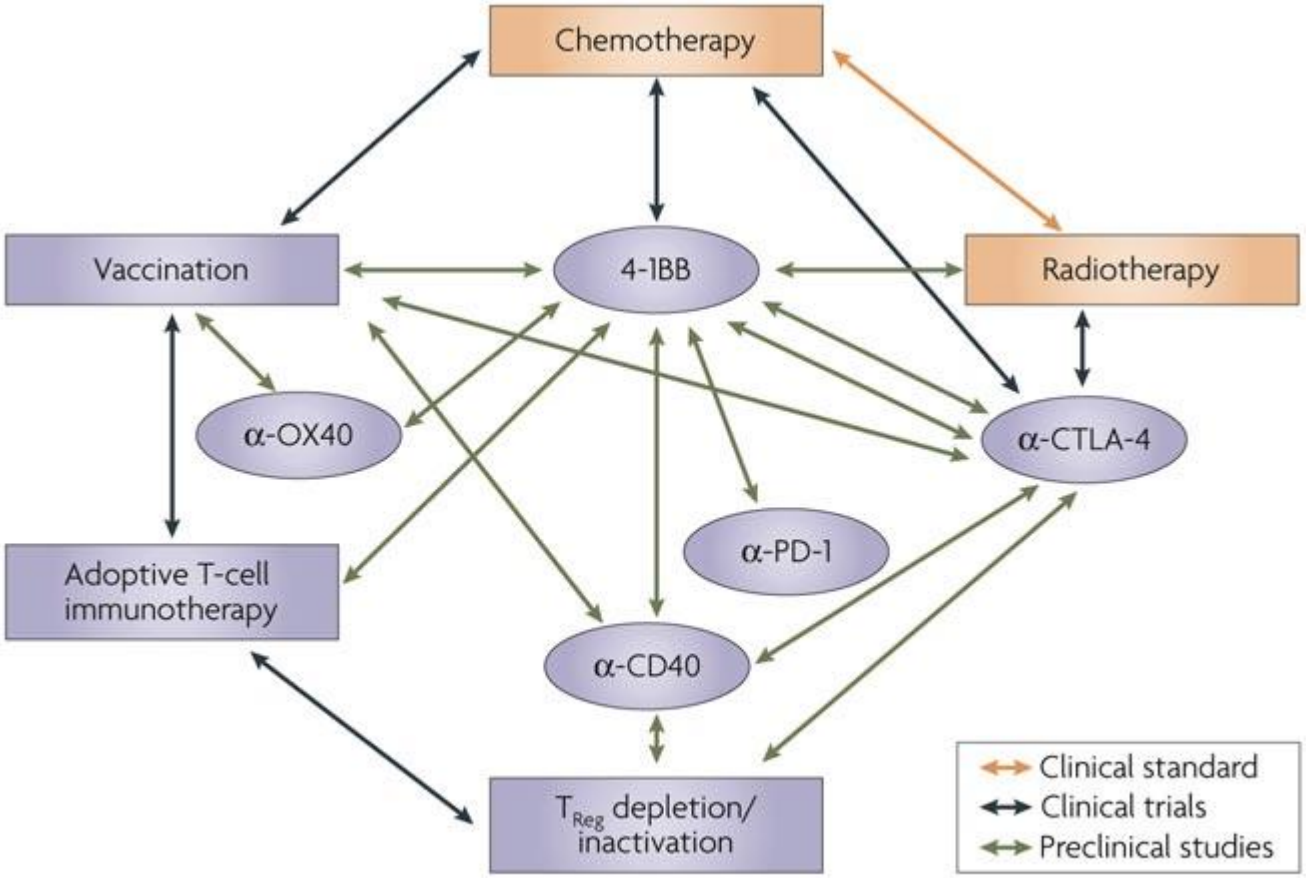
Umansky et al., 2016

TUMOR-HOST INTERACTION-5: CANCER CACHEXIA

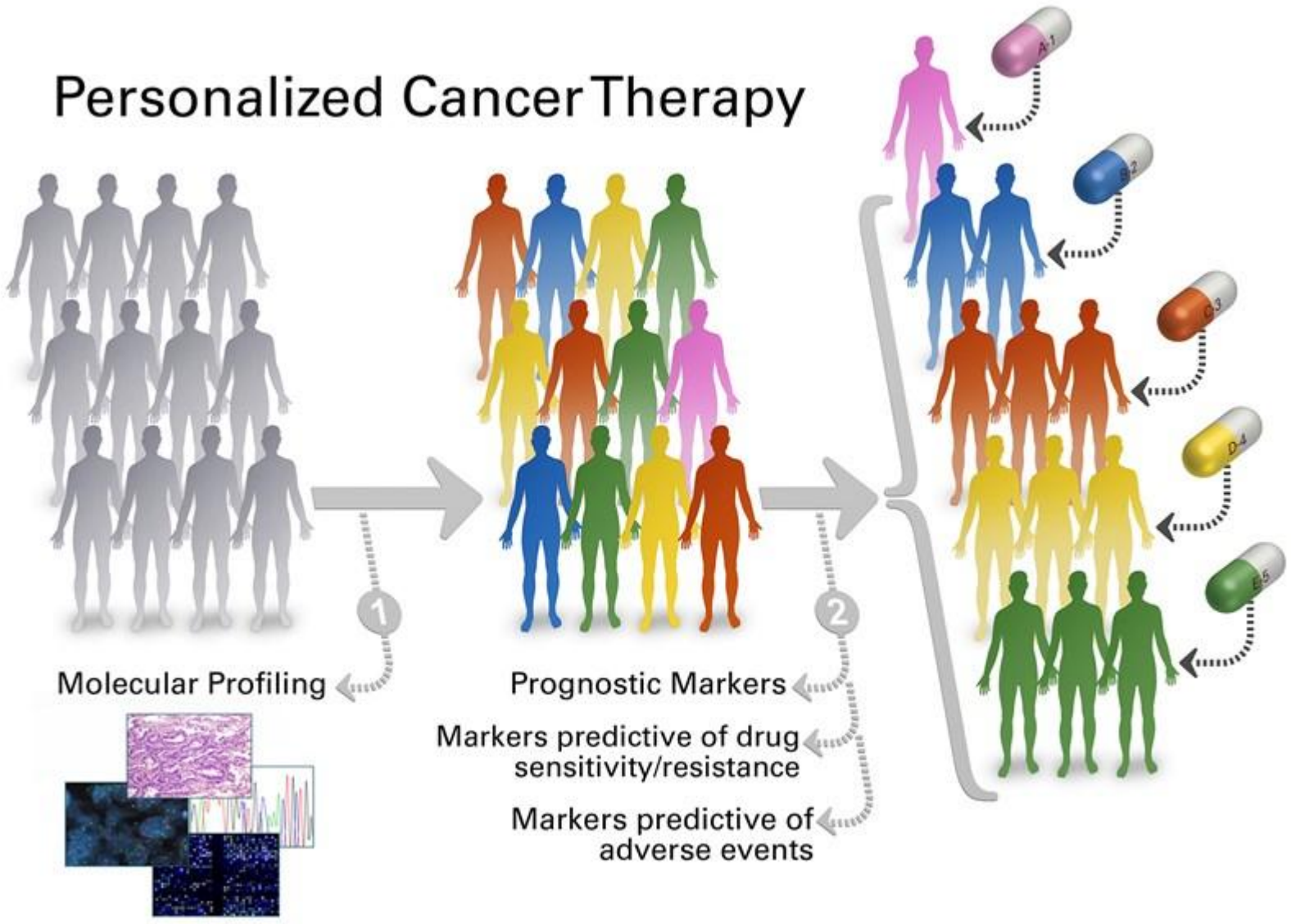


Argilés et al., 2014


CANCER CARE
SURGERY
RADIOTHERAPY
TRADITIONAL CHEMOTHERAPY
PRECISION THERAPY
IMMUNOTHERAPY
ancient times–present
1890s–present
1940s–present
1998–present
1997–present

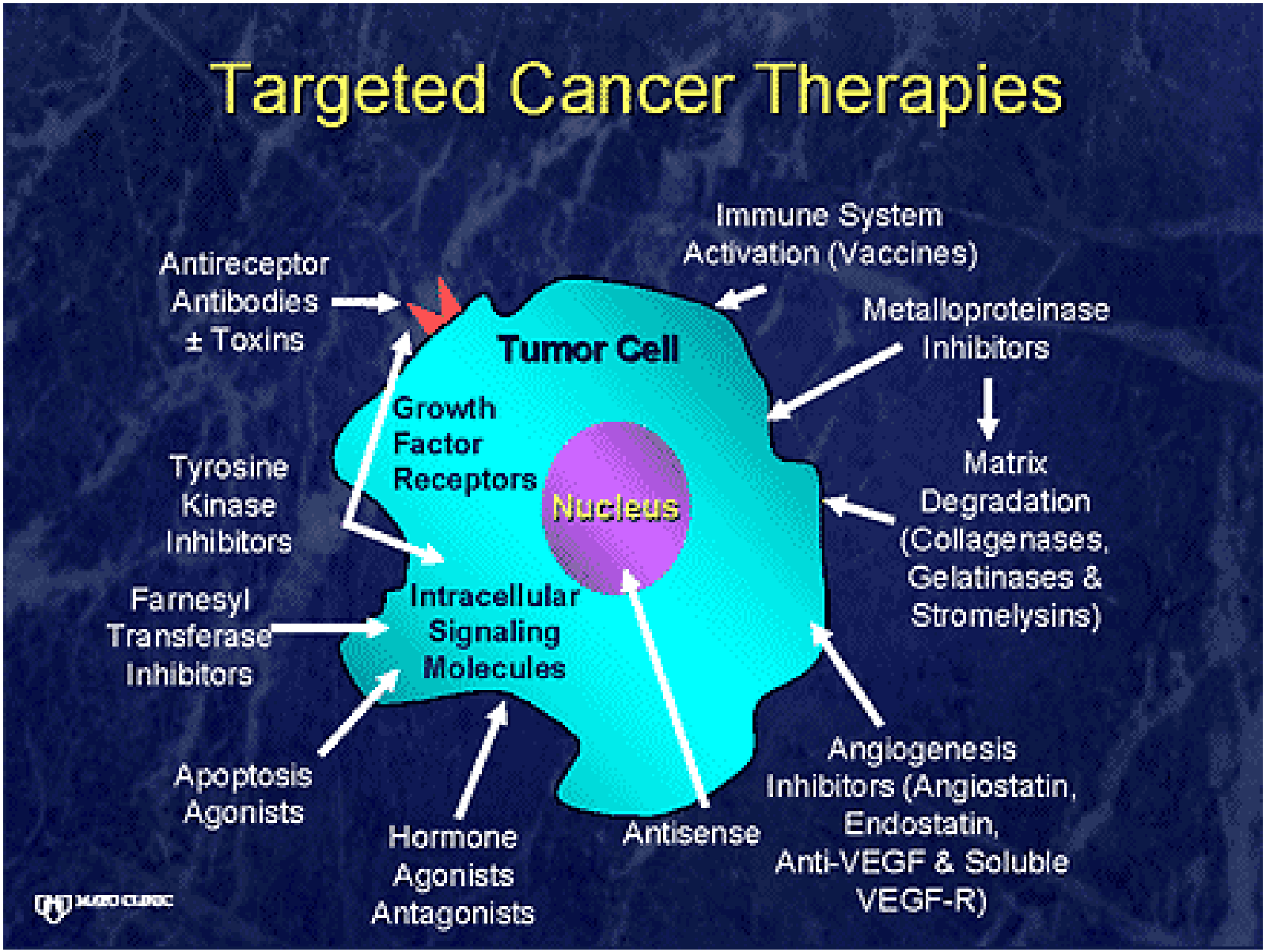


Nature Reviews | Cancer



https://pct.mdanderson.org/#/

Targeted Cancer Therapies



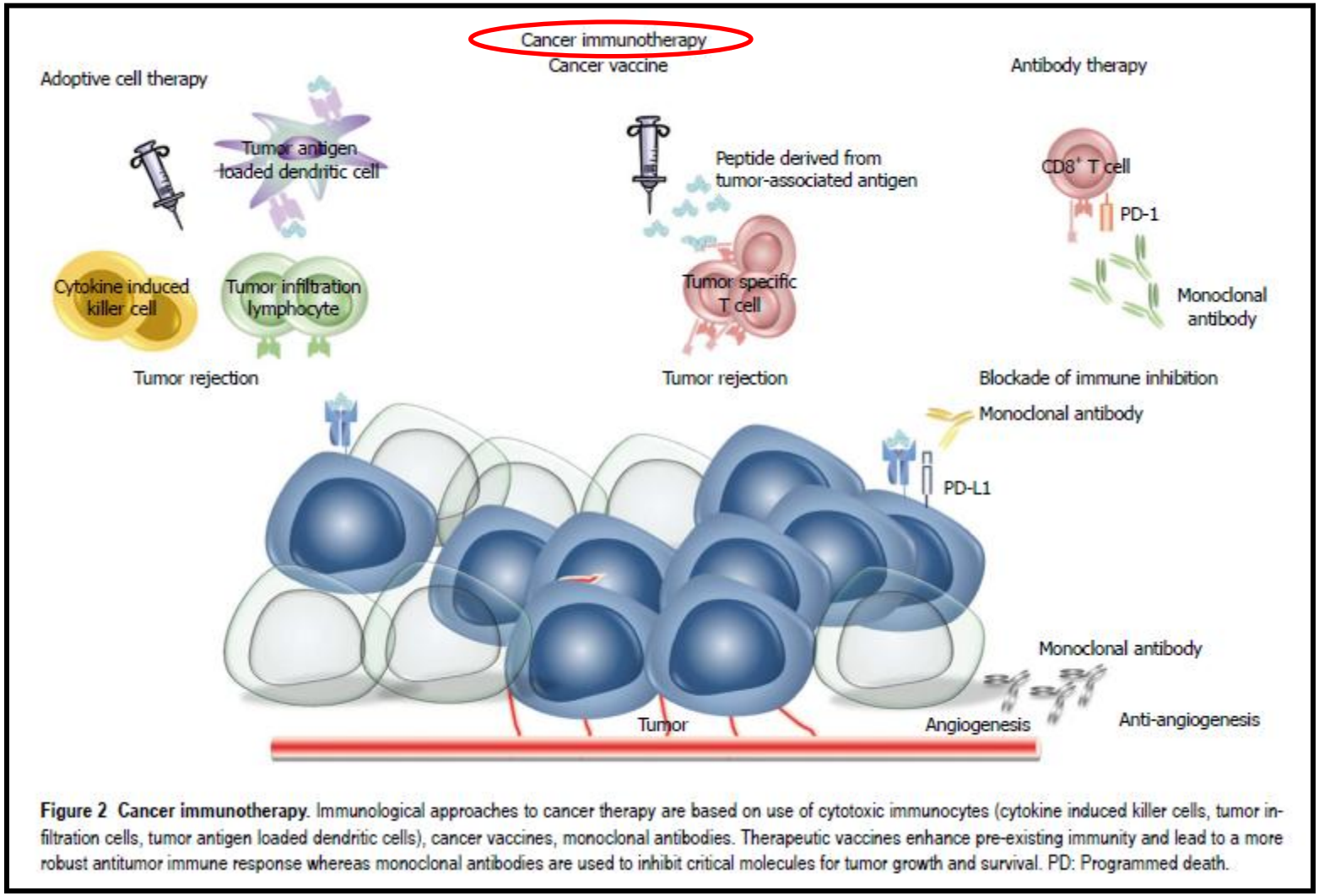
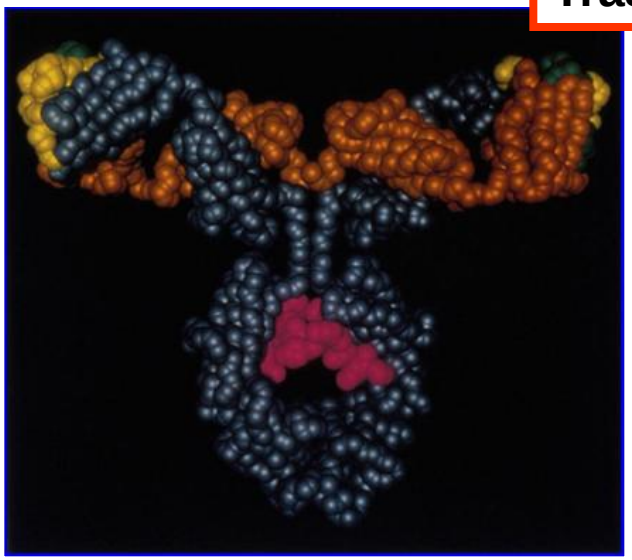


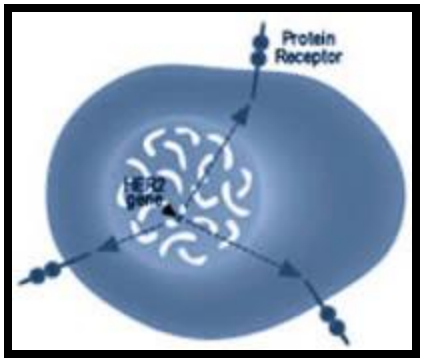
Figure 2 Cancer immunotherapy. Immunological approaches to cancer therapy are based on use of cytotoxic immunocytes (cytokine induced killer cells, tumor infiltration cells, tumor antigen loaded dendritic cells), cancer vaccines, monoclonal antibodies. Therapeutic vaccines enhance pre-existing immunity and lead to a more robust antitumor immune response whereas monoclonal antibodies are used to inhibit critical molecules for tumor growth and survival. PD: Programmed death.

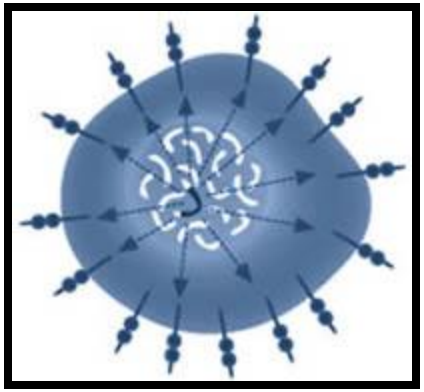
Matsueda & Graham, 2014

Trastuzumab: anti-Her2 (EGFR) monoclonal antibody

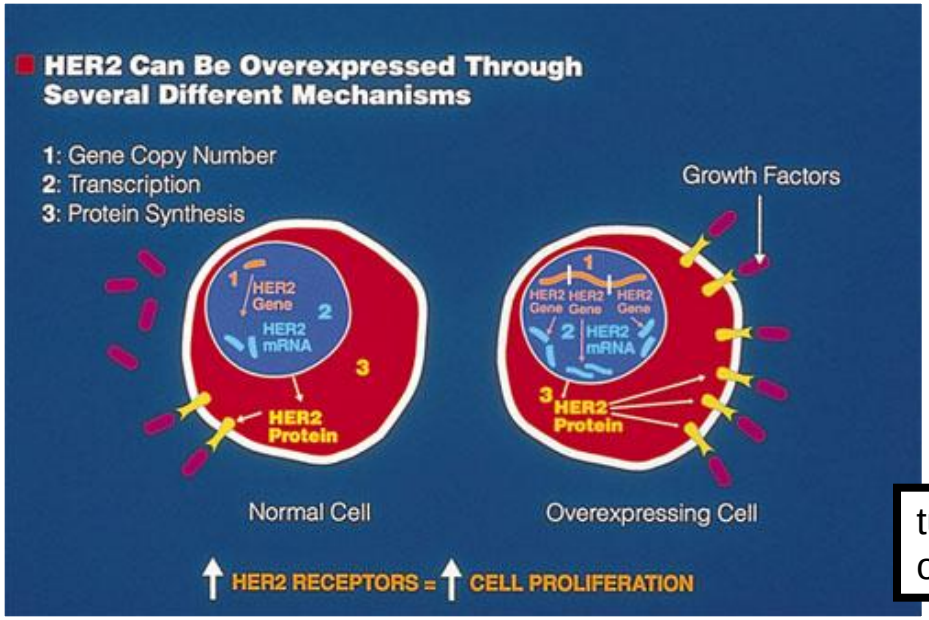


Normal cell

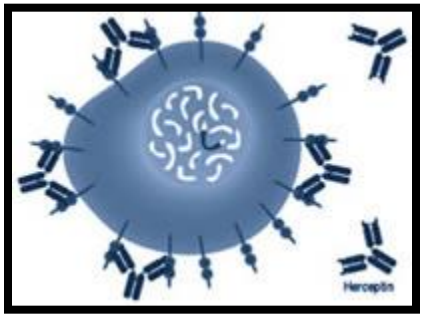




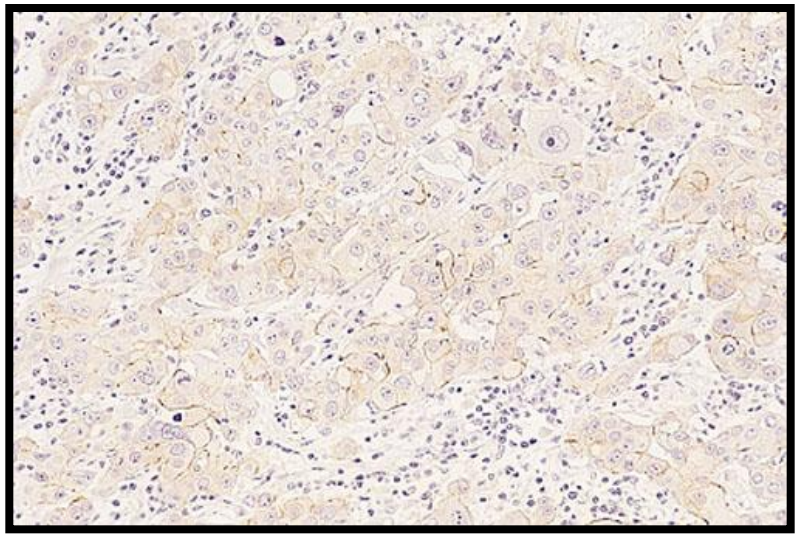
tumor cell



tumor cell in the presence of anti-Her2 antibodies



HercepTest (breast cancer)



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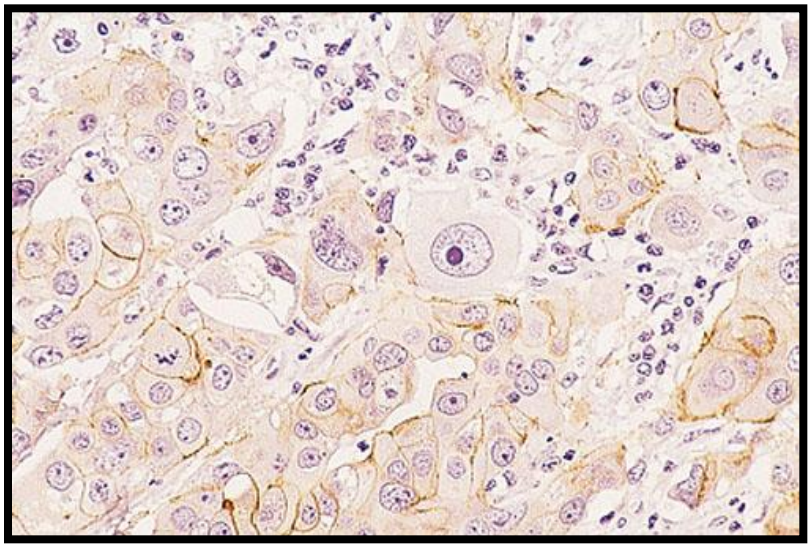
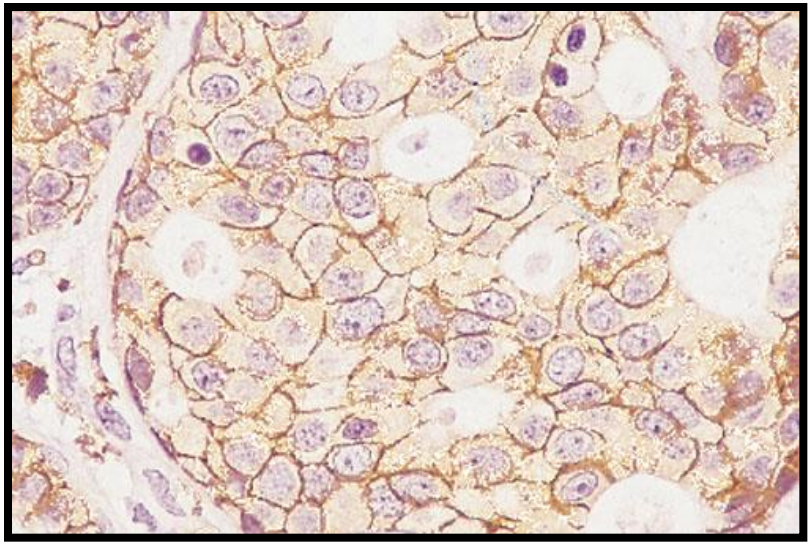
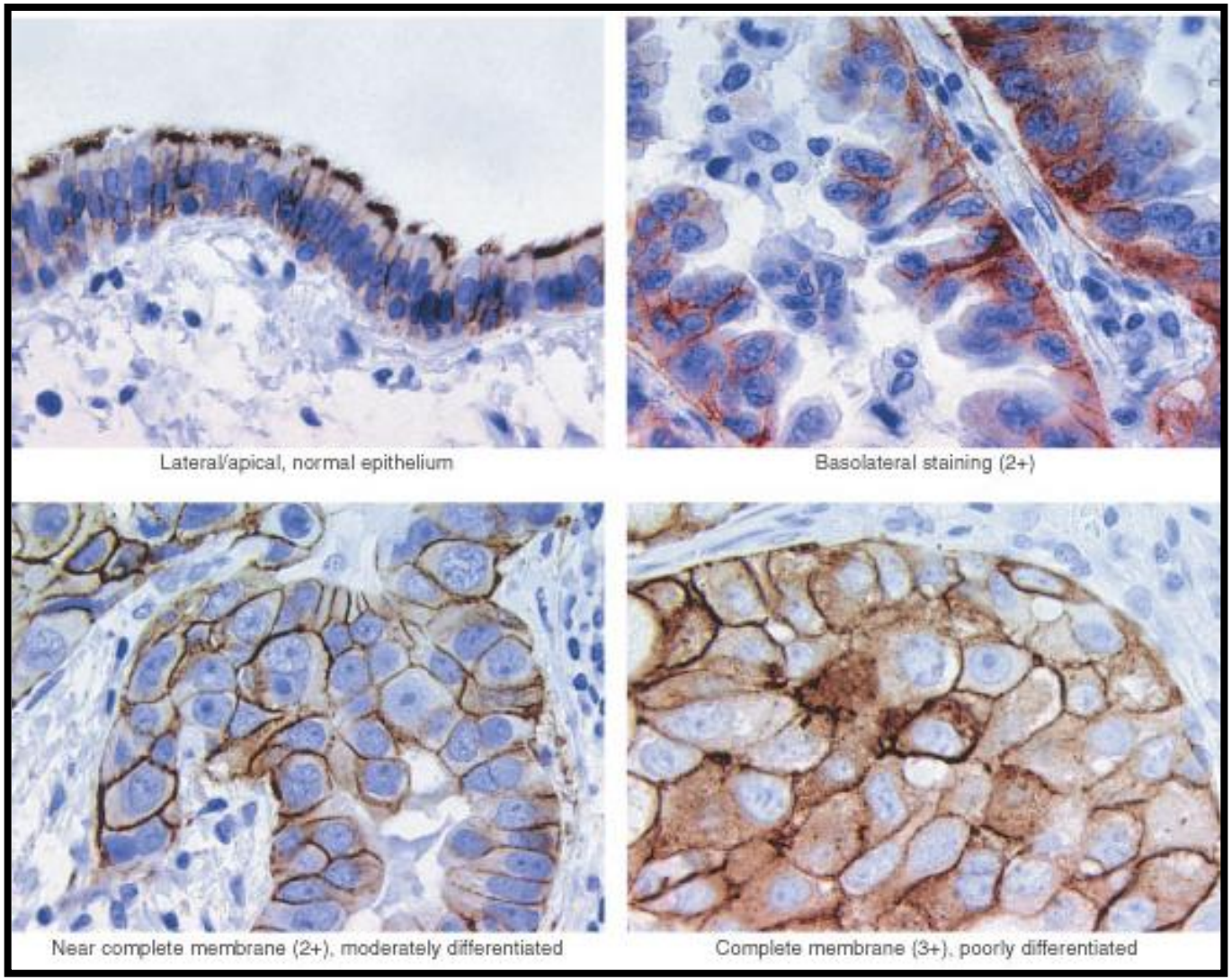


+2



+3

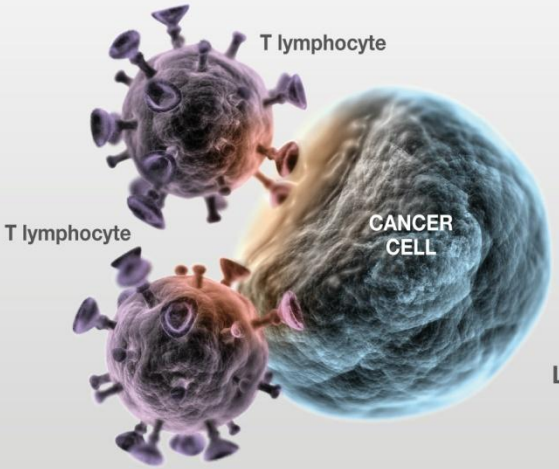
HercepTest (lung adenocarcinoma)



This is how the new immunotherapy for cancer works

1. Normal work of the immune system

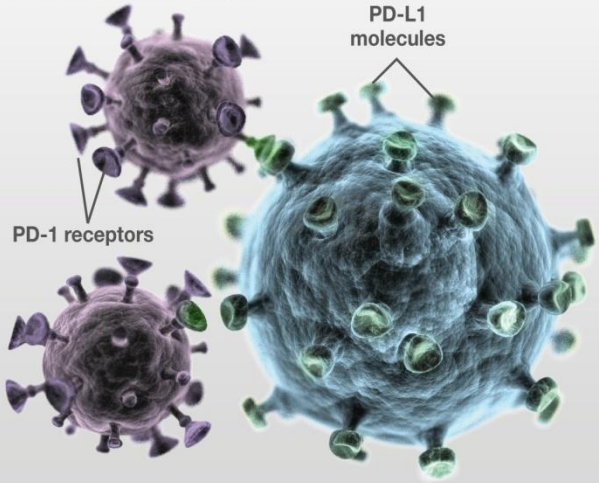
T lymphocytes are the cells of the immune system that identify tumour cells and destroy them.

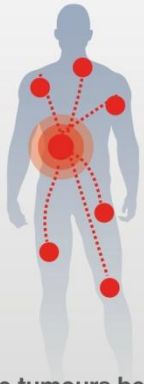


Lymphocytes prevent the tumour from developing.

2. Camouflage of tumour cells

Some tumour cells arm themselves with a shield of molecules called PD-L1. Lymphocytes possess PD-1 receptors which, by bonding to these traps, destroy their capacity to attack.

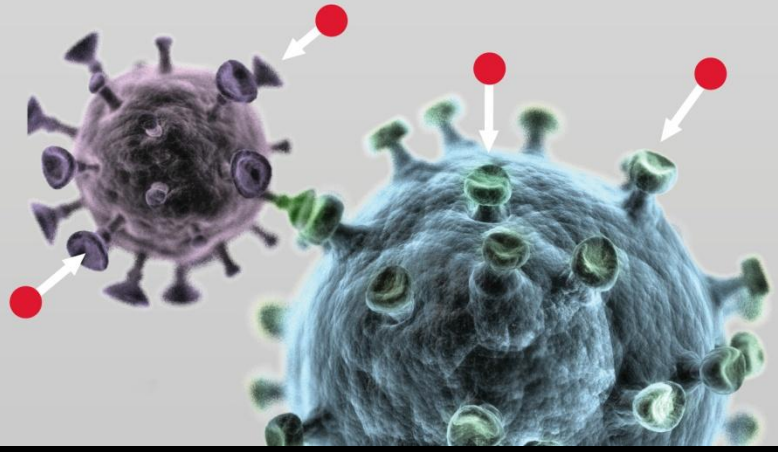




The tumours become invisible to our defences and they spread.

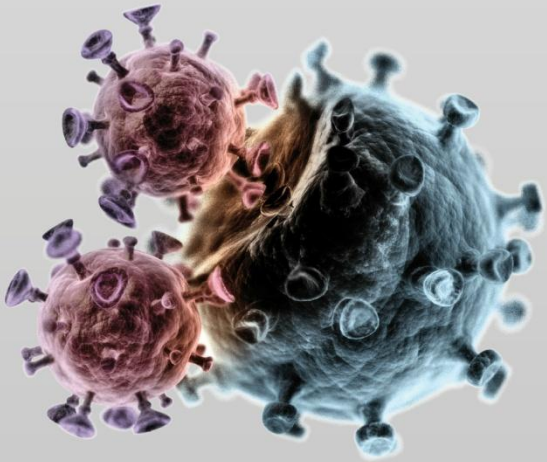
3. Action of the new inhibitor drugs

The new drugs based on antibodies block PD-1 from the cells of the immune system and PD-L1 from tumour cells to prevent their fatal action.



4. Result of immunotherapy

Lymphocytes, once freed from their blindness by the drug, regain their defence potential. They recognise cancer and reduce it.



This treatment, although still in its experimental stage, has had preliminary results on lung, kidney and skin cancers.

Table 2 *Overview of adoptive cell transfer for cancer immunotherapy*

Method	TAAs	Cancer types	References
TILs, *ex vivo* expanded	Unselected, various different epitopes (neoepitopes, tissue-differentiation antigens, cancer–testis antigens, viral antigens)	Melanoma, leukaemia, cervical cancer	[51, 206–211]
Tumour-antigen-specific expanded TIL	Neoepitopes (ERBB2IP), cancer–testis antigen (NY-ESO-1), tissue-differentiation antigens (WT-1)	Cholangiocarcinoma, melanoma, leukaemia	[53, 212, 213]
Engineered TCR with autologous T cells	Tissue-differentiation antigens (MART1), cancer–testis antigen (NY-ESO-1)	Melanoma, synovial cell sarcomas	[55, 56, 214, 215]
CAR T cells	CD19, GD2, mesothelin	ALL, CLL, B-cell lymphoma, malignant pleural mesothelioma, pancreatic cancer	[57, 59, 60, 216–221]

TAAs, tumour-associated antigens, TIL, tumour-infiltrating lymphocyte, TCR, T-cell receptor, CAR, chimeric antigen receptor, ALL, acute lymphoblastic leukaemia, CLL, chronic lymphocytic leukaemia.

Table 3 *Overview of relevant clinical trials of inhibitors of CTLA-4 and PD-1/PD-L1*

Agent	Target	Cancer types	References
Ipilimumab (Yervoy, BMS)	CTLA-4	Melanoma	[156, 157]
Pembrolizumab (Keytruda, MSD)	PD-1	Melanoma, NSCLC, mismatch repair-deficient cancers (CRC, etc), etc	[172–174, 222]
Nivolumab (Opdivo, BMS)	PD-1	Melanoma, NSCLC, RCC, Hodgkin's lymphoma, HCC, etc	[162, 163, 165, 167, 169], J Clin Oncol 33, 2015, suppl; abstr LBA101)
Pidilizumab (CureTech)	PD-1	NHL	[223, 224]
Atezolizumab (MPDL3280A, Roche)	PD-L1	Bladder cancer, NSCLC, melanoma, RCC, etc.	[175, 176]
Nivolumab and ipilimumab	PD-1 and CTLA-4	Melanoma	[171, 225]

PD, programmed death; PD-L1, programmed death ligand; CTLA-4, cytotoxic T-lymphocyte antigen 4; CRC, colorectal cancer; NSCLC, nonsmall-cell lung cancer; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; NHL, non-Hodgkin lymphoma.

Muenst et al., 2016

http://www.cancerresearch.org/news-publications/our-blog/december-2015/immunotherapy-approvals-in-2015