Overview sui meccanismi biologici legati all'infiammazione nelle patologie tumorali e rilevanza clinica

(i.e. Infiammazione e cancro)

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Aviano, 20 febbraio 2020

Infiammazione

It is a protective response of the organism to stimulation by **invading pathogens** or **endogenous signals** such as damaged cells, thus resulting in the elimination of the initial cause of injury, the clearance of necrotic cells and tissue/wound repair

Cancro

The wound that never heals

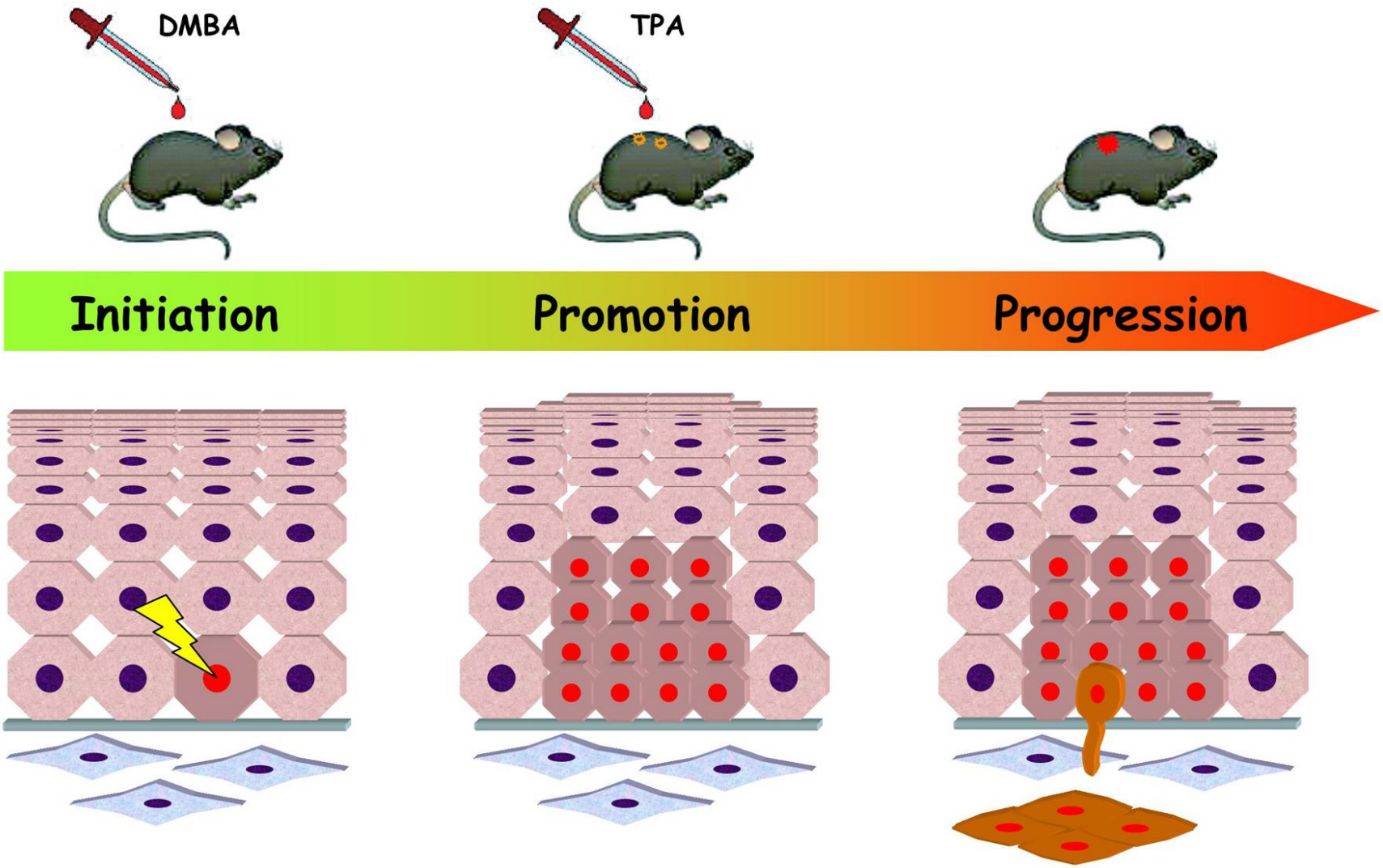
Table 1 | Acute inflammation versus systemic chronic inflammation

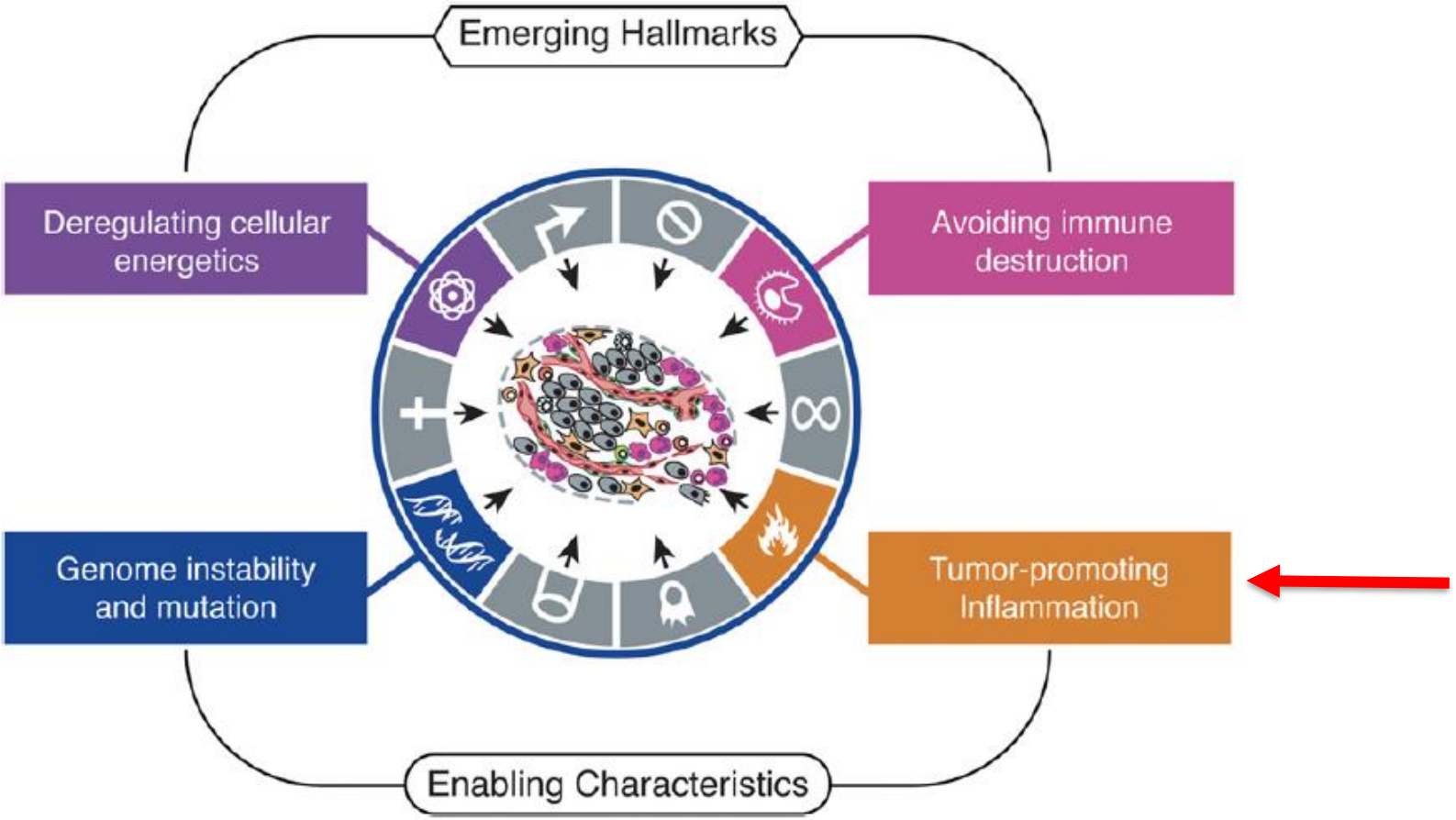
	Acute Inflammation	Systemic chronic Inflammation
Trigger	PAMPs (infection), DAMPs (cellular stress, trauma)	DAMPs ('exposome', metabolic dysfunction, tissue damage)
Duration	Short-term	Persistent, non-resolving
Magnitude	High-grade	Low-grade
Outcome(s)	Healing, trigger removal, tissue repair	Collateral damage
Age-related	No	Yes
Biomarkers	IL-6, TNF-α, IL-1β, CRP	Silent—no canonical standard biomarkers

DAMP, damage-associated molecular pattern; PAMP, pathogen-associated molecular pattern.

D Furman et al., 2019

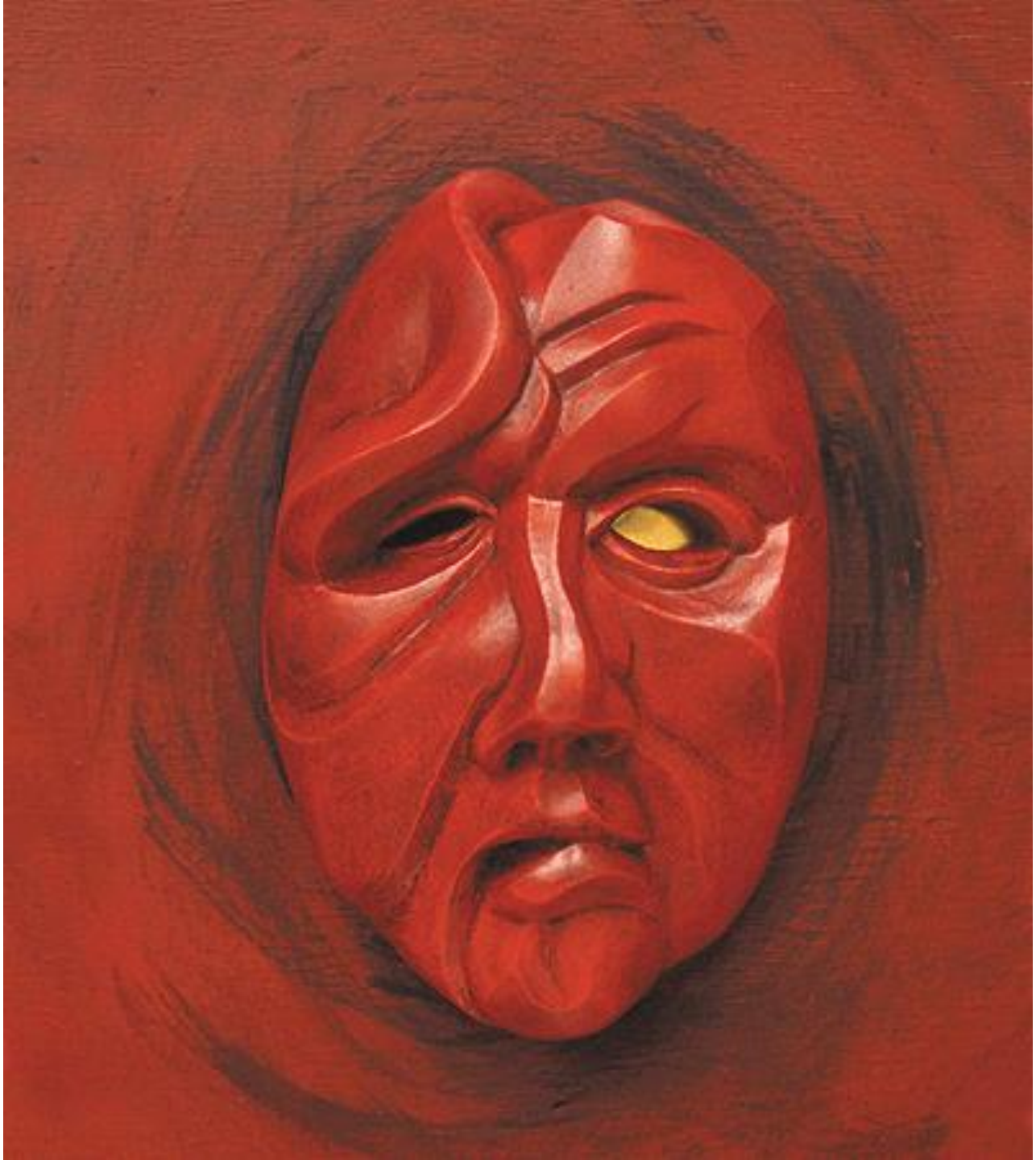
- 1863 - Rudolf Virchow proposed that chronic irritation and inflammation cause cancer
- 1915 - Virchow's student, Katsusaburō Yamagiwa, demonstrated experimentally that chronic inflammation can result in cancer
- 1990s - the importance of inflammation in the onset of cancer and the mechanisms through which it exerts its pro-tumorigenic effects are generally appreciated
- 2004 - two seminal studies demonstrated the critical role of nuclear factor-κB (NF-κB) in inflammation-driven colitis-associated cancer (**CAC**) and hepatocellular carcinoma (**HCC**)


DMBA
TPA
Initiation
Promotion
Progression



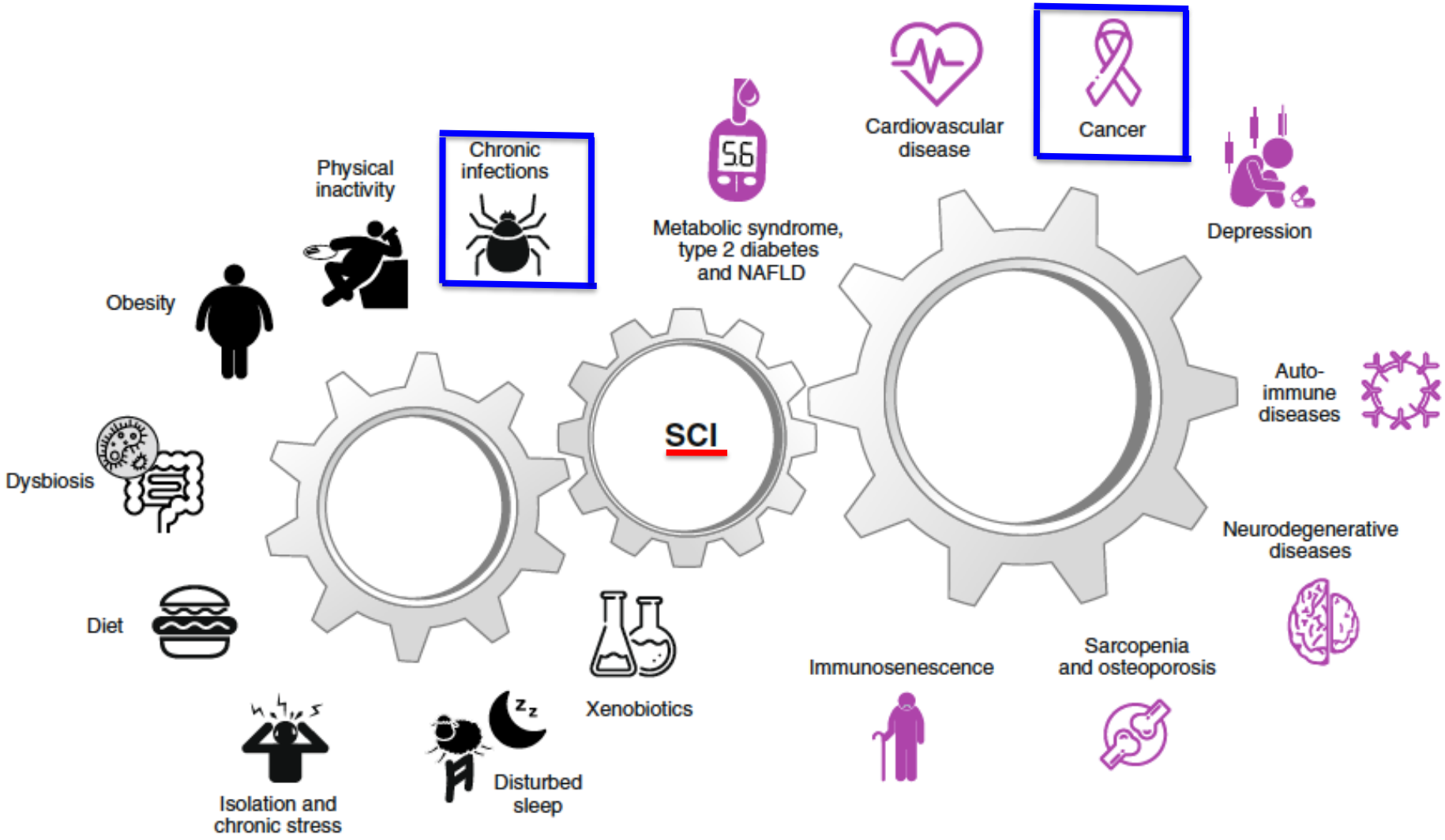
Hanahan D and Weiberg RA 2011

Infiammazione cronica pro-tumorale:
l’altra faccia del sistema immune



CAUSE

CONSEGUENZE



SCI = Systemic chronic inflammation

D Furman et al., 2019

Neoplasie e % mortalità

- Inflammation can also be provoked after tumor initiation owing to the necrotic death of cancer cells subject to an insufficient blood supply or microbial invasion into the tumor bed caused by barrier deterioration

- Chemotherapy and radiotherapy induce necrotic cell death and can further enhance tumor-associated inflammation and cause therapy resistance or induction of antitumor immunity

- Thus, inflammation is a relevant contributing factor in most solid and haematopoietic malignancies.

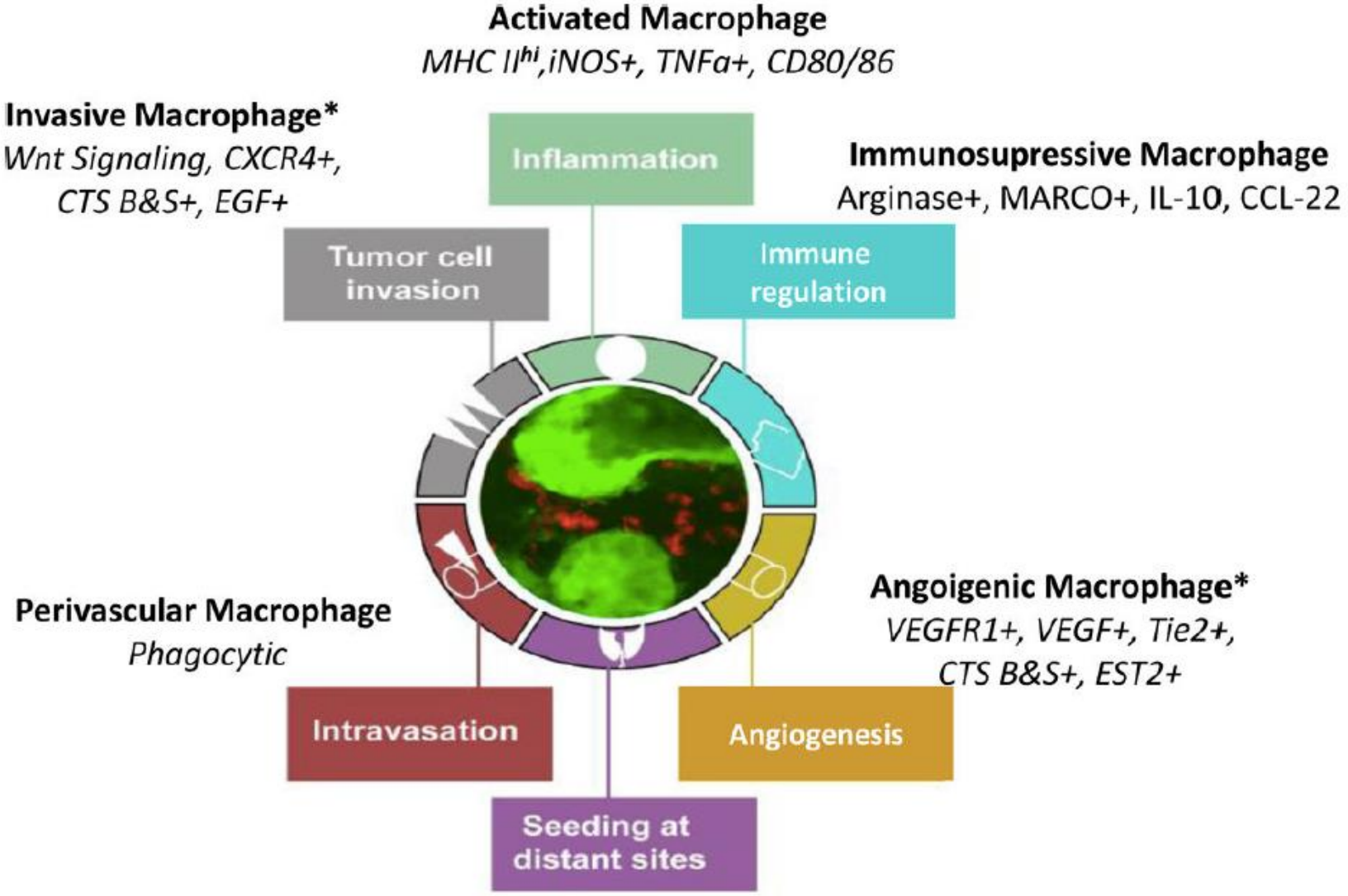
Cellule del microambiente infiammatorio

- tumor-associated macrophages (**TAMs**)
- dendritic cells (DCs)
- myeloid-derived suppressor cells (MDSCs)
- tumor-associated neutrophils (TANs)
- mast cells
- Treg
- natural killer (NK) cells
- natural killer T (NKT) cells
- T cells
- B cells
- cancer-associated fibroblasts (CAFs)
- endothelial cells (of blood and lymphatic vessels)
- pericytes/myofibroblasts

Molecole bioattive del microambiente infiammatorio

- growth factors that sustain proliferative signaling
- survival factors that limit cell death
- proangiogenic factors
- extracellular matrix (ECM)-modifying enzymes that facilitate angiogenesis, invasion, and metastasis
- inductive signals that lead to activation of EMT
- ECM and degradation products

I macrofagi (TAM) costituiscono fino al 40% della massa tumorale e sono caratterizzati da ampia diversità e plasticità e sono coinvolti nelle fasi iniziali, nella progressione e nelle metastasi



B Qian and JW Pollard, 2010

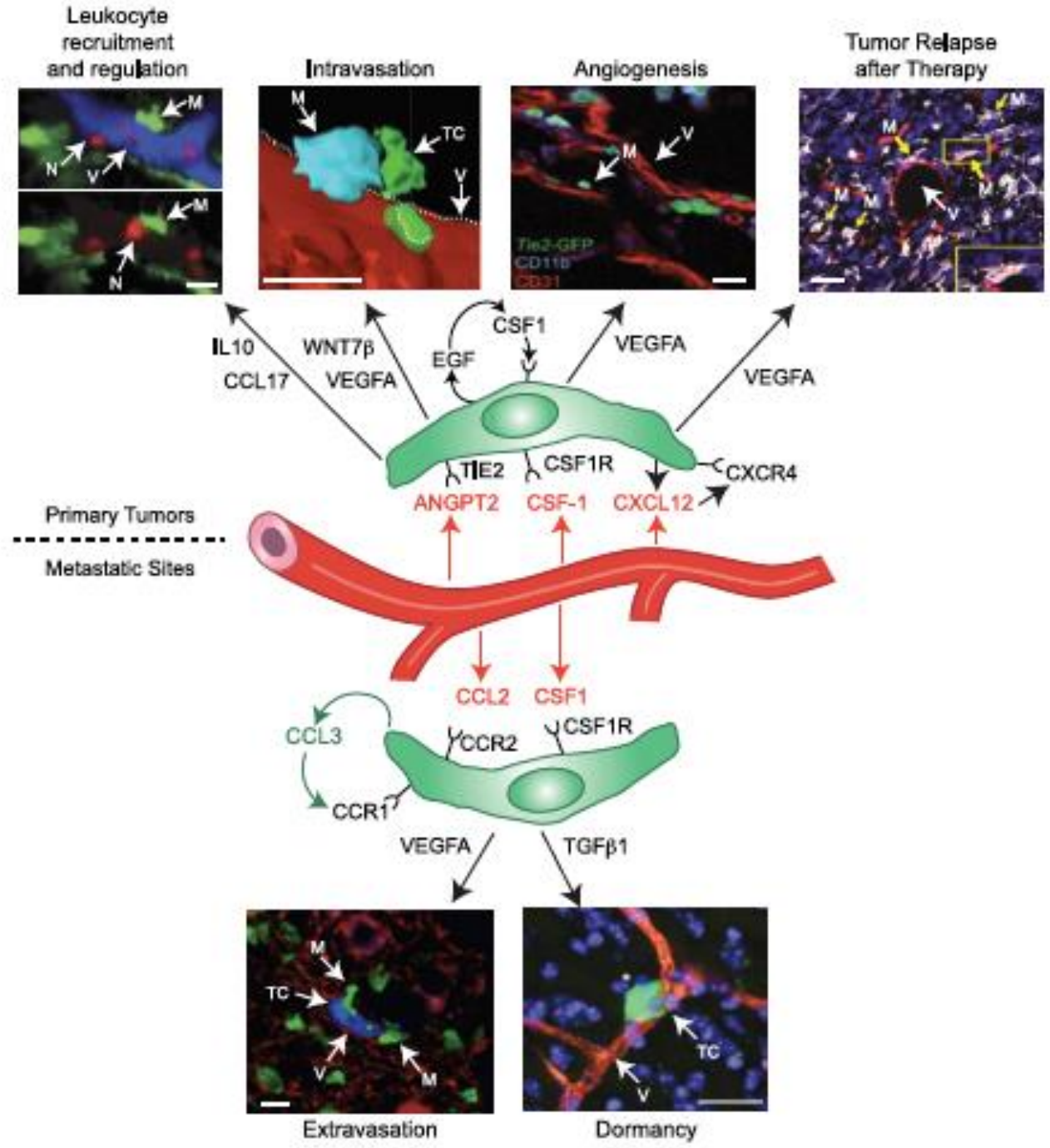


Figure 1. The Roles of Perivascular Macrophages in Tumor Progression

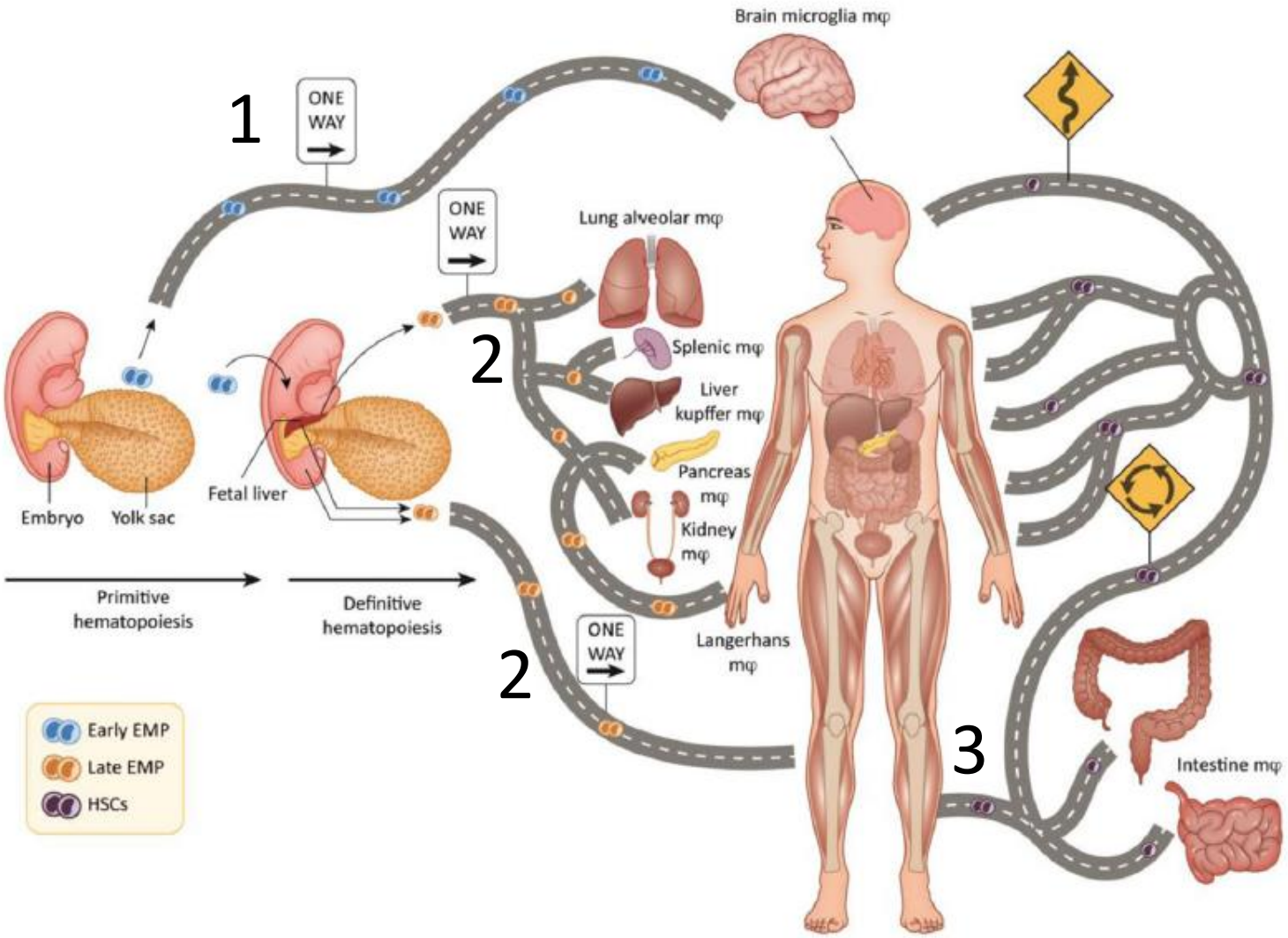
Clair E Lewis et al., 2016

Trends Box

- Macrophages in tissues arise from distinct sources
  - Tissue resident macrophages (TRM) derive from yolk sac and fetal liver progenitors
  - Bone-marrow derived macrophages (BDM) arise from HSC
- Tissue macrophages have distinct transcriptional profiles between tissues
- Tumor associated macrophages (TAMs) populate tumors through local proliferation of TRM or recruitment from BDM
- Involvement of TAMs is tumor tissue specific; where TRM or BDM differentially promote tumorigenesis depending on the tissue type
- Targeting TAMs for anti-cancer therapy has shown signs of pre-clinical and clinical success using either blunt targeting strategies (CSF-1R inhibitors) or more recently developed novel strategies such as PI3Kγ and class IIa HDAC inhibitors

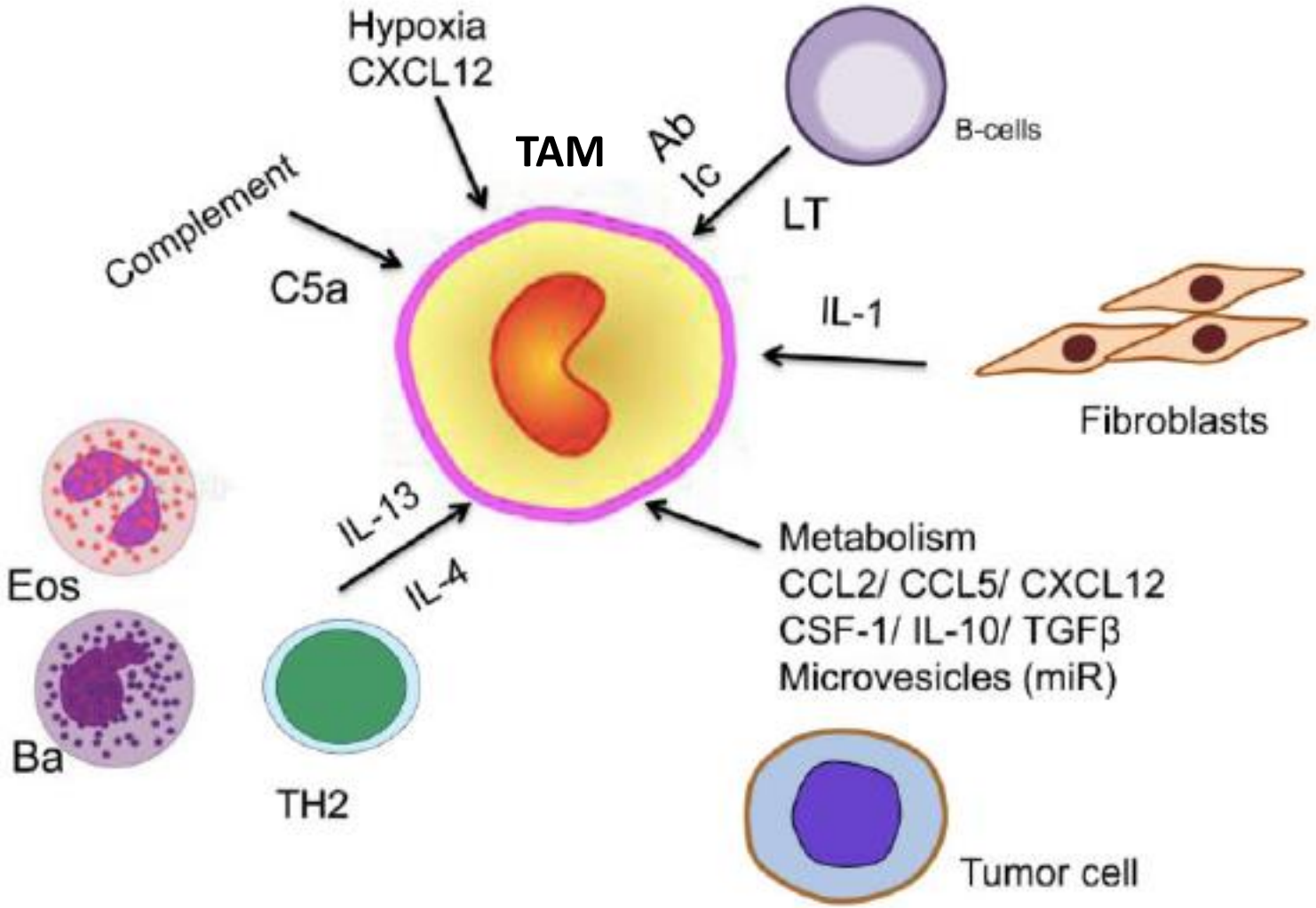
Jennifer L Guerriero 2018

Origine dei macrofagi tissutali



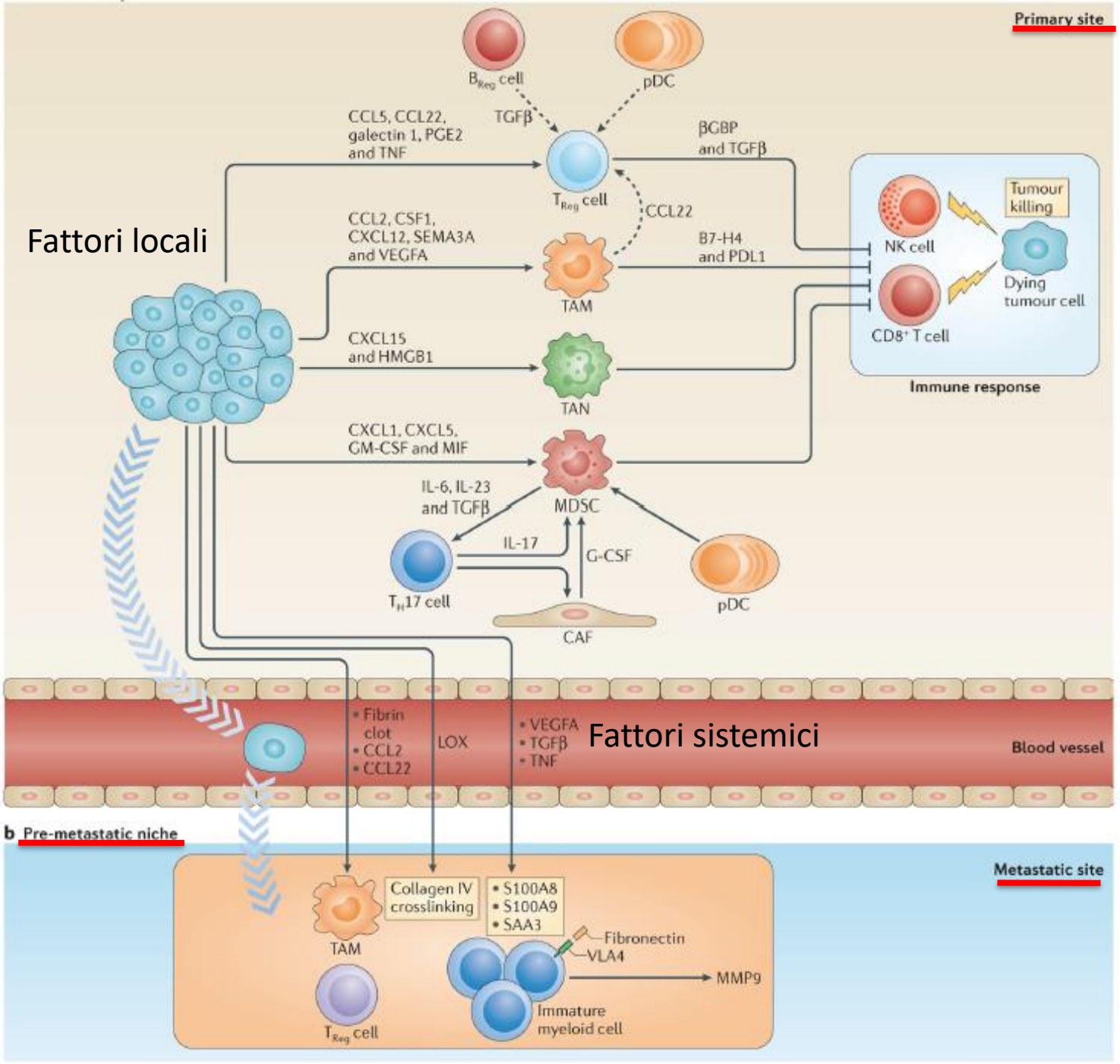
Jennifer L Guerriero 2018

Functional Polarization

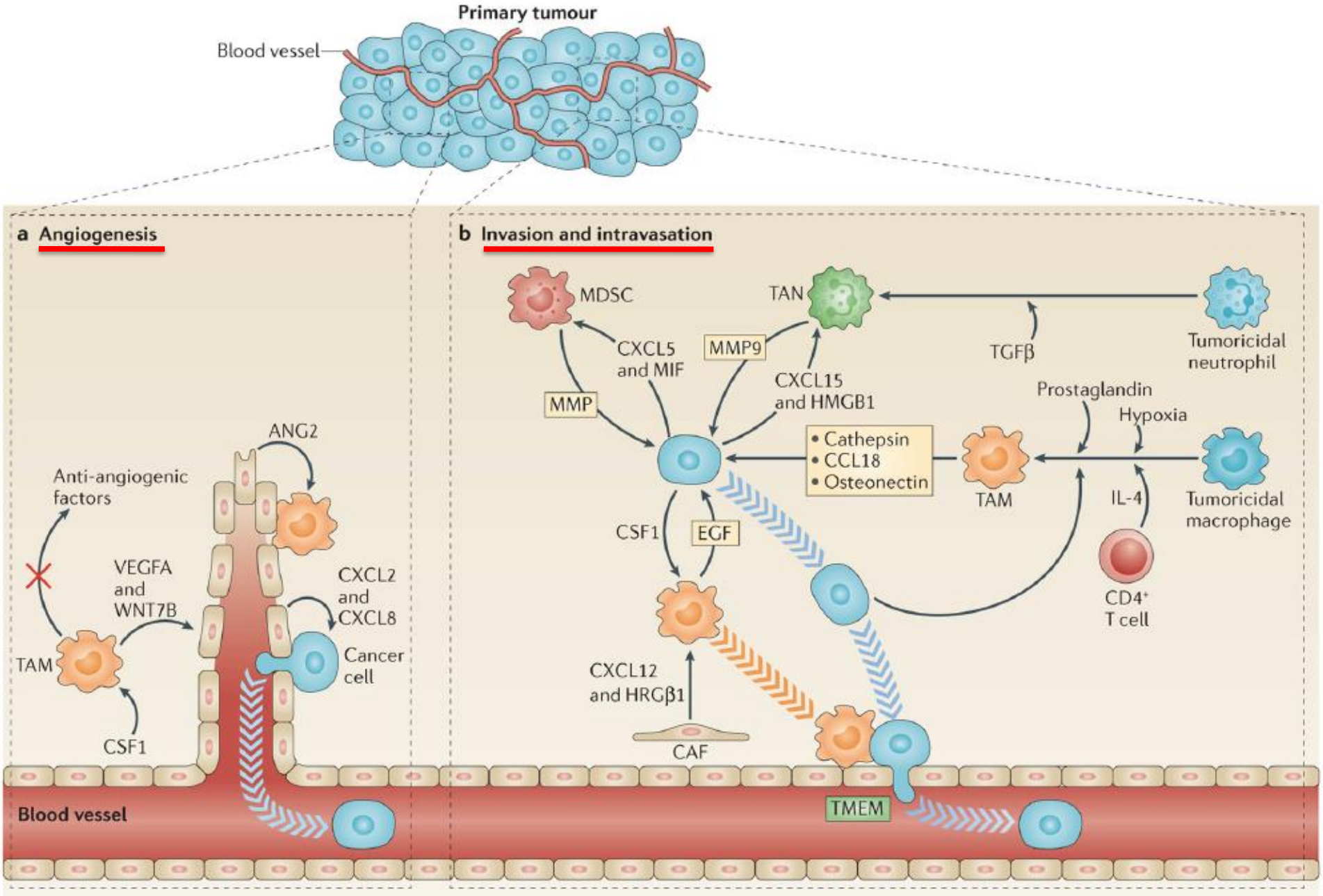


Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2016.217

A Mantovani et al., 2017

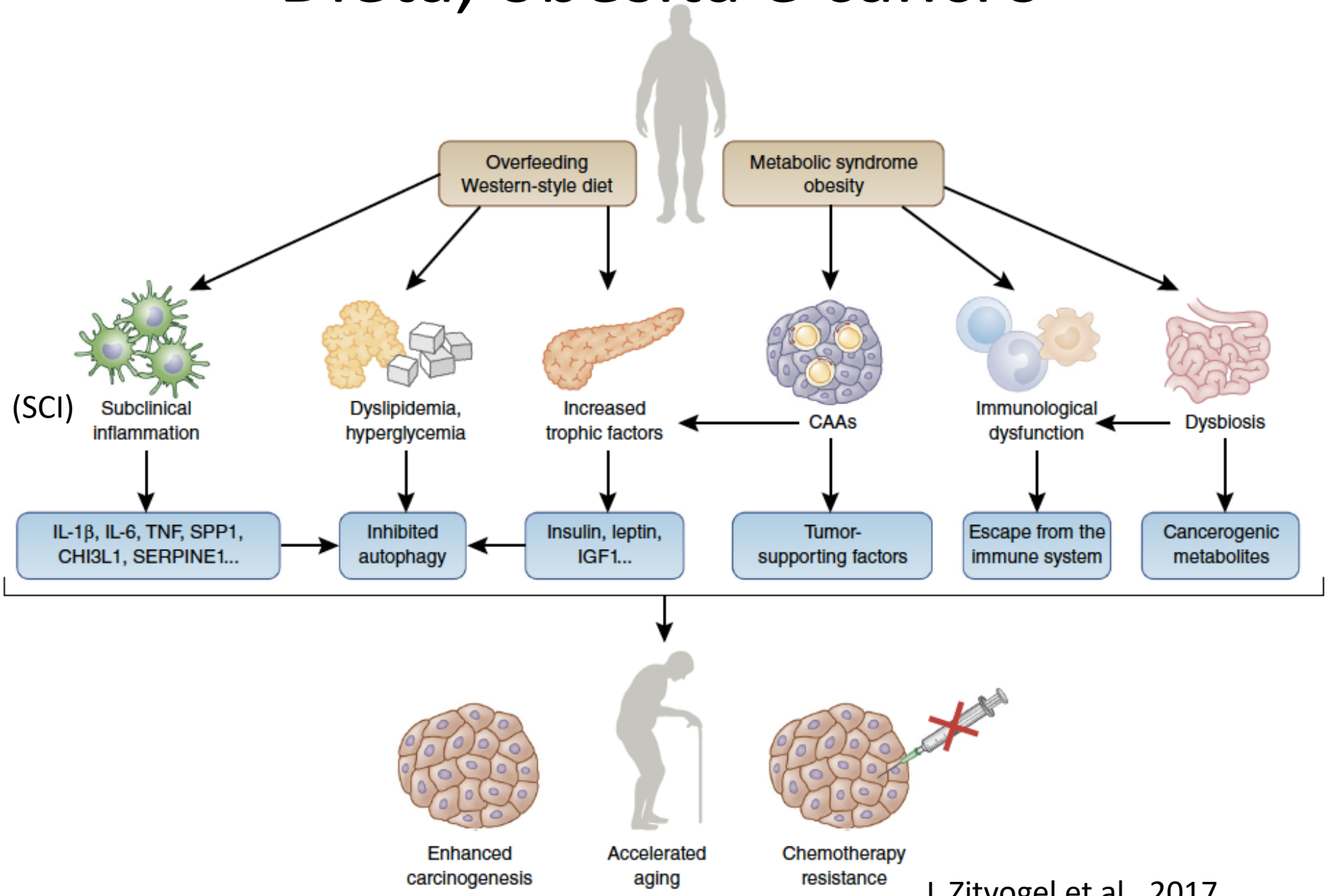


T Itamura et al., 2015



T Itamura et al., 2015

Dieta, obesità e cancro



L Zitvogel et al., 2017

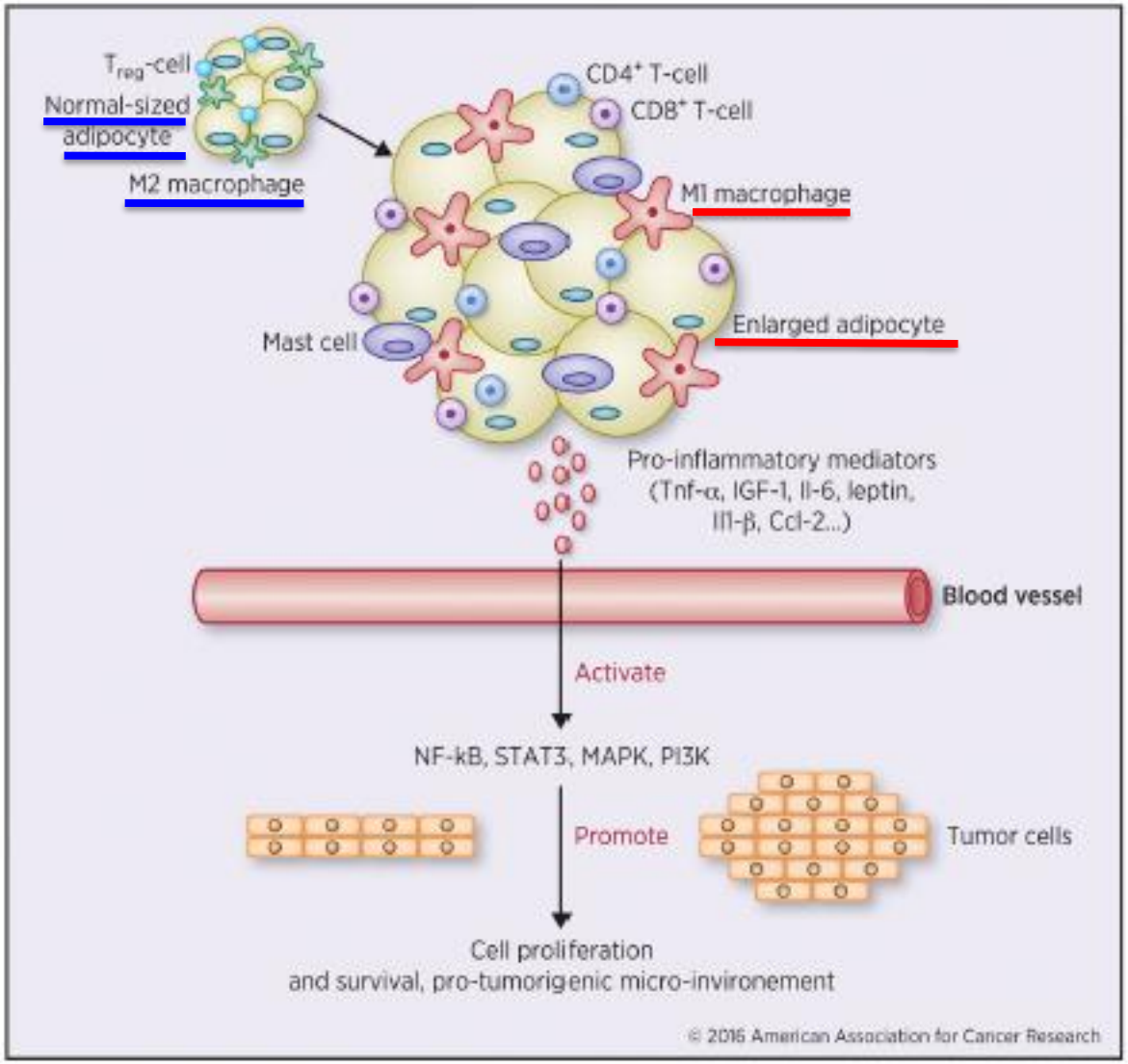


Figure 1. Mechanisms linking obesity, inflammation and cancer

Jelena Todoric et al., 2016

Metainflammation = metabolism-related-SCI (systemic chronic inflammation) following major changes in adipose tissue and metabolic dysfunction

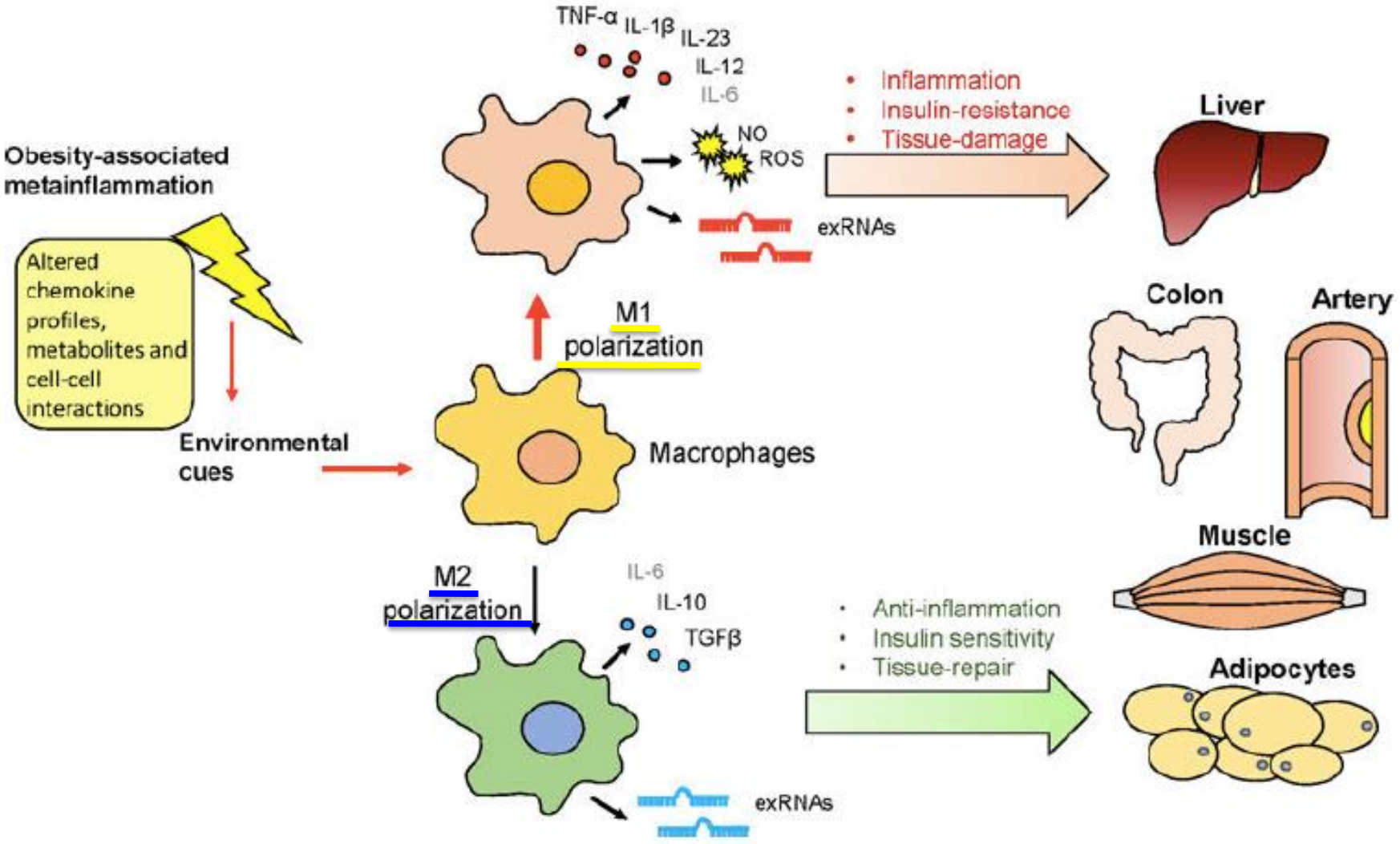
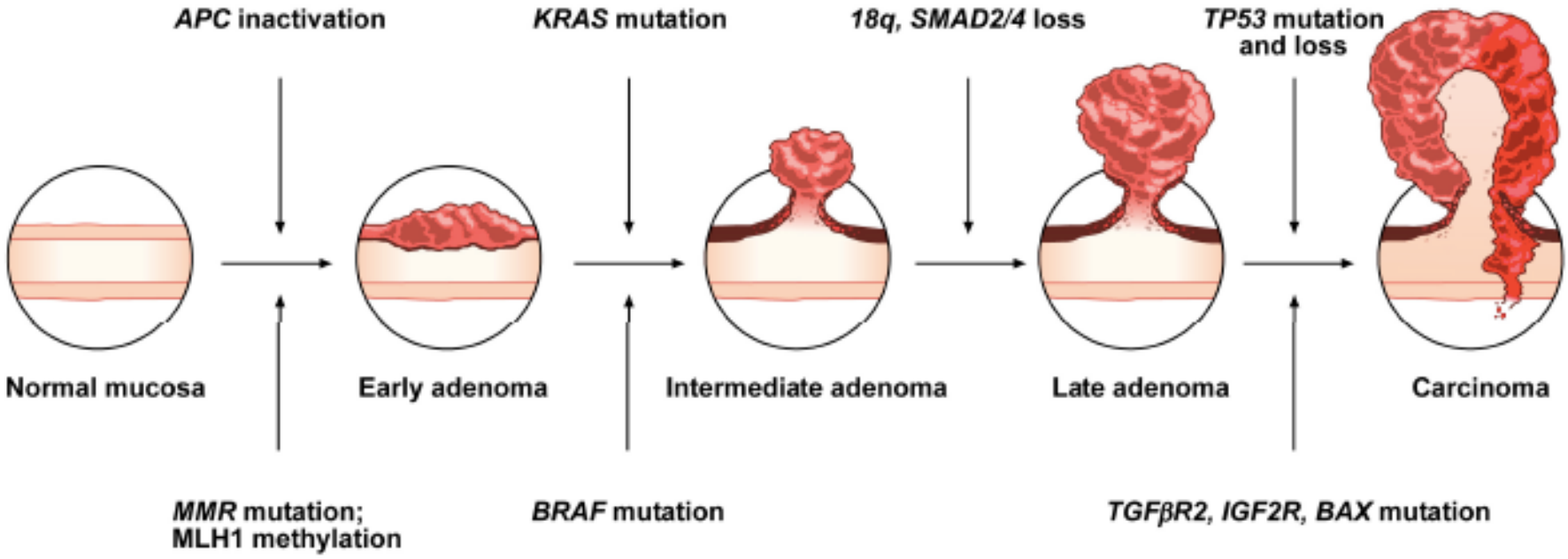


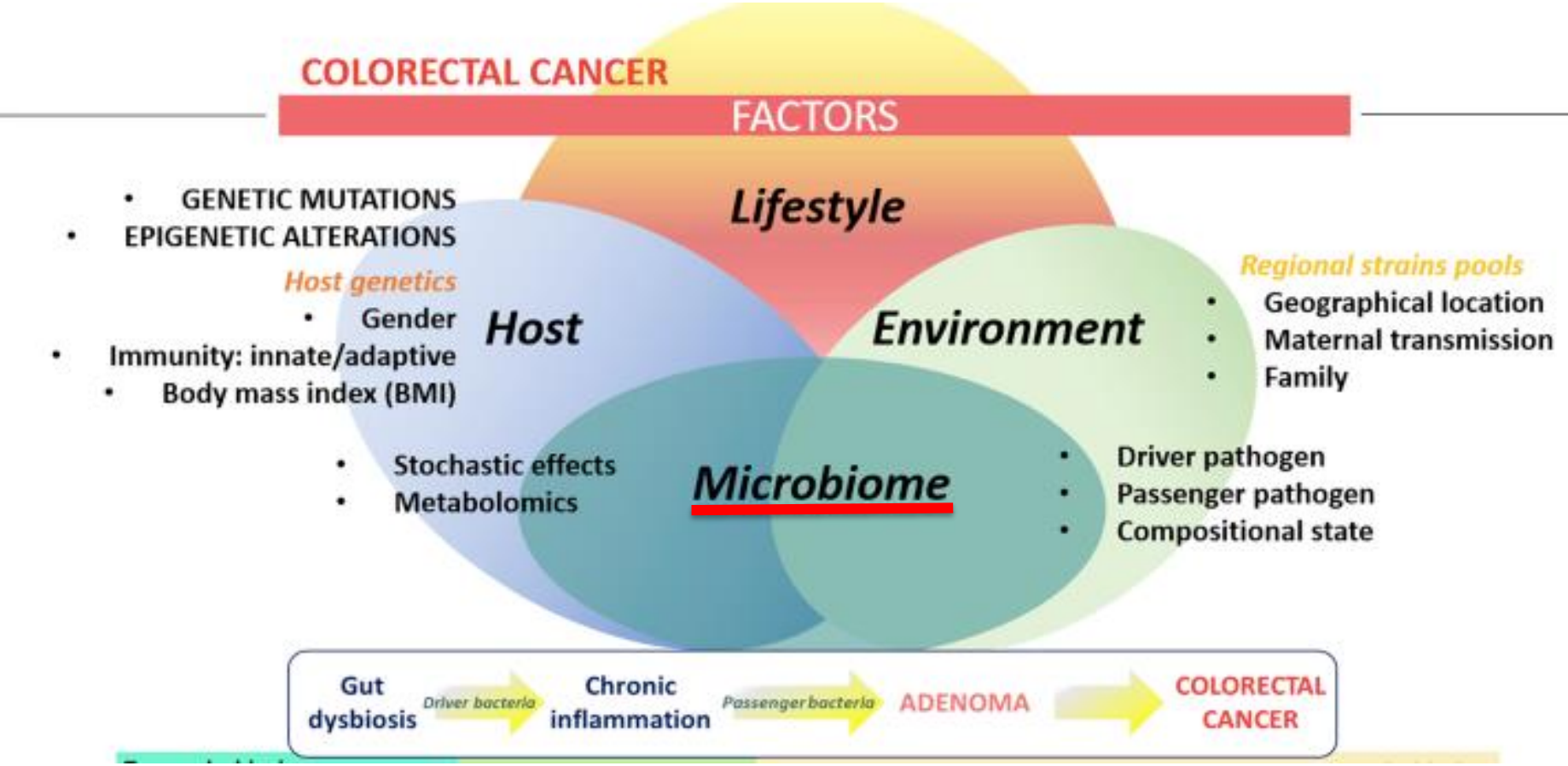
Figure 2. Macrophage polarization modulated tissue/organ functions during obesity-induced metainflammation

C Li et al., 2018

Colon multistep carcinogenesis and progressive accumulation of genetic alterations



COLON CARCINOGENESIS



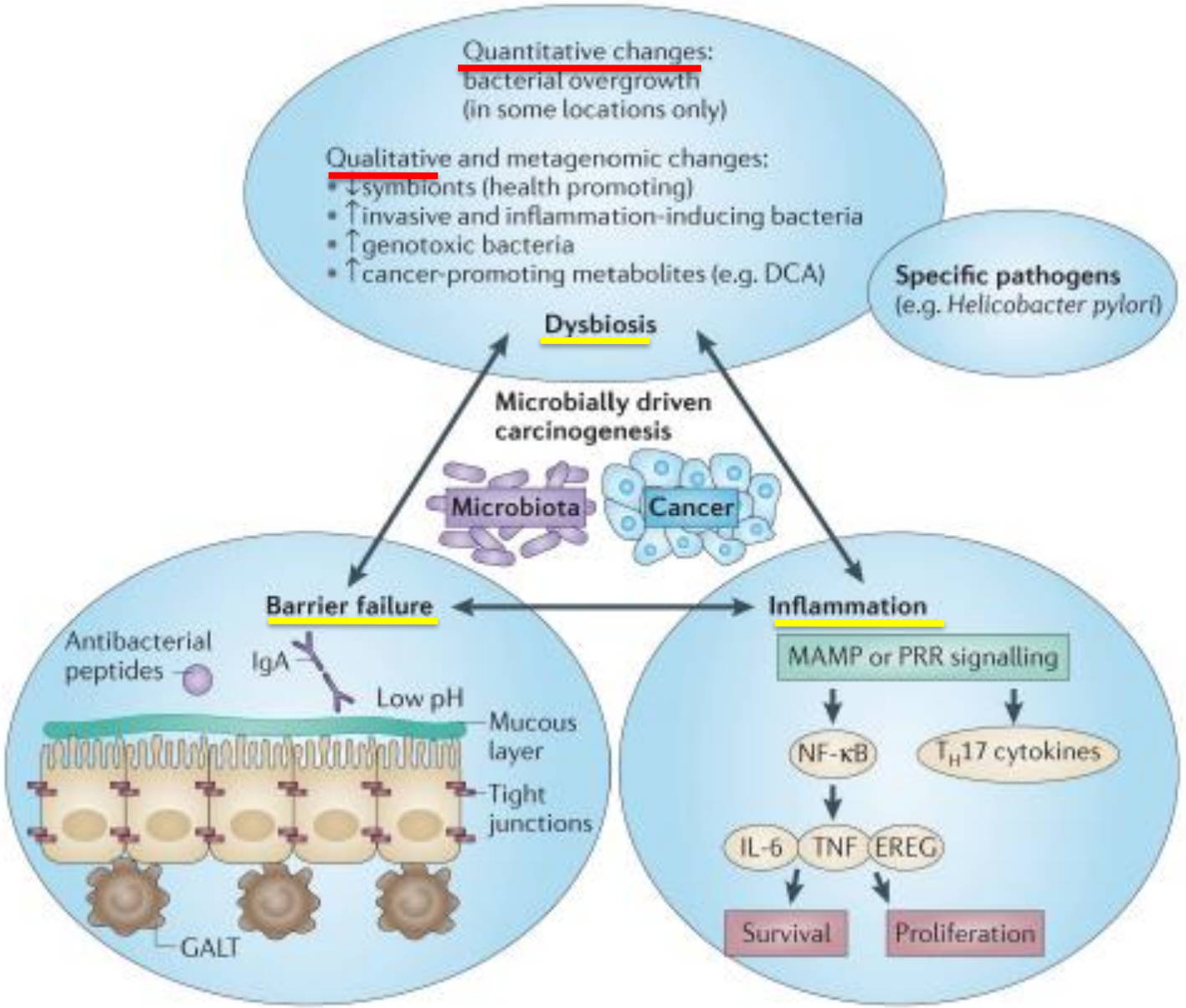
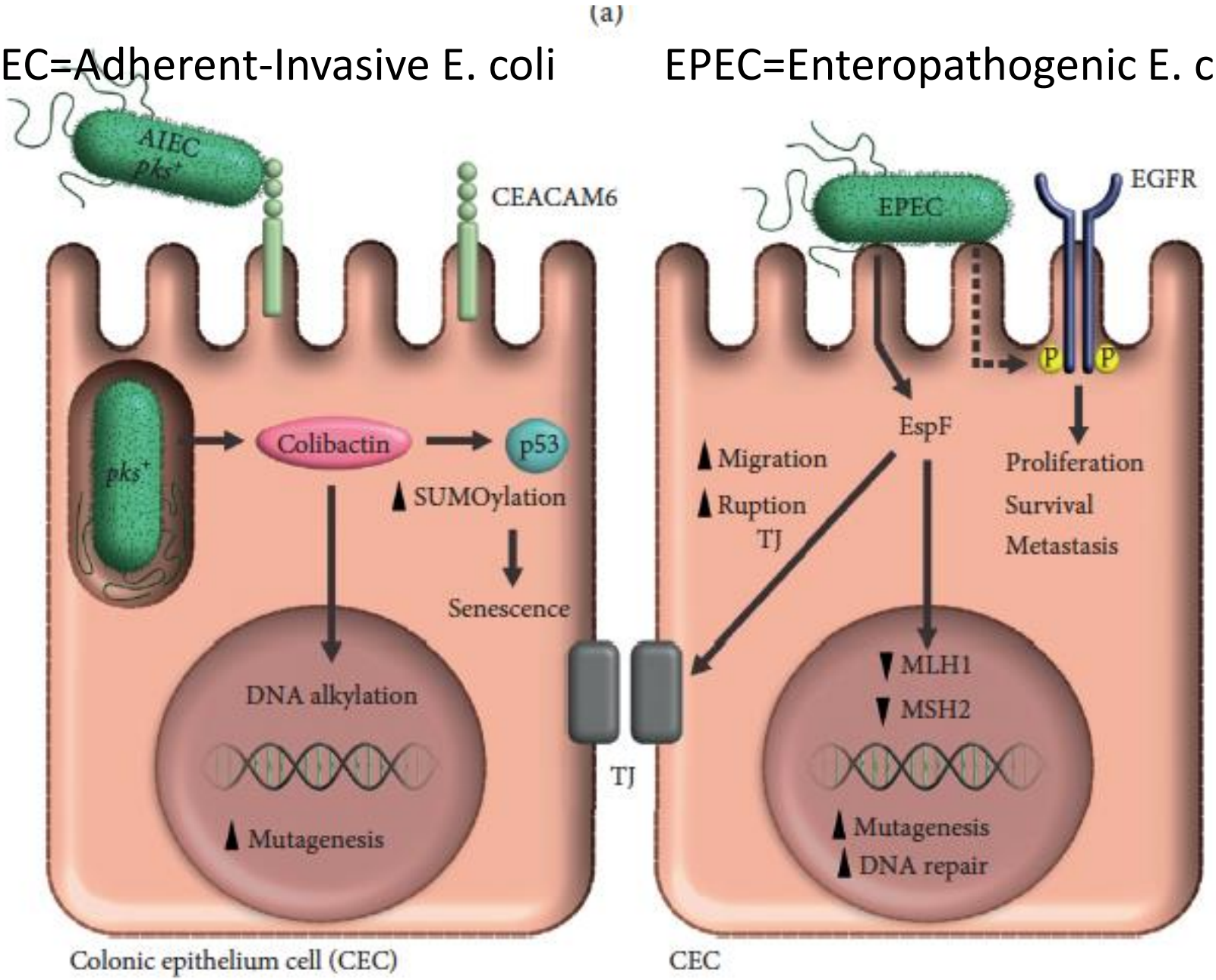


Figure 1. Mechanisms controlling host–microbiota interactions and associated failures implicated in cancer development

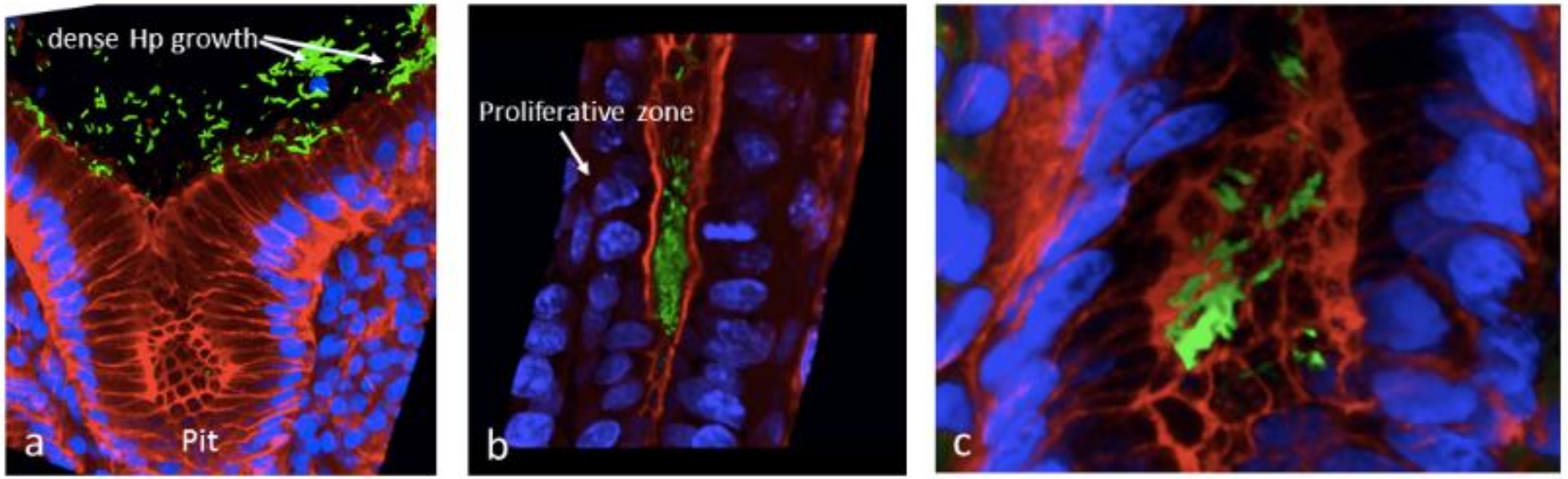
RA Schwabe, 2013

AIEC=Adherent-Invasive E. coli EPEC=Enteropathogenic E. coli



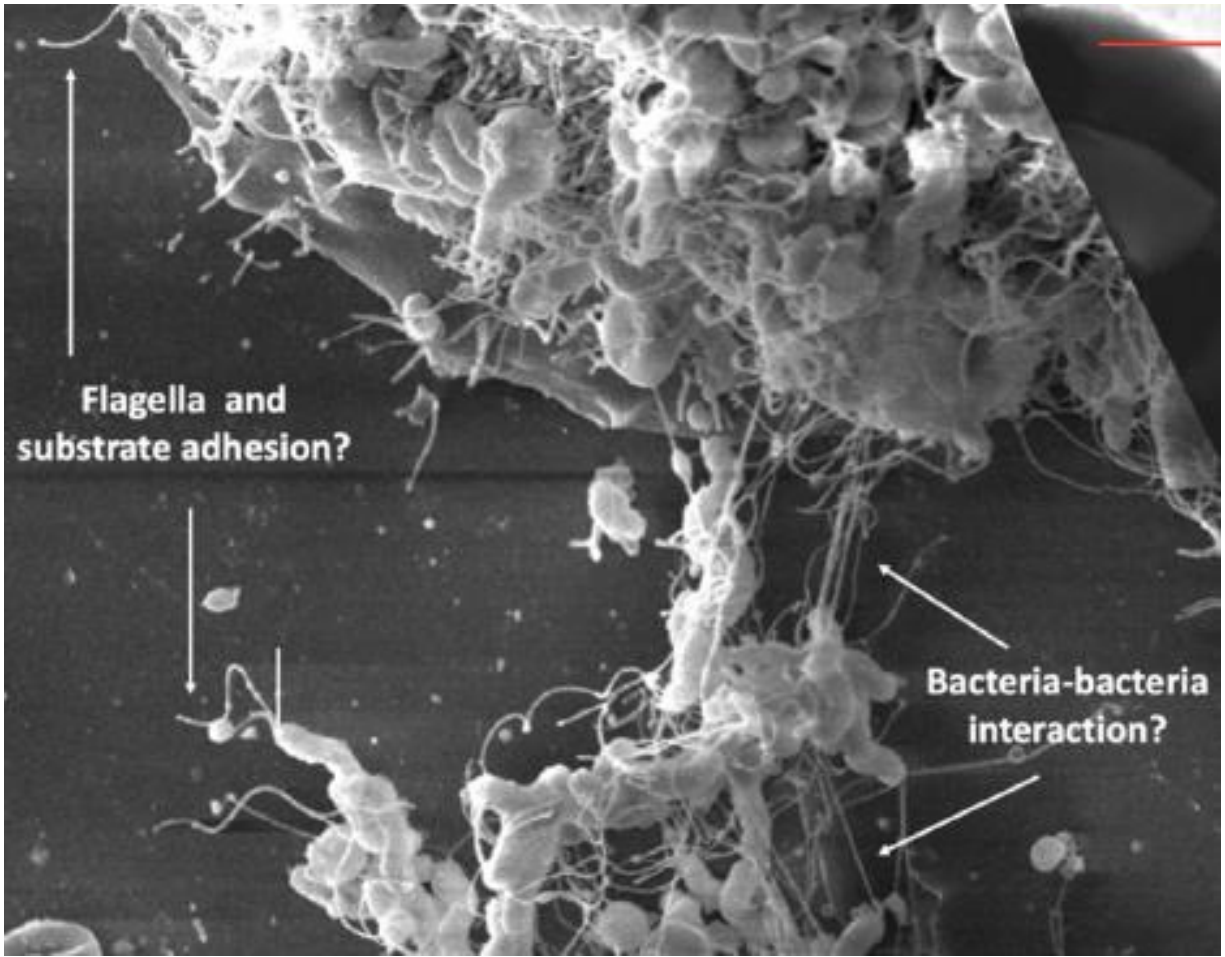
MA Hernandez-Luna et al., 2019

Aggregati (= biofilms) di H. pilori (verde) nelle ghiandole dello stomaco actina (rosso) nuclei (blu)



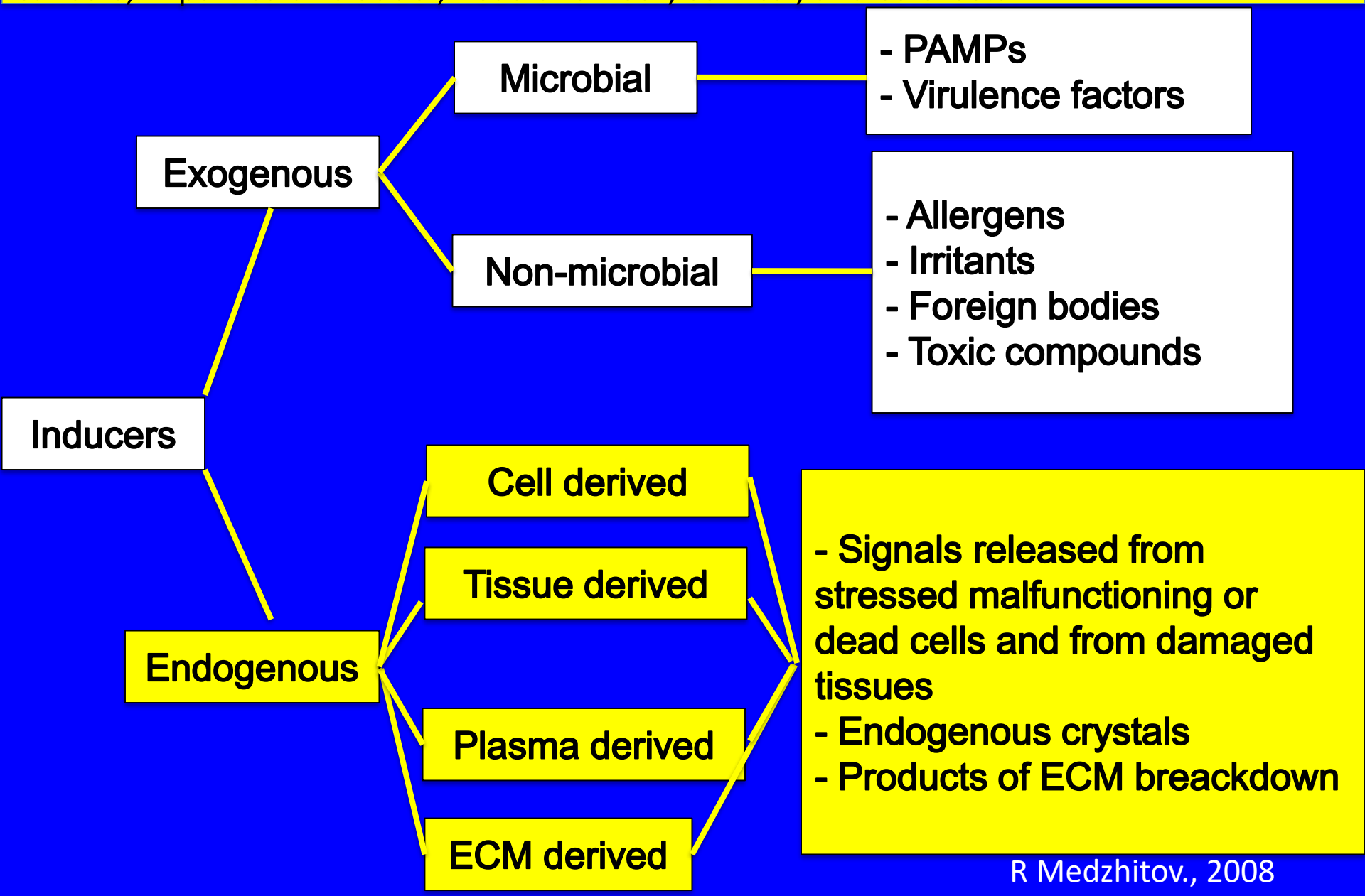
C Rizzato et al., 2019

Biofilms = a temporary multicellular lifestyle through prolific intercellular interactions, both social and physical, immersing in a complex and specialized matrix formed by both the bacteria and the host

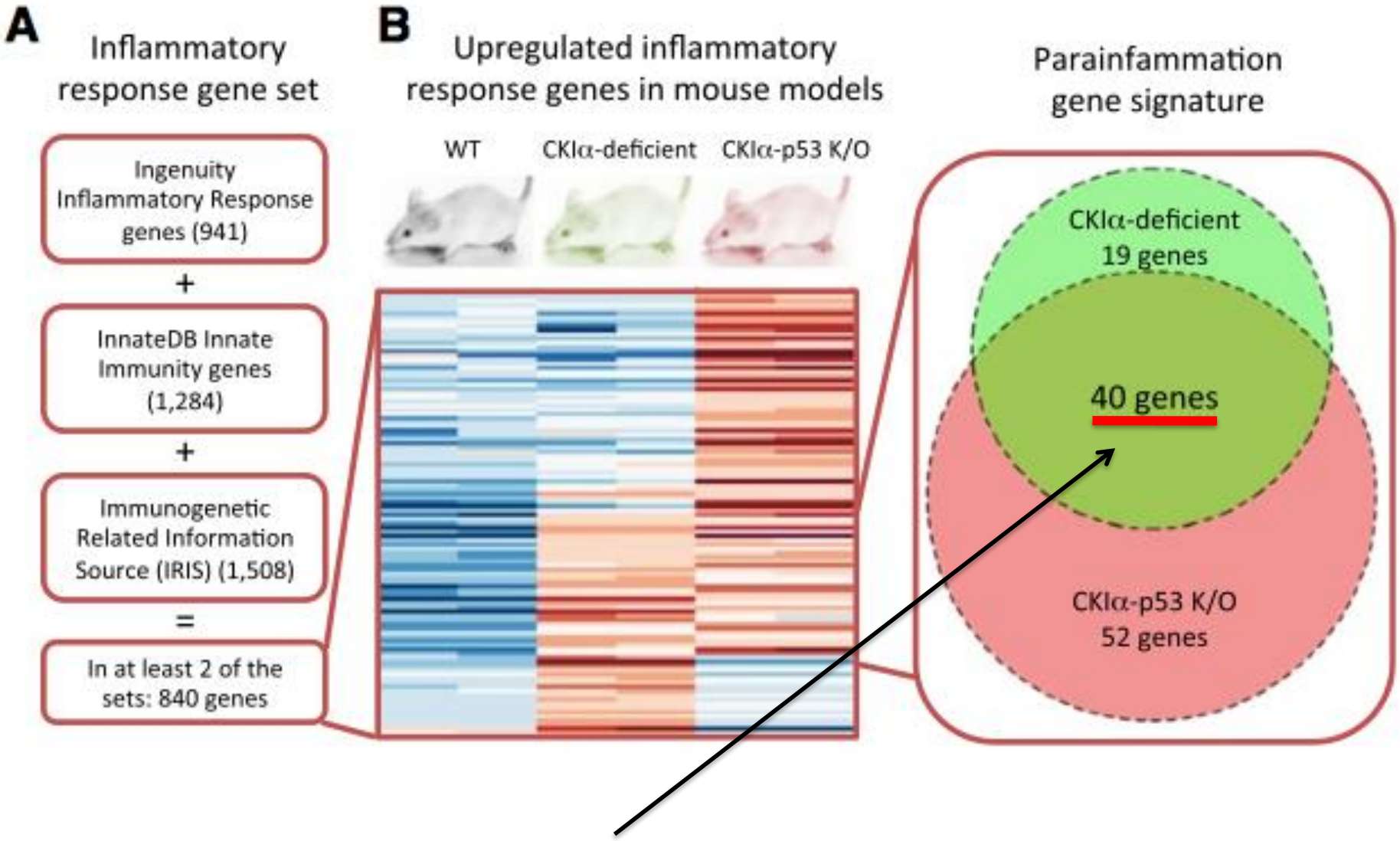


C Rizzato et al., 2019

Parainflammation = epithelial cell-autonomous chronic inflammatory response detected first in mouse models and also shown to be a common feature of some human cancers, in particular bladder, head and neck, cervical, and colorectal

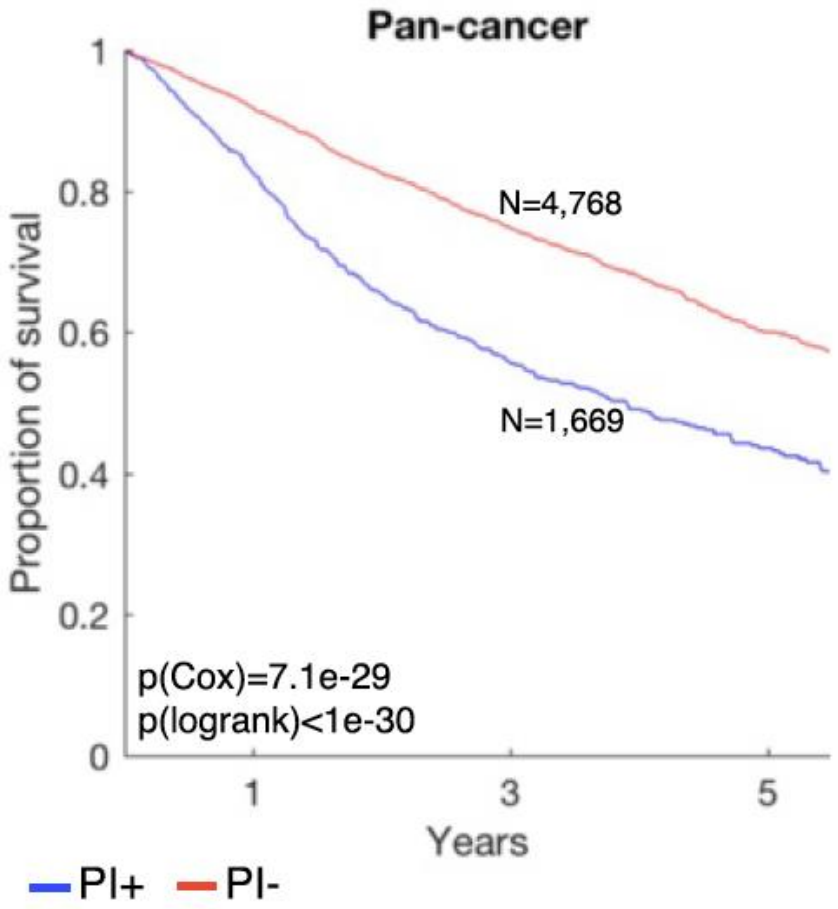


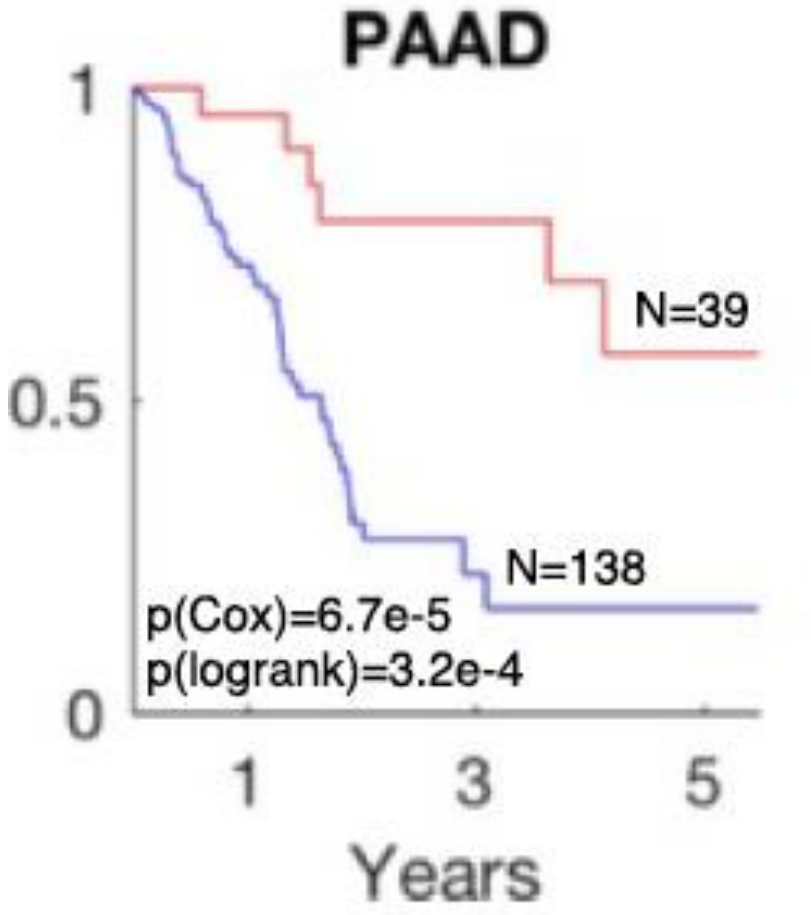
R Medzhitov., 2008



Simili a LPS response genes

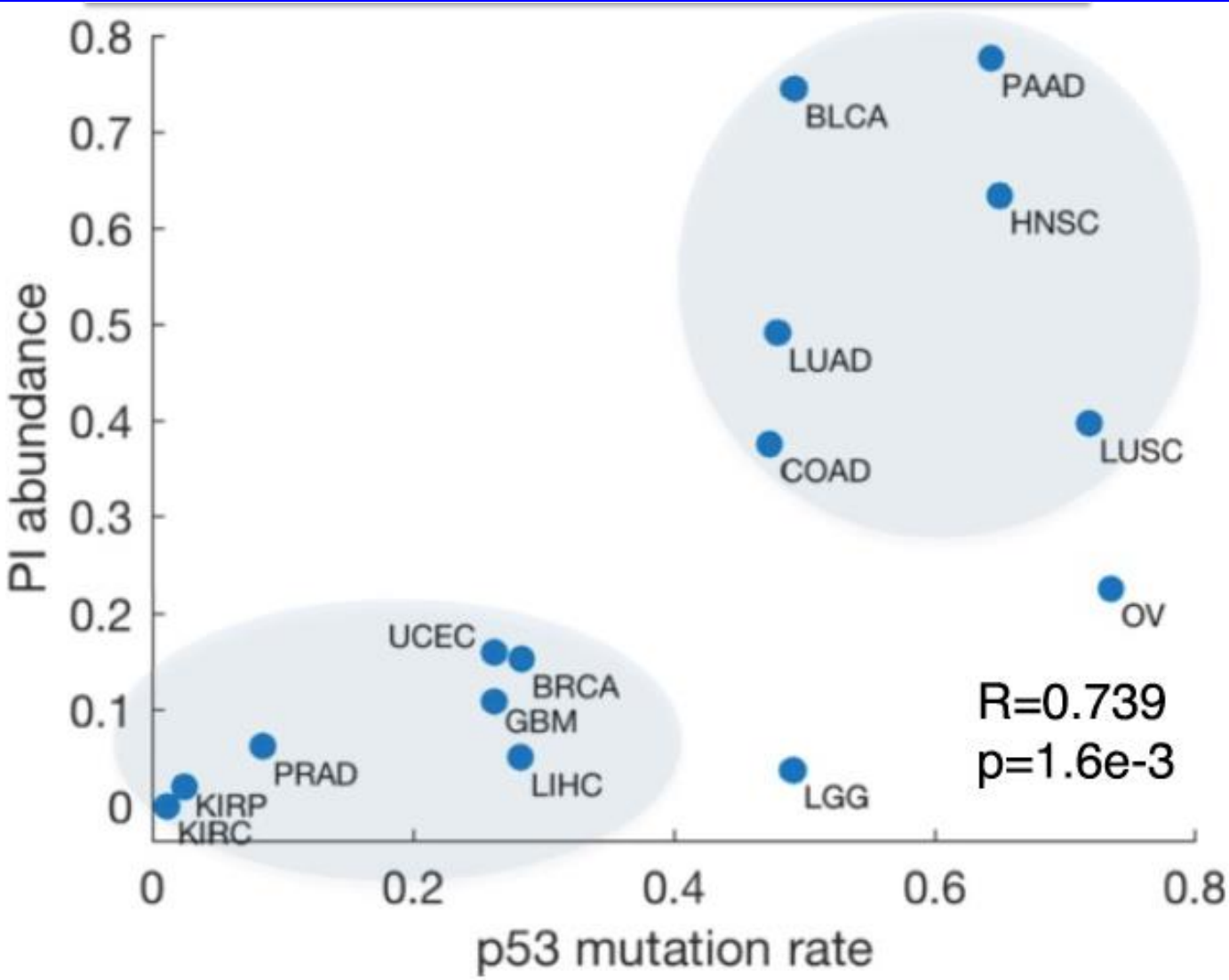
D Aran et al., 2016





D Aran et al., 2016

Correlation between parainflammation and p53 mutations



D Aran et al., 2016

Cancer Type	Estimated new cases in 2016	Risk factors correlated with inflammation
Pancreas	53,070	Cigarette smoking, chronic pancreatitis diabetes, obesity, Lynch syndrome
Lung & bronchus	224,390	Cigarette, cigar and pipe smoking, bronchitis.
Stomach	26,370	Helicobacter pylori (H. pylori)
Colon & rectum	134,490	obesity, physical inactivity, long-term smoking, alcohol consumption, chronic inflammatory bowel disease (e.g., ulcerative colitis or Crohn disease).
Esophagus	16,910	Reflux oesophagitis, Barret's oesophagus
Lymphoma	81,080	Epstein-Barr virus, human immunodeficiency virus [HIV].
Liver & intrahepatic bile duct	39,230	Hepatitis B virus (HBV) and/or hepatitis C virus (HCV), heavy alcohol consumption, obesity, diabetes, tobacco smoking, Cholangitis.
Melanoma of the skin	76,380	Skin inflammation.
Uterine cervix	12,990	human papillomavirus HPV
Uterine Corpus (Endometrium)	60,050	Obesity and abdominal fatness Lynch syndrome and diabetes.
Brest cancer	246,660	Obesity, long-term, heavy smoking, physical inactivity, and alcohol consumption.
Urinary Bladder	76,960	Smoking, Cystitis/Bladder Syndrome
Oral Cavity and Pharynx	48,330	Excessive alcohol consumption. HPV infection, tobacco use.
Kidney & renal pelvis	62,700	Obesity and tobacco smoking, chronic renal failure.
Leukemia	60,140	Obesity, Cigarette smoking, T-cell leukemia virus type I (HTLV-I)

Jelena Todoric et al., 2016

Hodgkin Lymphoma

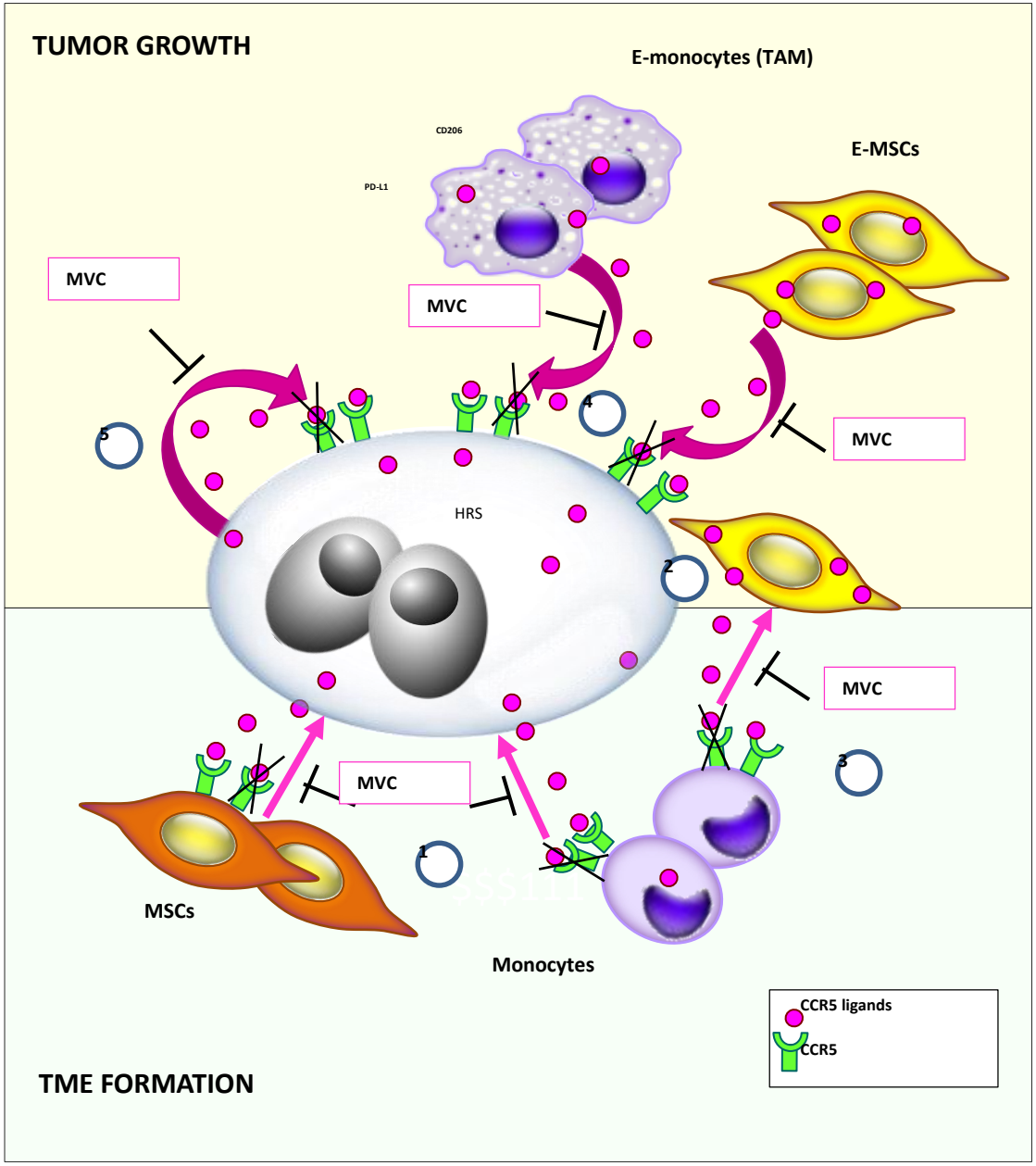
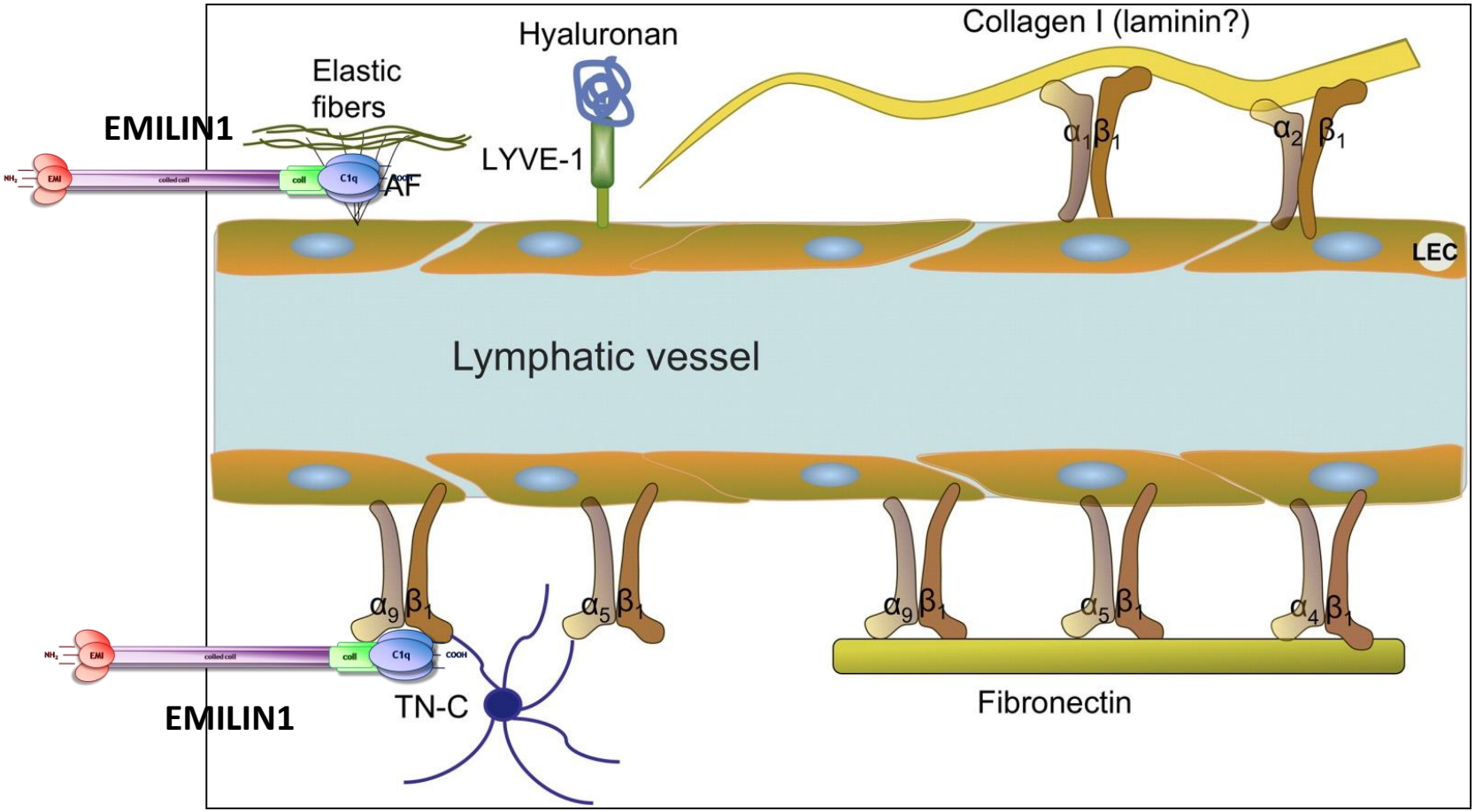


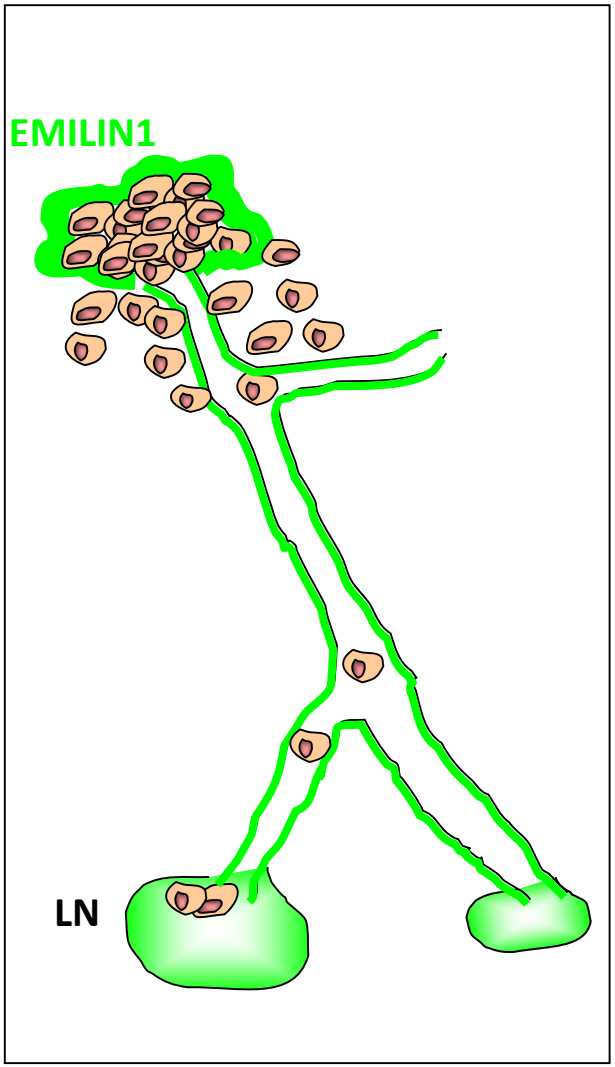
Figure 8. Schematic representation of the proposed mechanism of the CCR5 antagonist MVC in TME formation and tumor growth. (1) Blocking the CCR5 receptor by MVC inhibits the recruitment of monocytes and MSCs by cHL cells. (2) The "education" of MSCs cells (E-MSCs) induces the secretion of CCL5. (3) MVC inhibits the recruitment of monocytes by E-MSCs secreting CCL5. (4) MVC decreases the proliferation of cHL cells induced by CCR5 ligands secreted by tumor educated-monocytes (E-mon) and E-MSCs. Finally, (5) MVC inhibits the proliferation of cHL cells (autocrine growth).

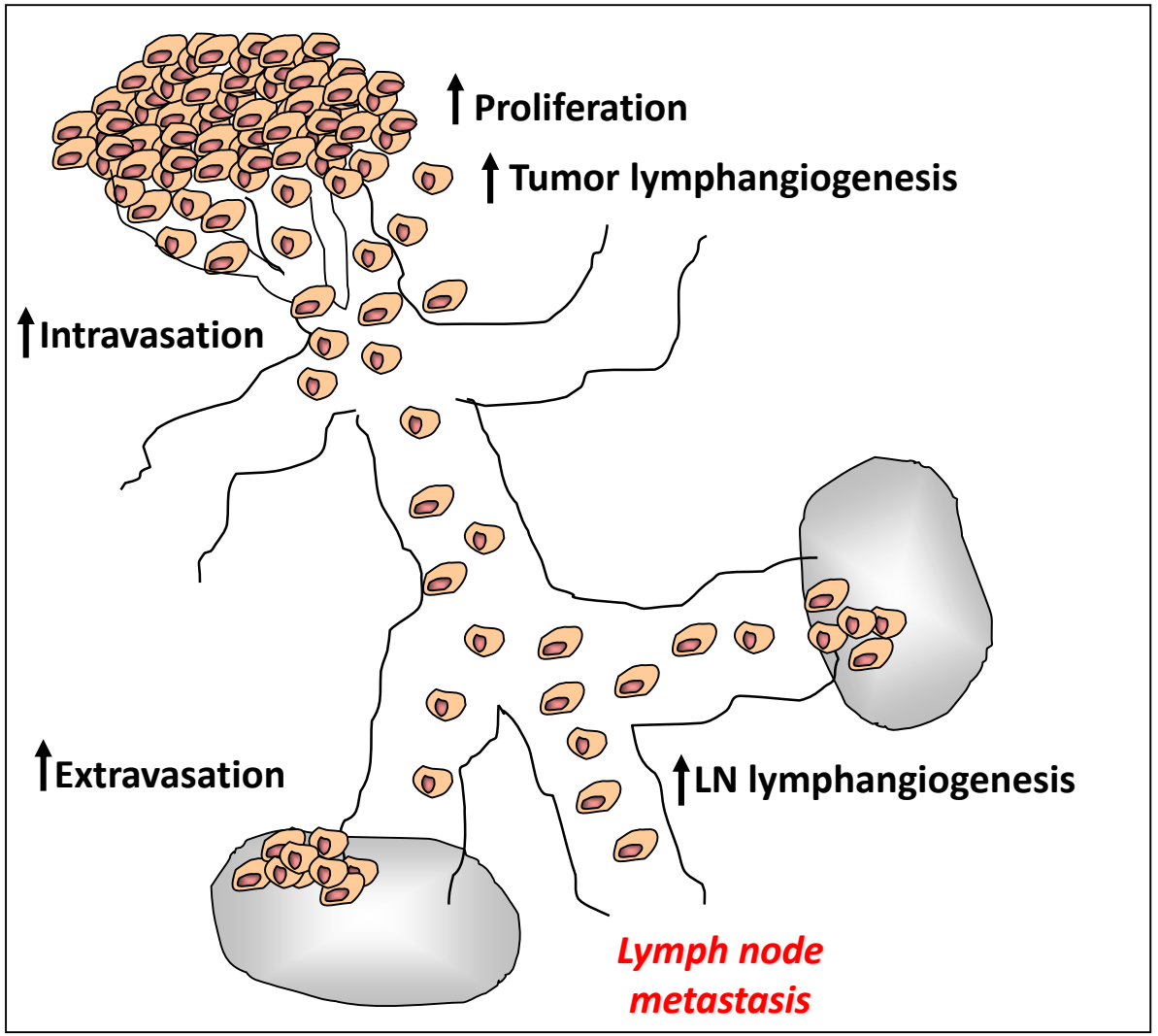
Donatella Aldinucci, CRO

LYMPHATIC VESSELS



Paola Spessotto, CRO

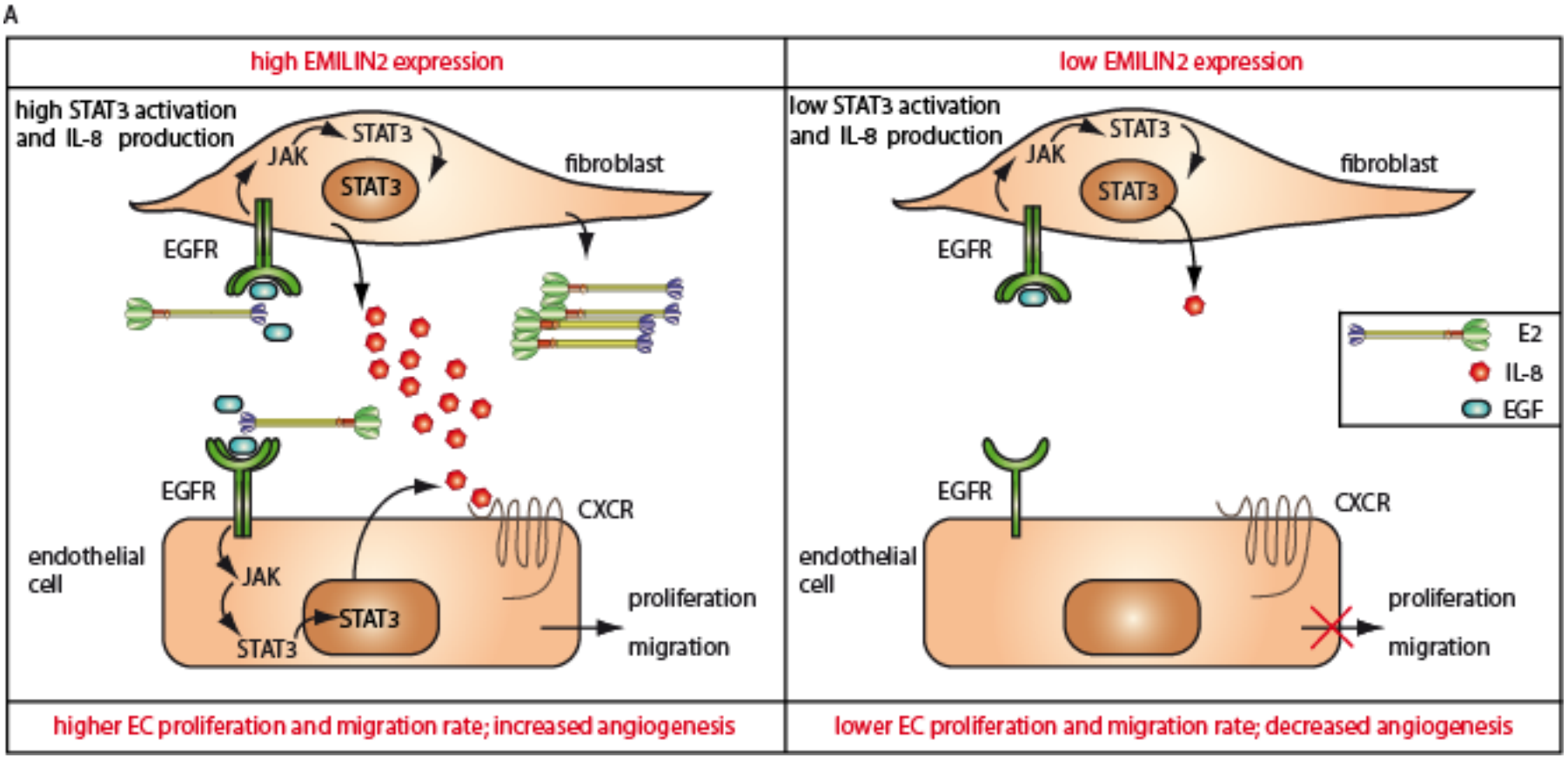




The presence/absence of EMILIN1 in the tumor microenvironment limits/promotes tumor growth and lymphatic metastasis

Paola Spessotto, CRO

EMILIN2 and promotion of angiogenesis



M Mongiat, CRO