Fisiopatologia do Câncer de Origem Infecciosa

Algumas definições iniciais....

Câncer –

Oncogene –

Supressor de tumor –

Fator de Crescimento –

Mutação –

Inflamação –

Fator de risco –

Correlação

Correlação causal

Mecanismos de Carcinogênese

DIRETOS

Mutação

Translocação

Inserção

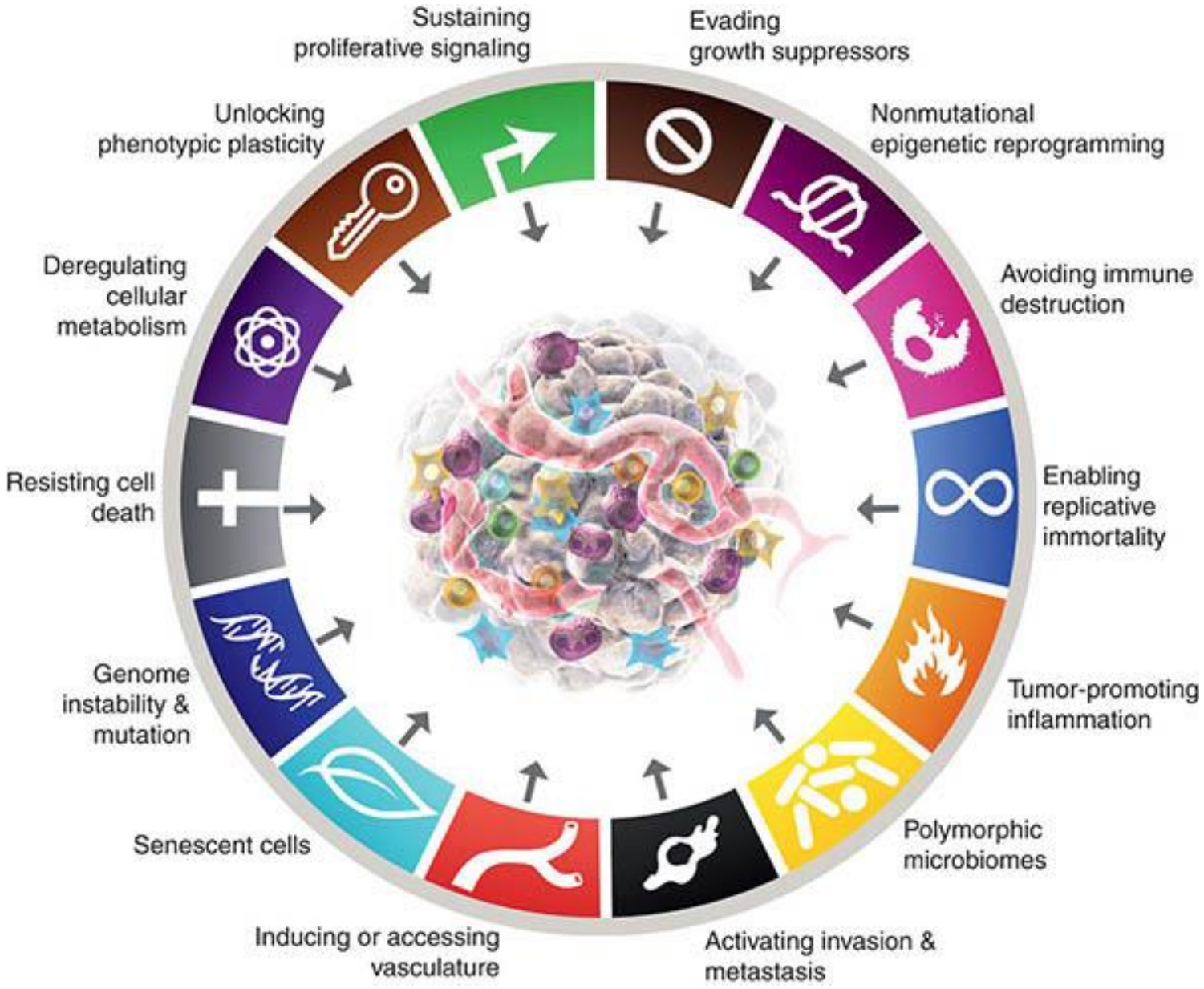
Oncogenes virais

INDIRETOS

Inflamação crônica

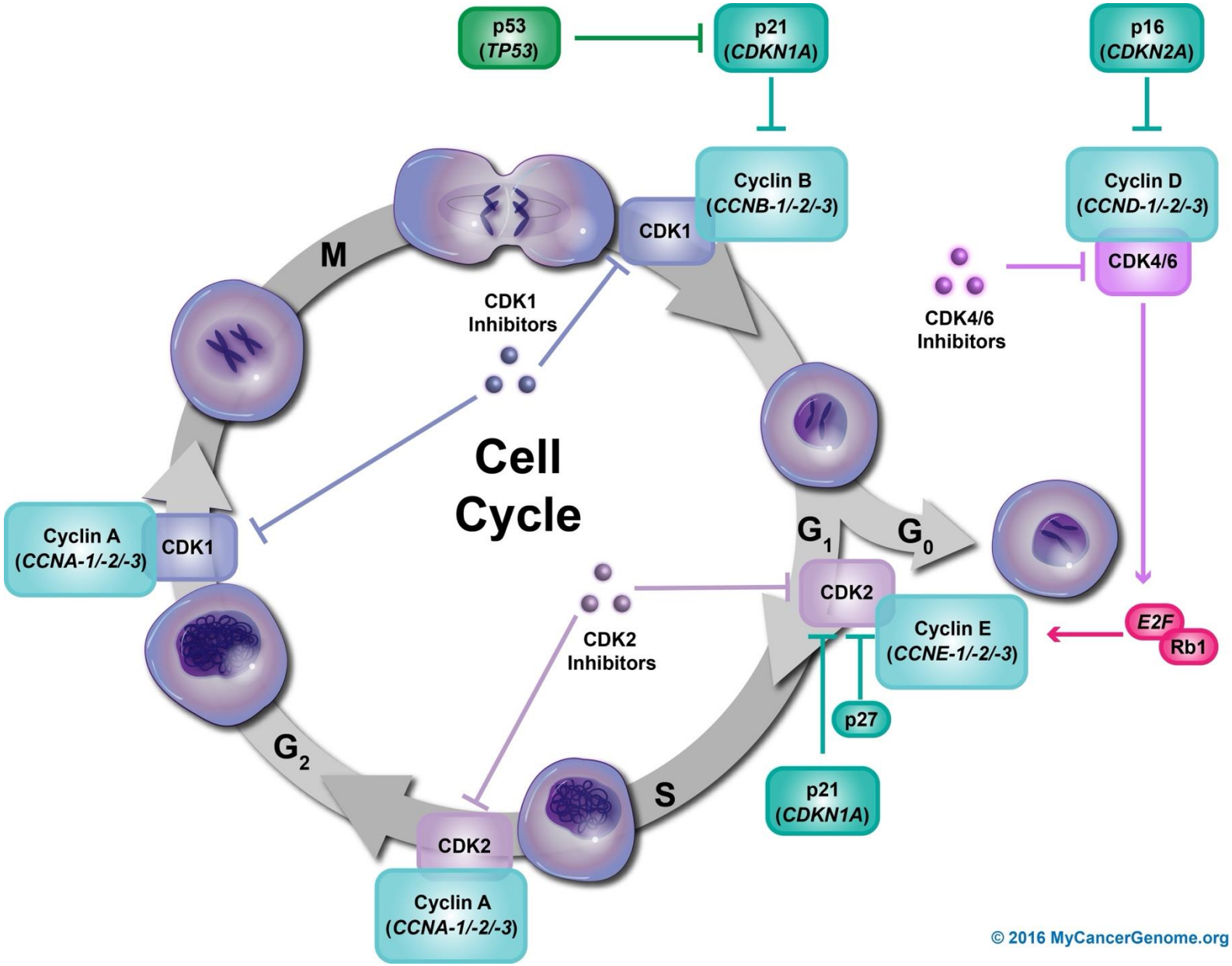
Imunossupressão

Hallmarks of Cancer

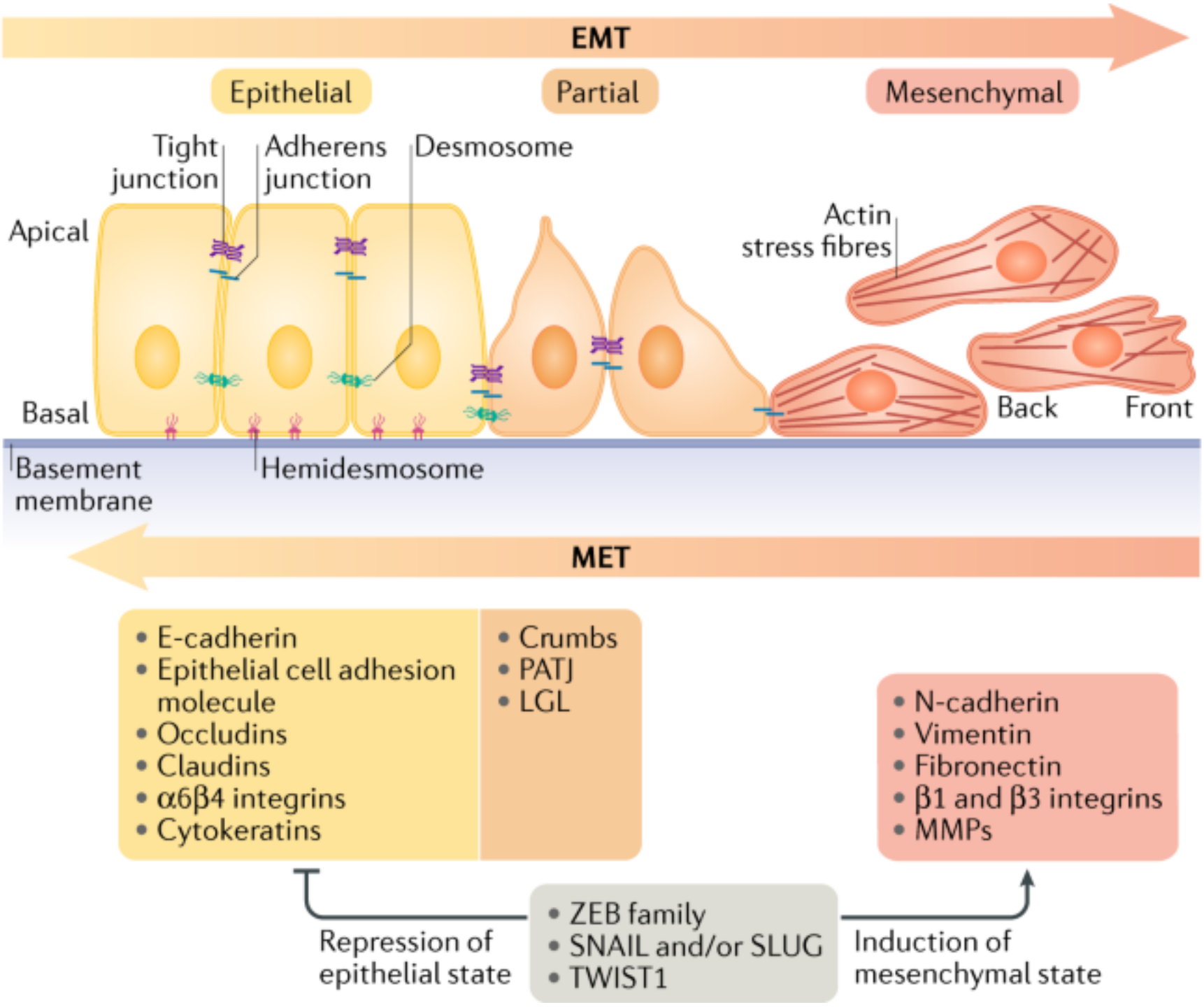


Hanahan and Weinberg

Ciclo Celular



EMT
Transição Epitélio-mesênquima



Agentes infecciosos que causam câncer

Vírus
Bactérias
Helmintos
Células

Infecções crônicas ou recorrentes

Mecanismos de carcinogênese diretos e/ou indiretos

De 15 a 20% dos casos de câncer em humanos são associados a infecções

Vírus

Virus	Target Organ	Tumor Type	Oncogenes
High-risk HPVs	Uterine cervix	Squamous cell carcinoma Adenocarcinoma	E6/E7
	Head and neck (oropharynx)	Squamous cell carcinoma	
	Vagina	Squamous cell carcinoma	
	Vulva	Squamous cell carcinoma	
	Penis	Squamous cell carcinoma	
HBV	Liver	Hepatocellular carcinoma Cholangiocellular carcinoma	HBX
HCV	Liver	Hepatocellular carcinoma Cholangiocellular carcinoma	NS5A/B, core
	Hematopoietic system	Malignant lymphoma	
EBV / HHV-4	Stomach	Adenocarcinoma	LMP1 e 2 EBNA1 EBER1 e 2 (latência)
	Nasopharynx	Nasopharyngeal carcinoma	
	Hematopoietic system	See Tables 3 and 4	
	Soft tissue	EBV-associated smooth muscle tumor	
KSHV / HHV-8	Soft tissue Hematopoietic system	Kaposi sarcoma See Table 5	LANA, vCyclin vIL-6
MCV	Skin	Merkel cell carcinoma	LT, ST
HTLV-1	Hematopoietic system	Adult T-cell leukemia/lymphoma	Tax
HIV	various		

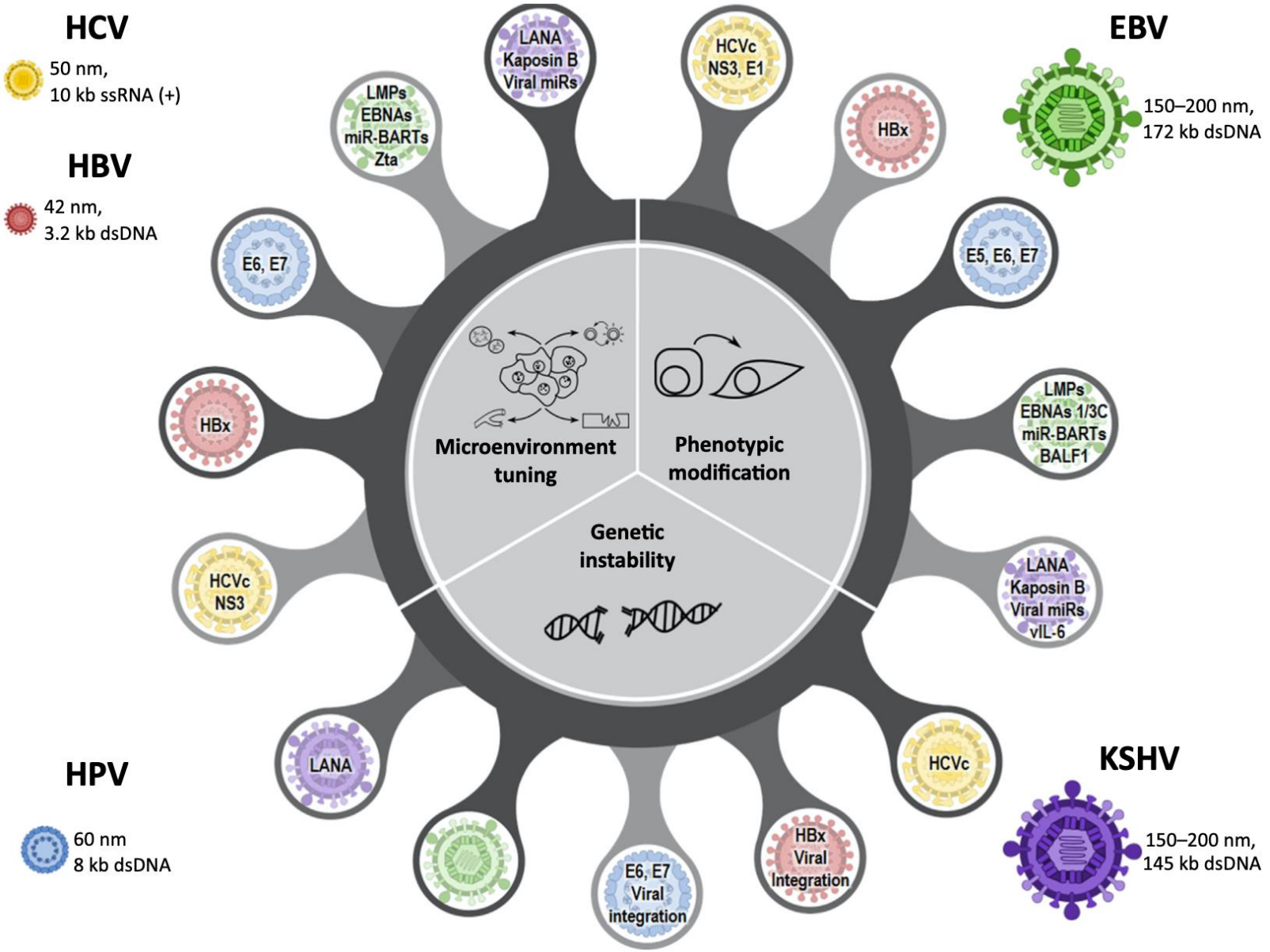
Vírus

Mecanismos de carcinogênese

Diretos – expressão de oncoproteínas virais que regulam o ciclo celular (E6 e E7, Tax, LMP...)
inserção do genoma viral no genoma da célula hospedeira (contribuição menor do que outros mecanismos)

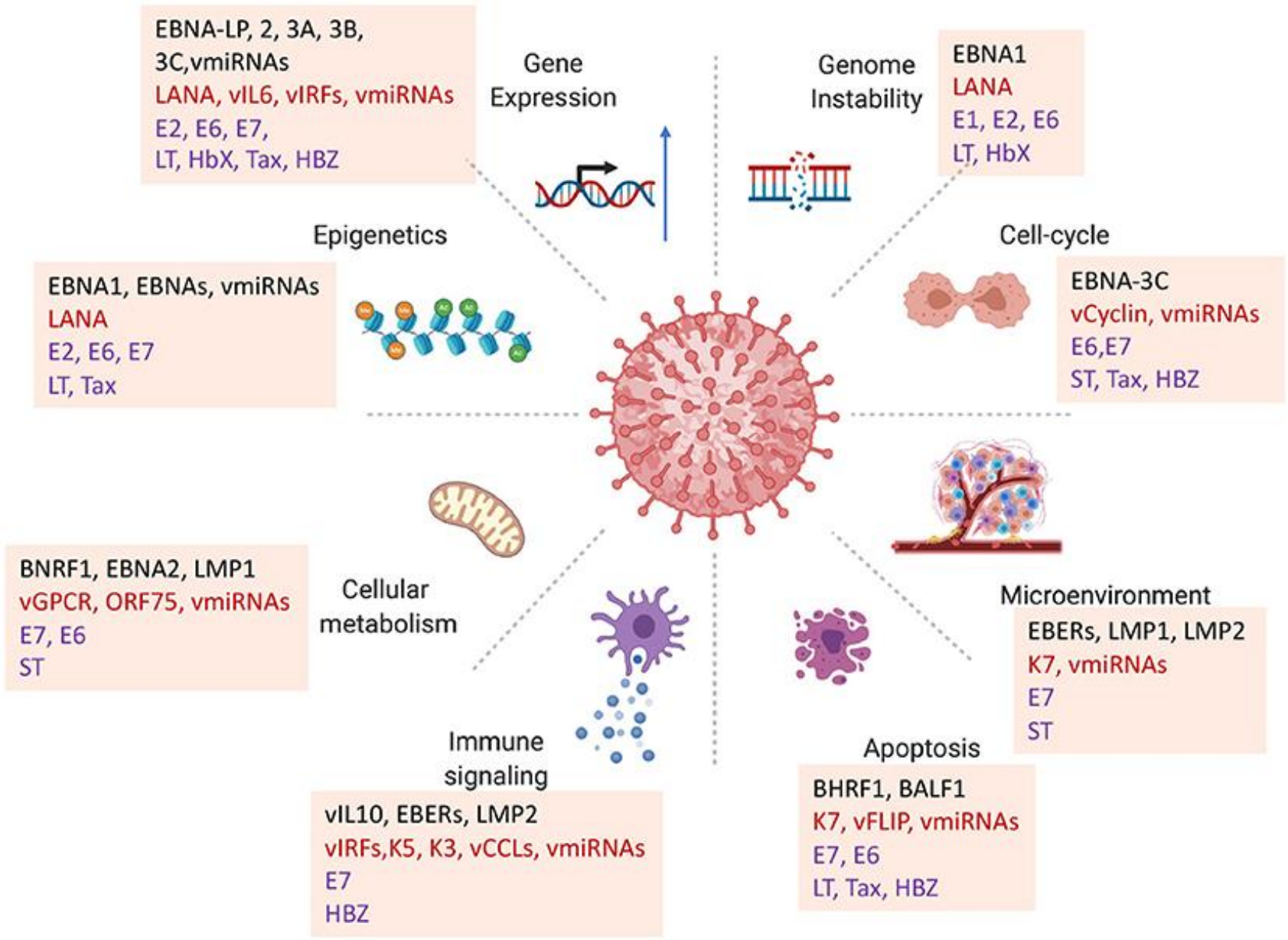
Indiretos – imunossupressão – HIV
inflamação crônica - HIV, em pacientes em tratamento com HAART, HCV, HBV

Mecanismos de carcinogênese

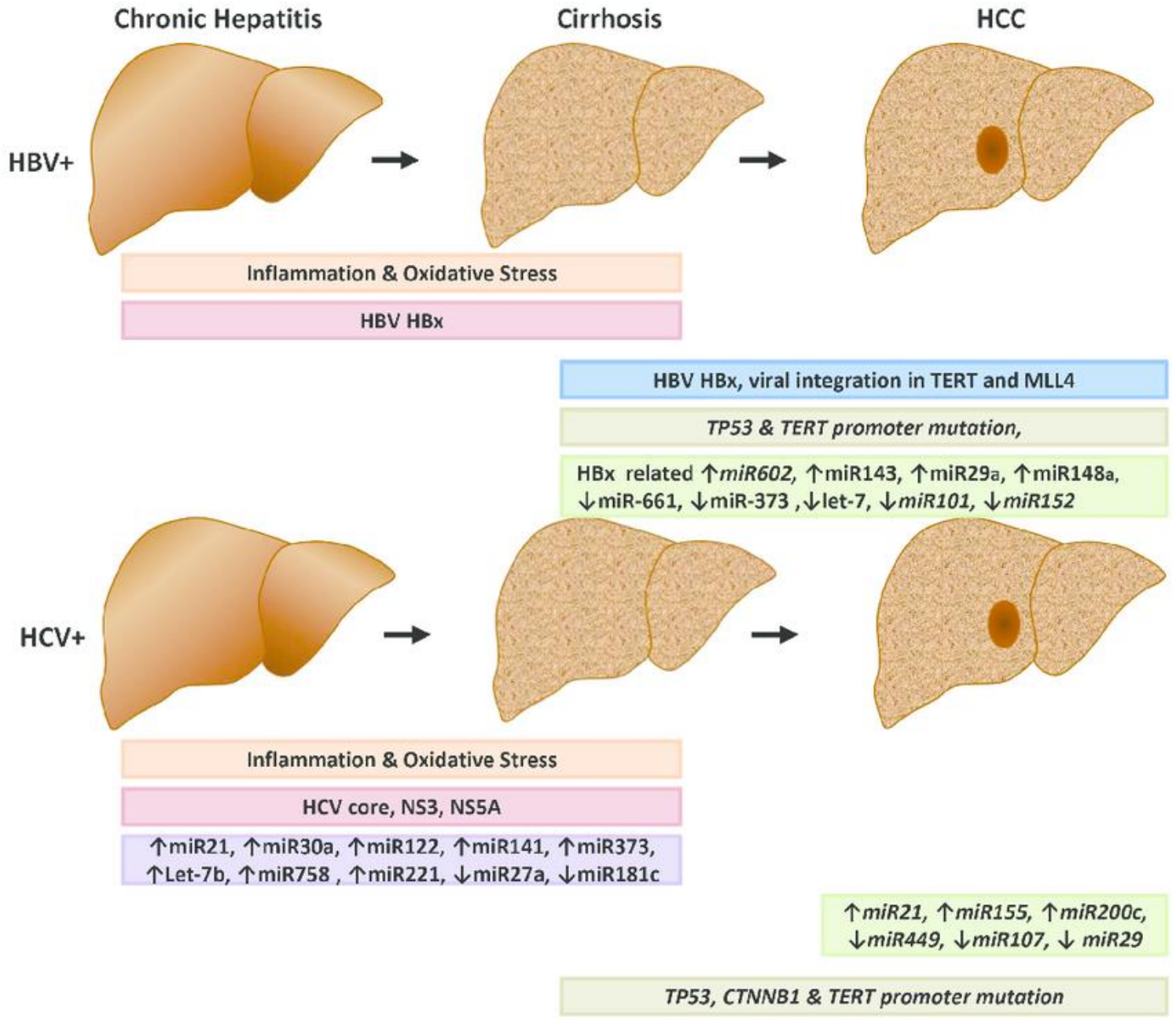


Müller-Coan et al
Trends in Cancer. 2018.

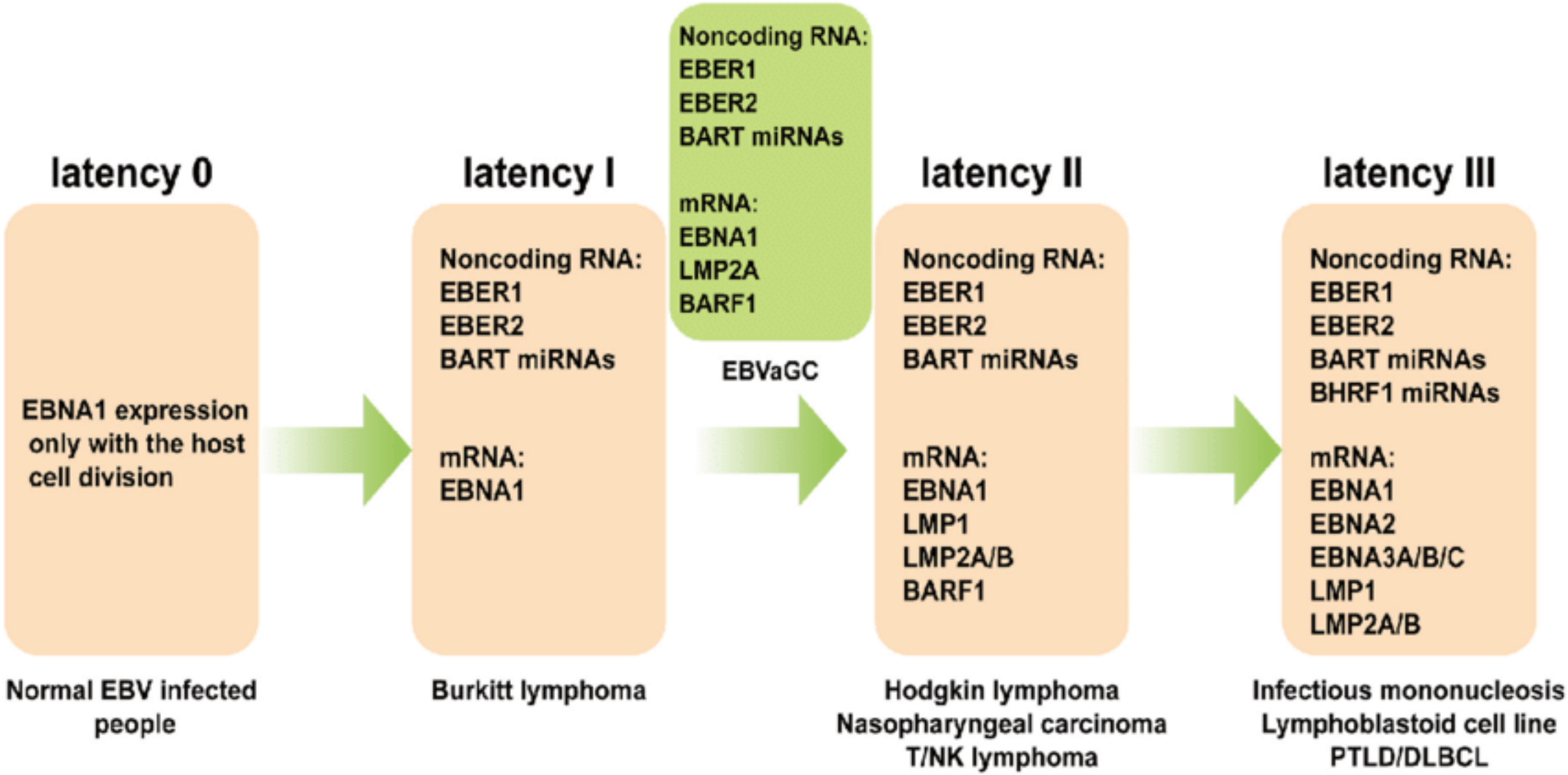
Mecanismos de carcinogênese – panorama geral



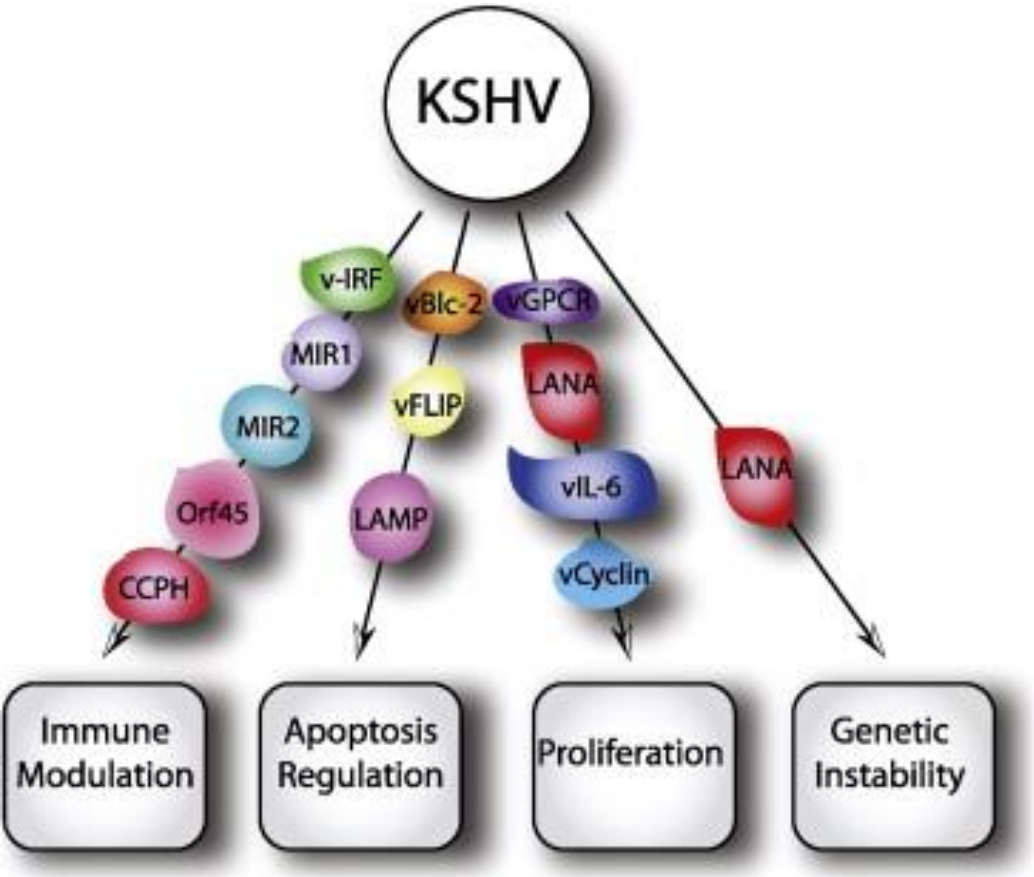
Mecanismos de carcinogênese – HCV e HBV

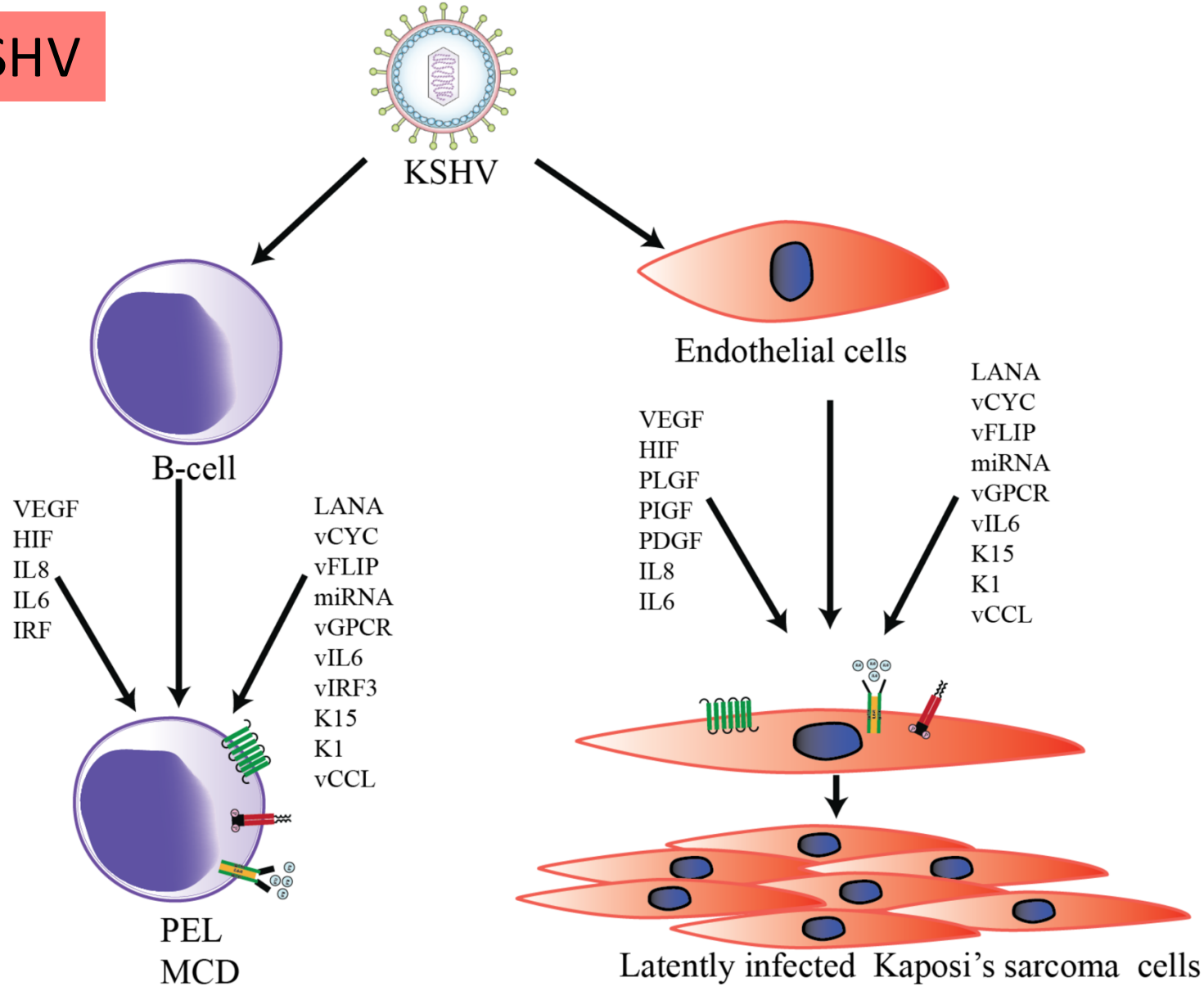


Mecanismos de carcinogênese - EBV



Mecanismos de carcinogênese - KSHV





Bactérias

Helicobacter pylori – câncer gástrico

Disbiose – variação na população de bactérias, com menor representação de comensais e predominância de espécies patogênicas/inflamatórias – câncer de coloretal, fator de risco para outros?

Mecanismos de carcinogênese

Indiretos – inflamação crônica

Diretos – Fatores de virulência

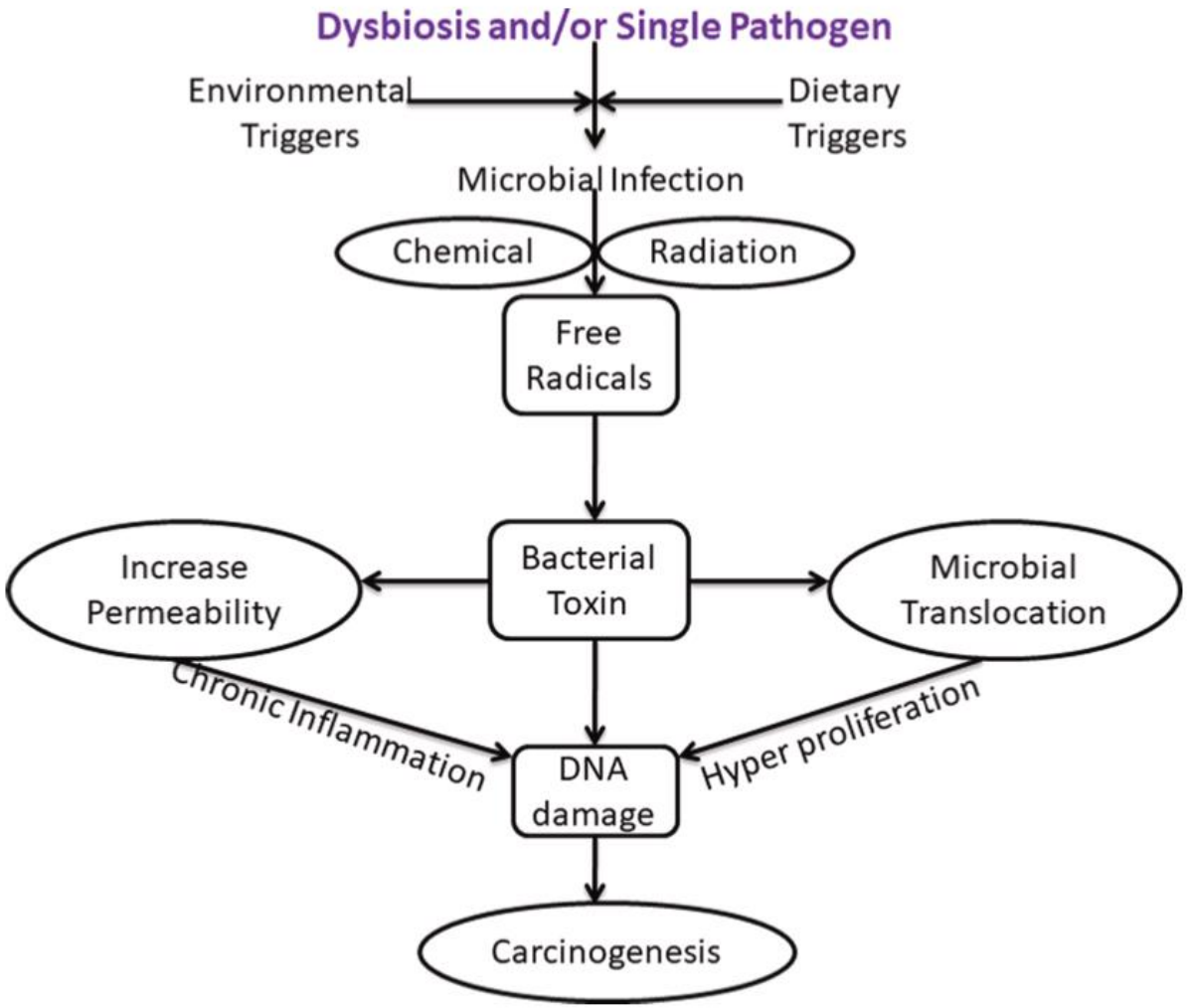
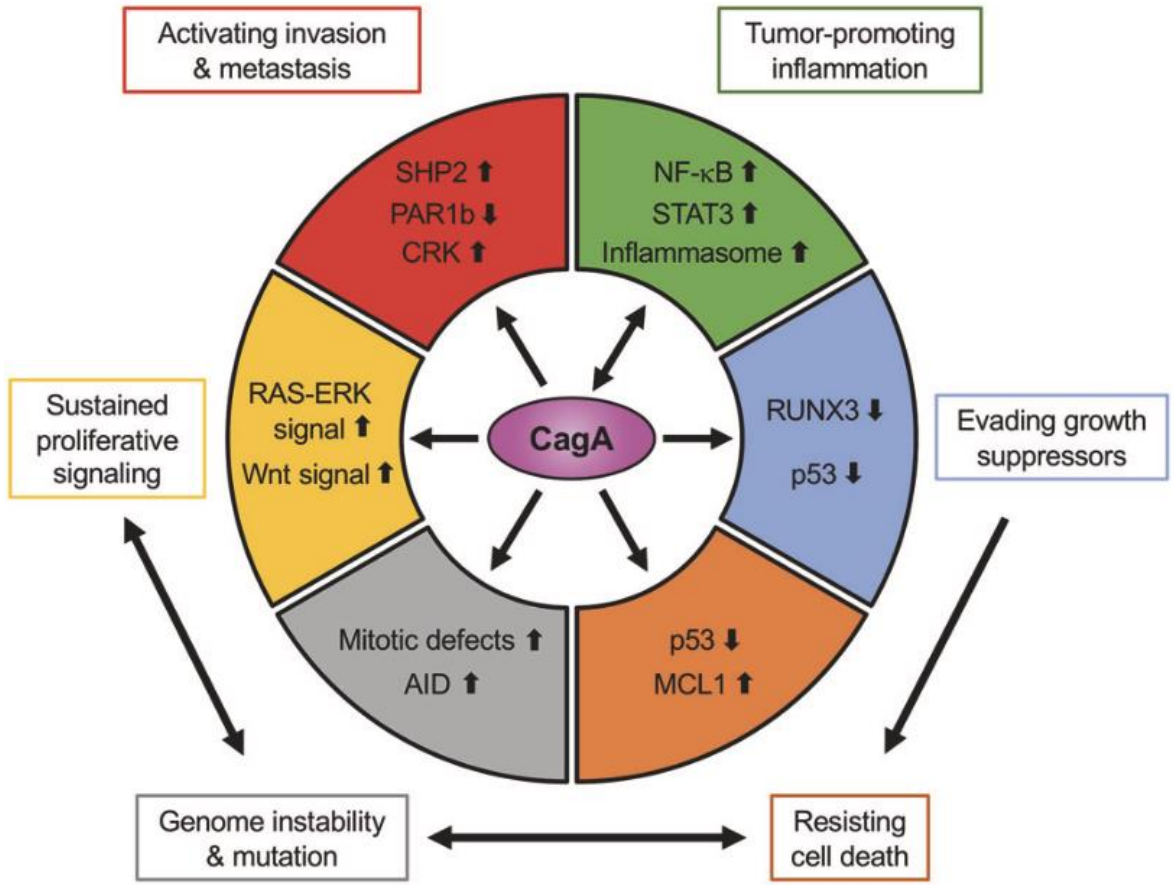
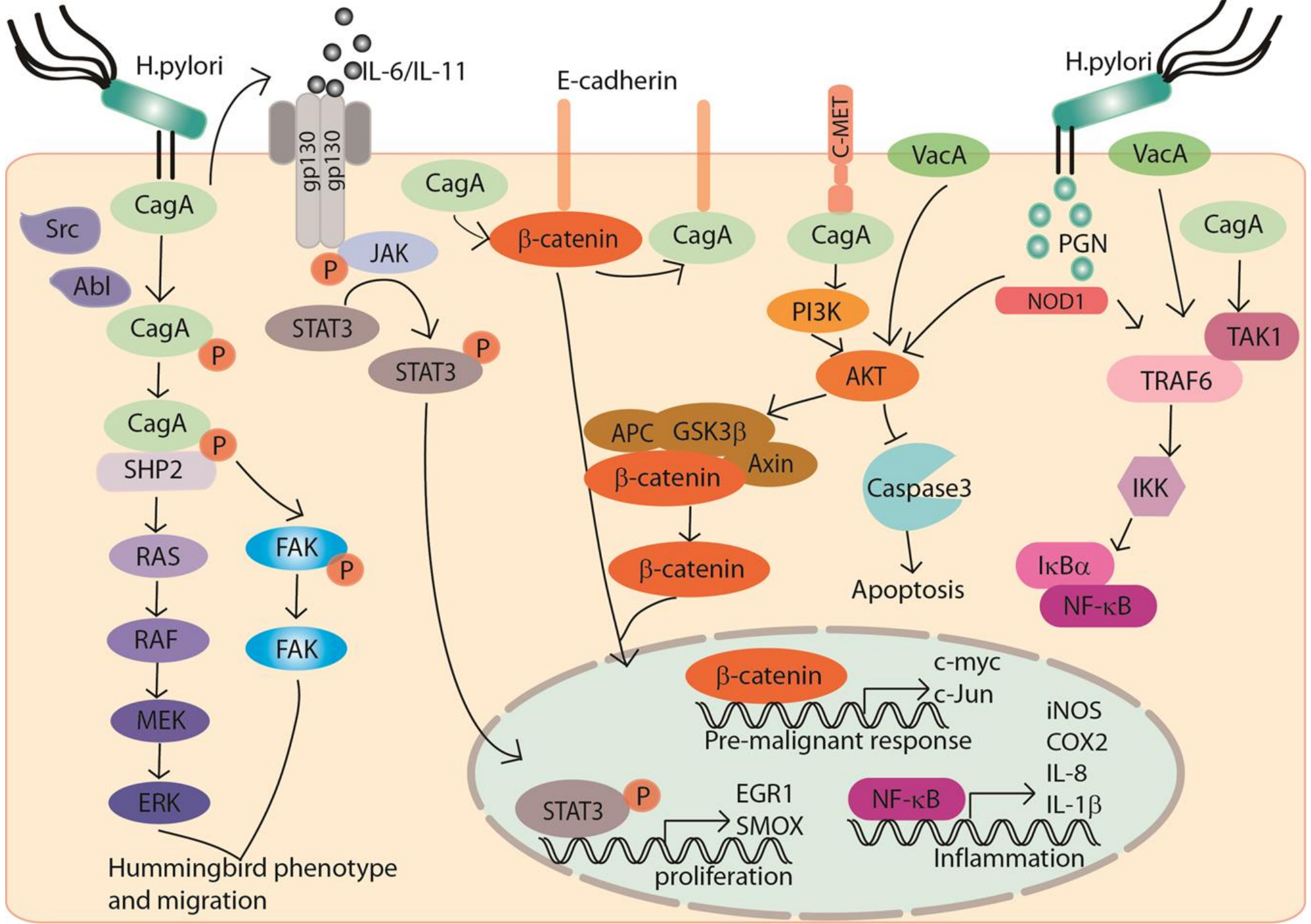


Fig. 1. General mechanism used by microbes in the progression of cancer.

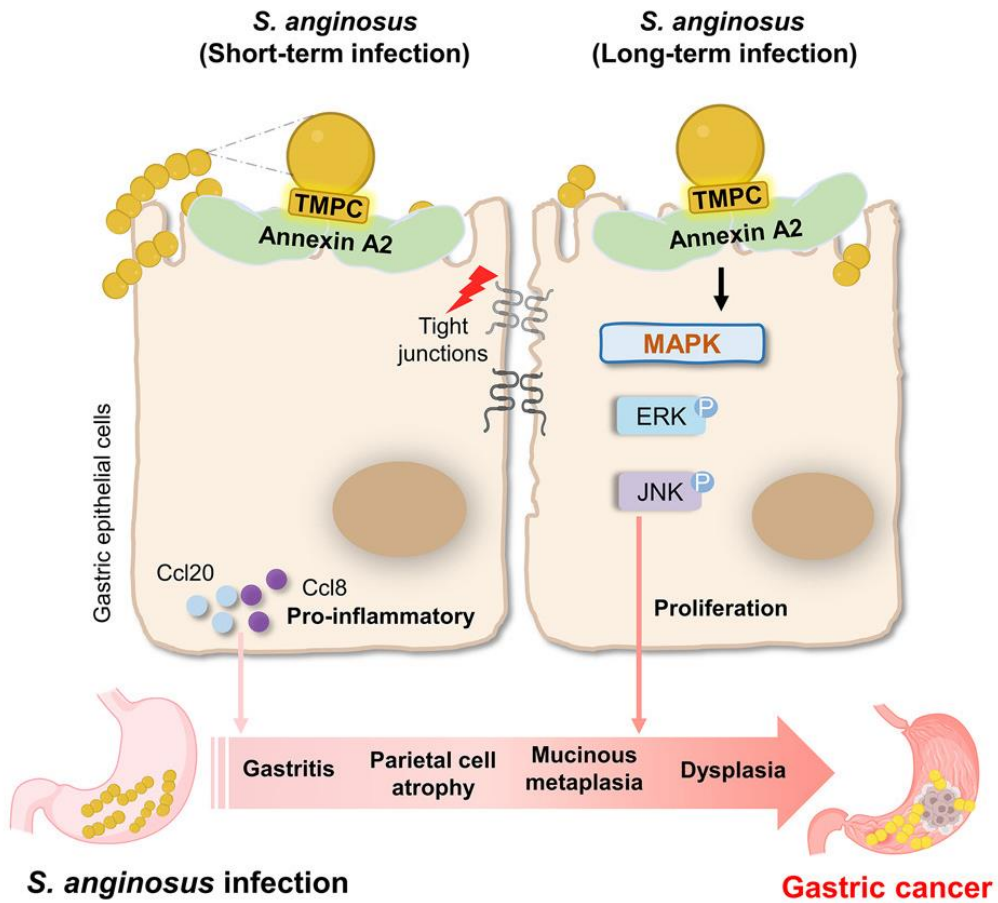
CagA – fator de virulência *H. pylori*




H.pylori
IL-6/IL-11
gp130
gp130
JAK
P
STAT3
STAT3
P
CagA
Src
Abl
CagA
P
CagA
P
SHP2
RAS
RAF
MEK
ERK
FAK
P
FAK
Hummingbird phenotype
and migration
CagA
β-catenin
CagA
E-cadherin
C-MET
CagA
PI3K
AKT
APC
GSK3β
Axin
β-catenin
β-catenin
Caspase3
Apoptosis
VacA
H.pylori
VacA
PGN
NOD1
CagA
TAK1
TRAF6
IKK
IκBα
NF-κB
β-catenin
c-myc
c-Jun
Pre-malignant response
iNOS
COX2
IL-8
IL-1β
STAT3
P
EGR1
SMOX
proliferation
NF-κB
Inflammation

Cell

Streptococcus anginosus promotes gastric inflammation, atrophy, and tumorigenesis in mice



Disbiose/infecção e cancer coloretal

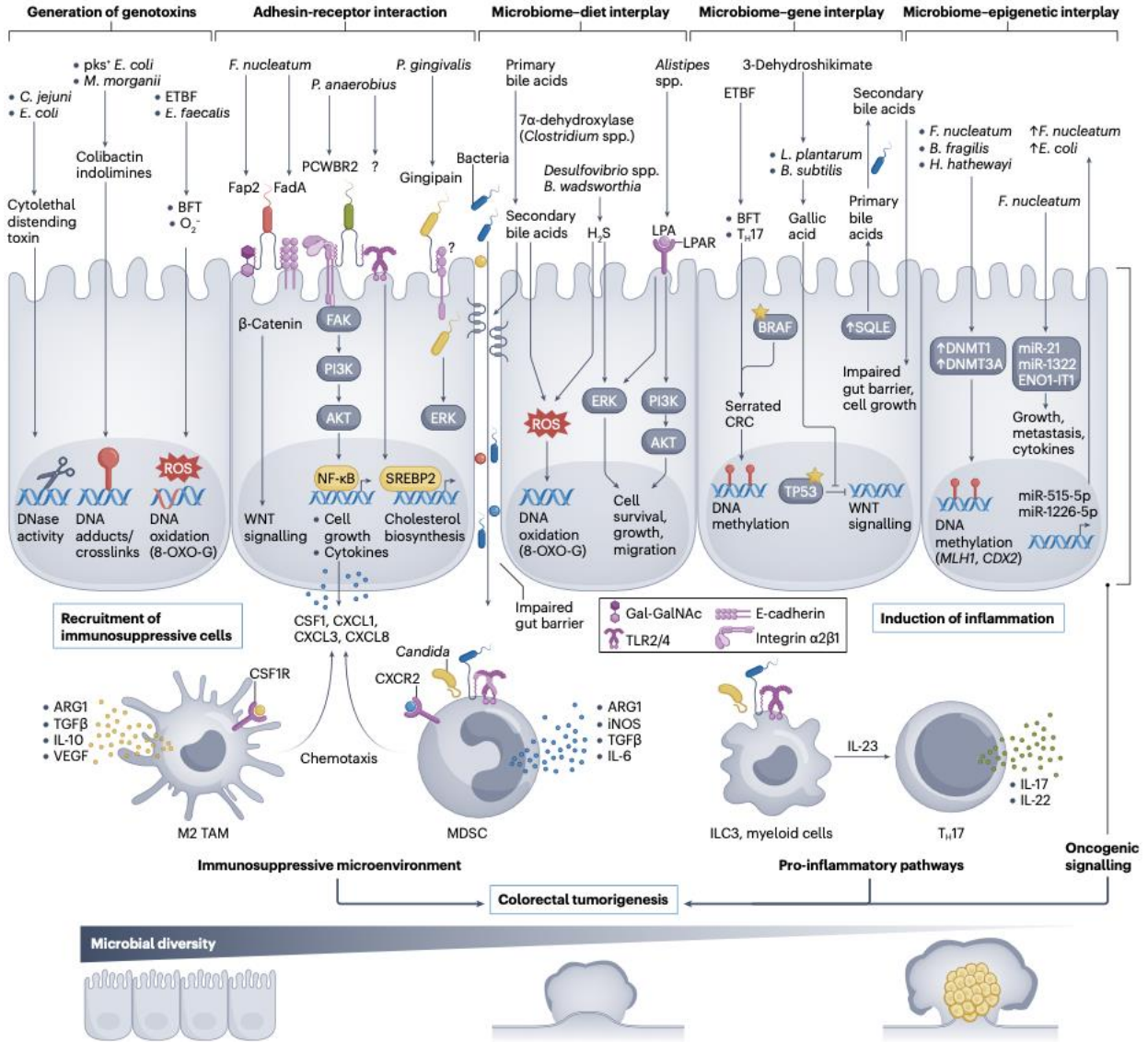
Correlação causal ainda não é consenso;
Experimentos de transferência de fezes de animais com câncer para animais sem câncer, mas com mutações iniciadoras contribuíram para estabelecimento de relação causal.

nature reviews clinical oncology
https://doi.org/10.1038/s41571-023-00766-x

Review article
Check for updates

Gut microbiota in colorectal cancer development and therapy

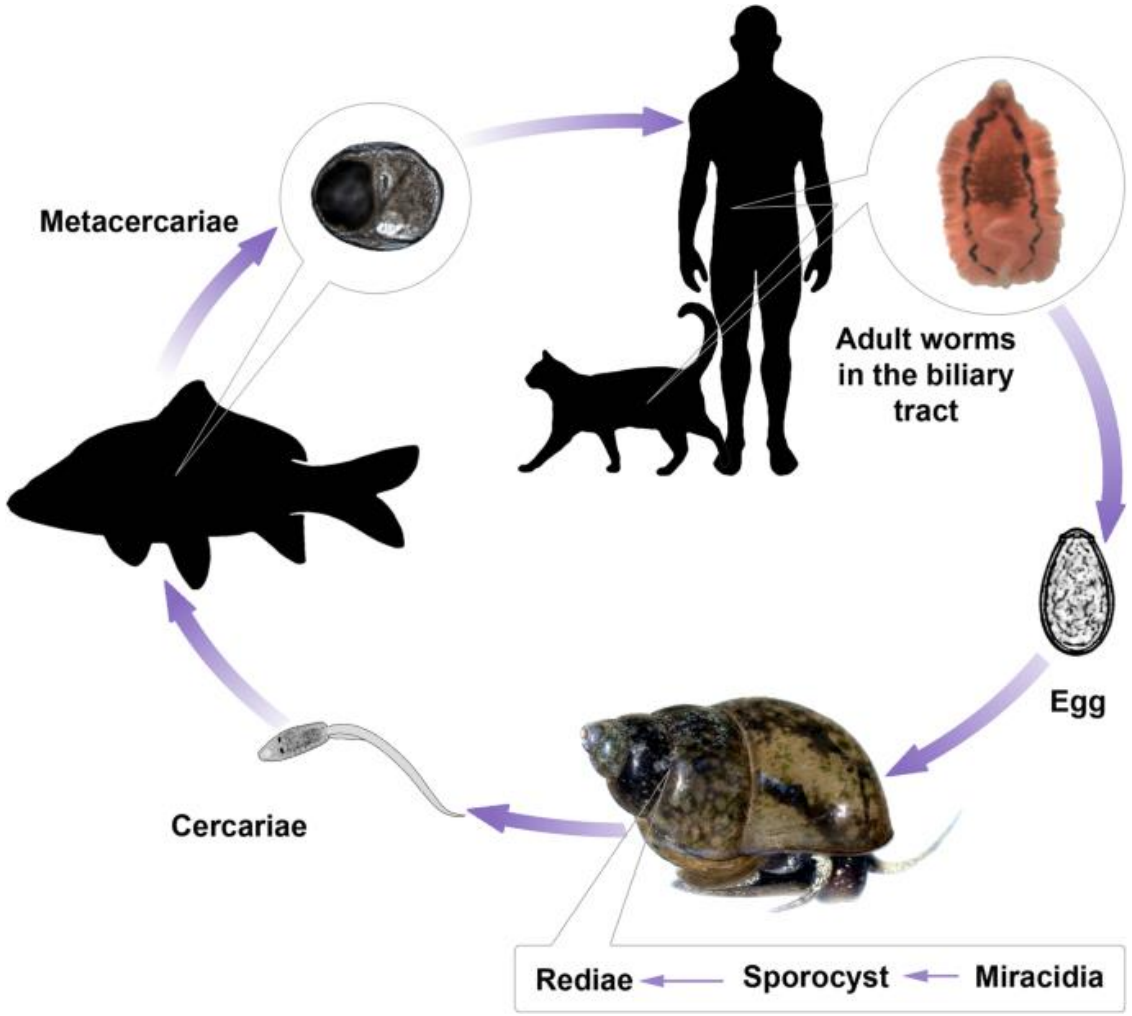
Chi Chun Wong & Jun Yu

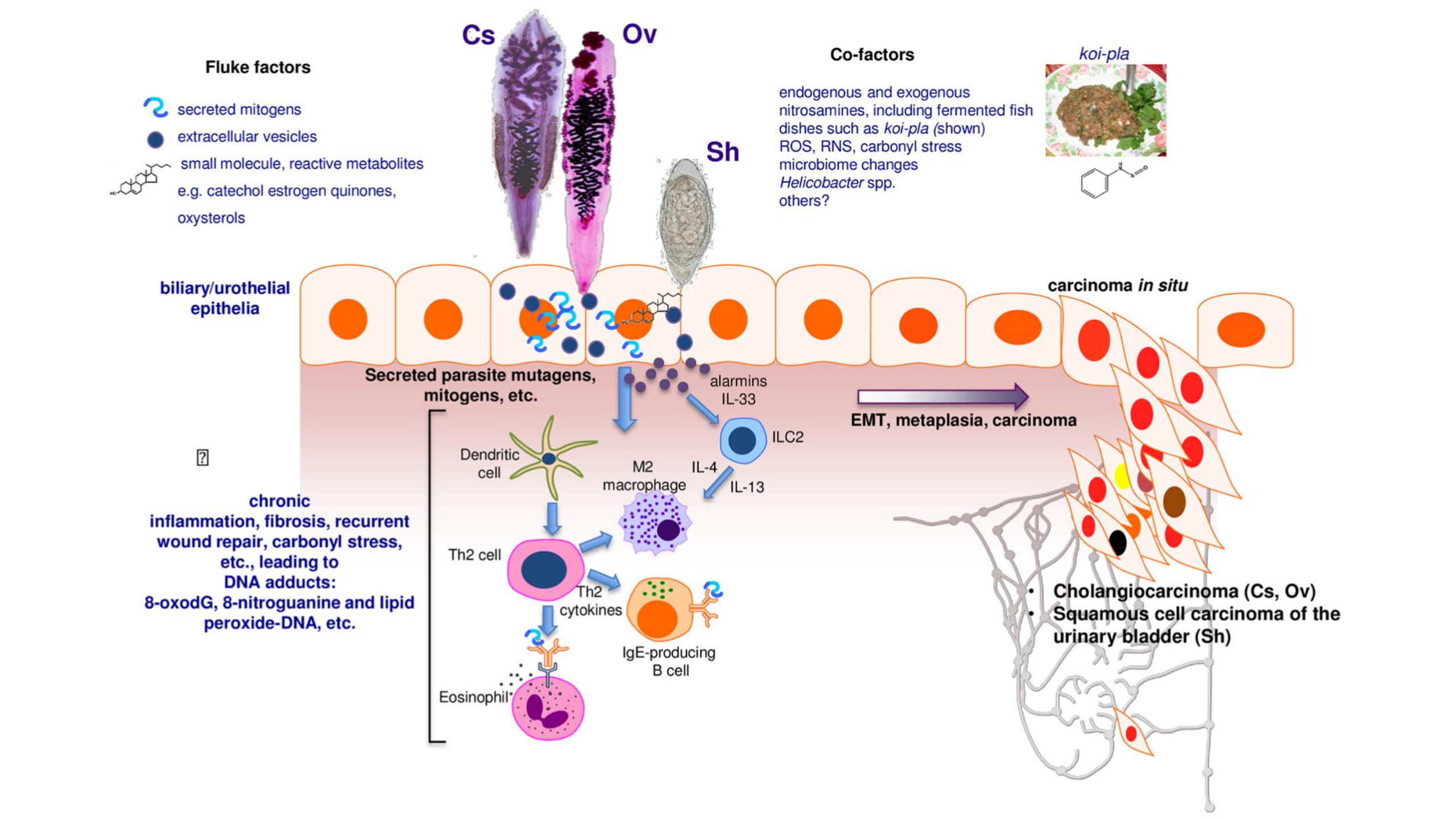


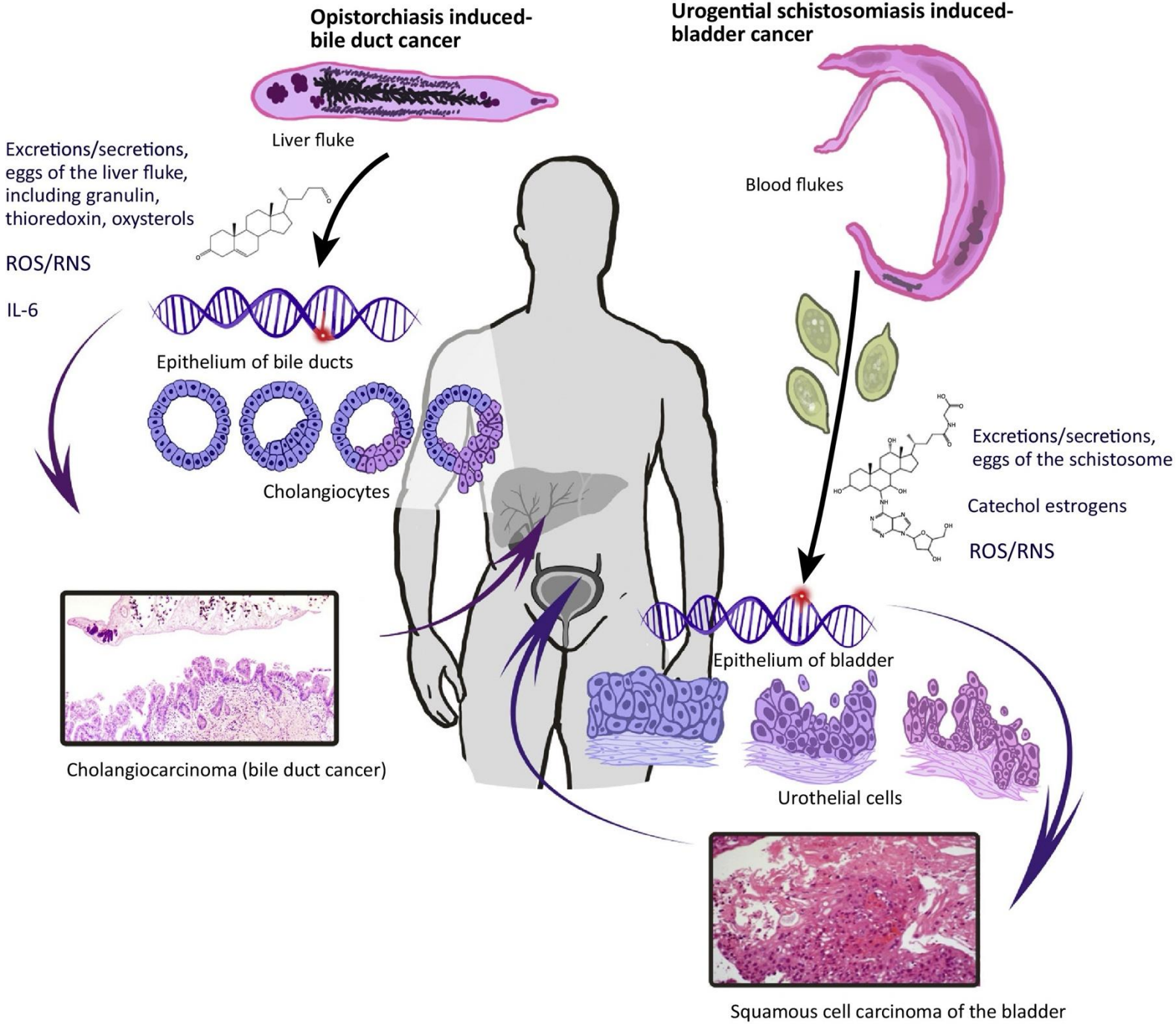
Helmintos

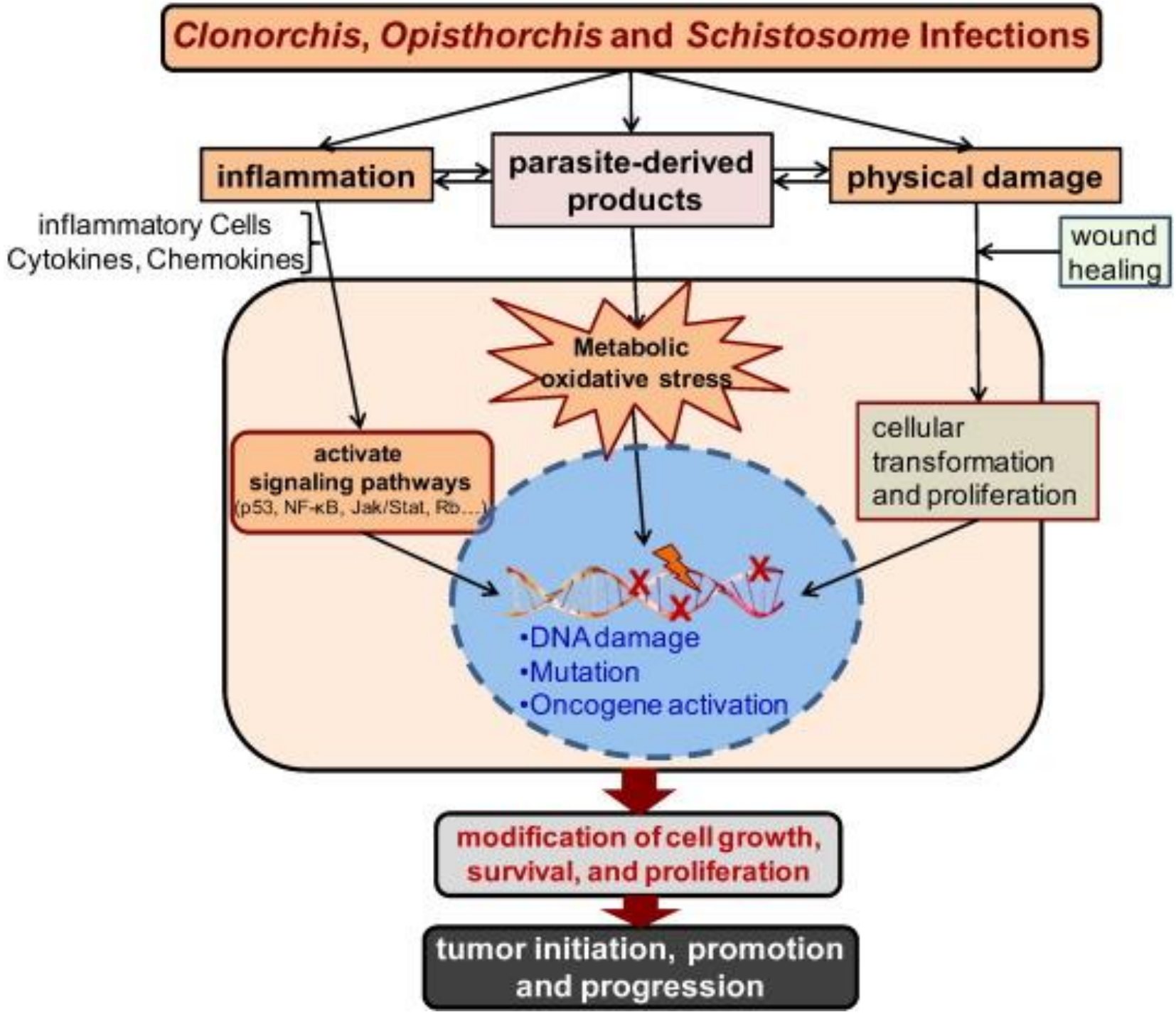
Opisthorchis viverrini and *Clonorchis sinensis* – colangiocarcinoma

Schistosoma haematobium – carcinoma de bexiga

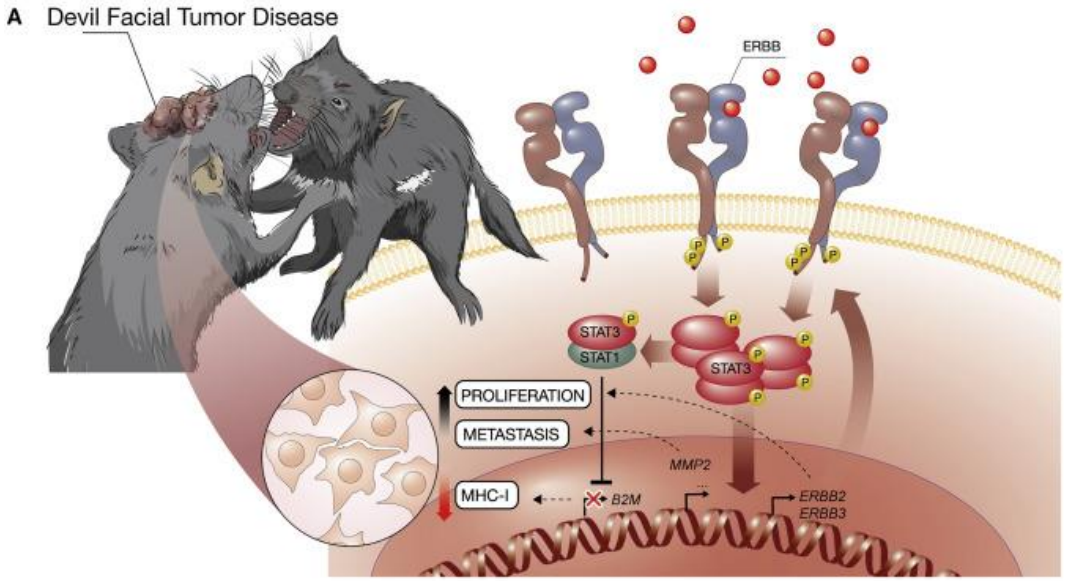


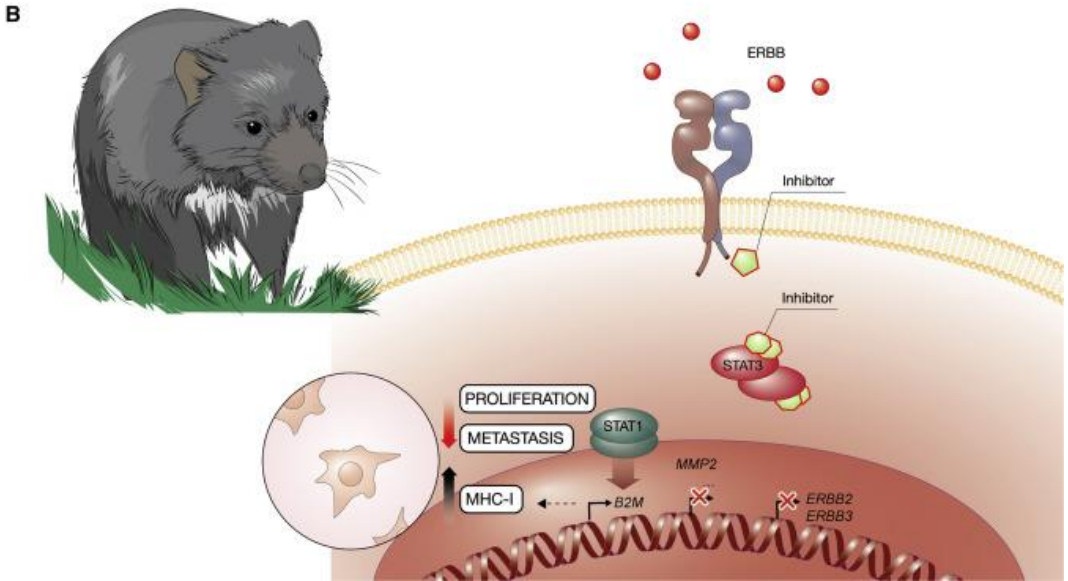

Cs
Ov
Sh
Fluke factors
secreted mitogens
extracellular vesicles
small molecule, reactive metabolites
e.g. catechol estrogen quinones,
oxysterols
Co-factors
endogenous and exogenous
nitrosamines, including fermented fish
dishes such as koi-pla (shown)
ROS, RNS, carbonyl stress
microbiome changes
Helicobacter spp.
others?
koi-pla
biliary/urothelial
epithelia
carcinoma in situ
Secreted parasite mutagens,
mitogens, etc.
alarmins
IL-33
ILC2
Dendritic
cell
M2
macrophage
IL-4
IL-13
Th2 cell
Th2
cytokines
IgE-producing
B cell
Eosinophil
EMT, metaplasia, carcinoma
chronic
inflammation, fibrosis, recurrent
wound repair, carbonyl stress,
etc., leading to
DNA adducts:
8-oxodG, 8-nitroguanine and lipid
peroxide-DNA, etc.
Cholangiocarcinoma (Cs, Ov)
Squamous cell carcinoma of the
urinary bladder (Sh)


Opistorchiasis induced-bile duct cancer
Liver fluke
Excretions/secretions, eggs of the liver fluke, including granulin, thioredoxin, oxysterols
ROS/RNS
IL-6
Epithelium of bile ducts
Cholangiocytes
Cholangiocarcinoma (bile duct cancer)
Urogential schistosomiasis induced-bladder cancer
Blood flukes
Excretions/secretions, eggs of the schistosome
Catechol estrogens
ROS/RNS
Epithelium of bladder
Urothelial cells
Squamous cell carcinoma of the bladder

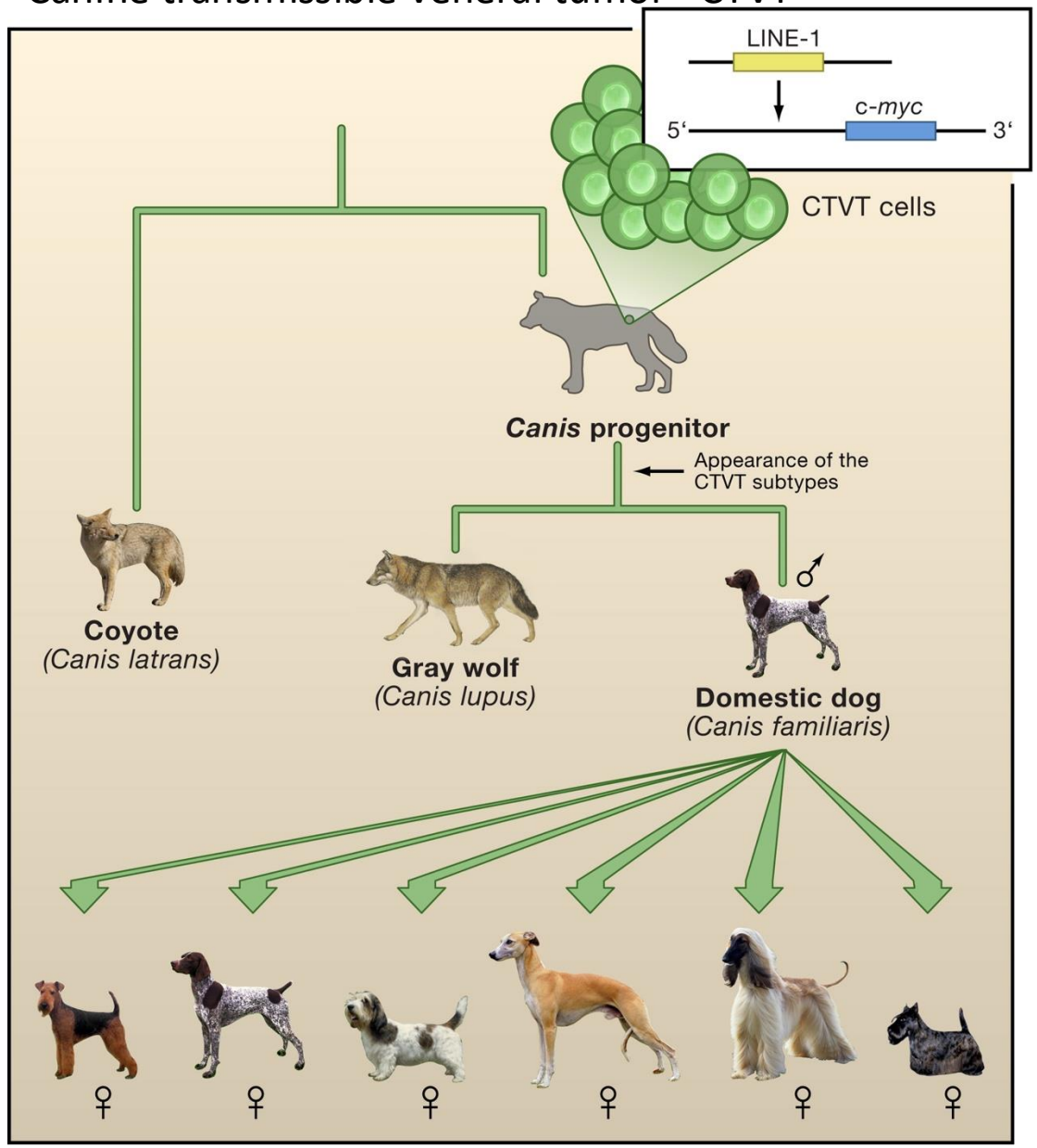

Clonorchis, Opisthorchis and Schistosome Infections
inflammation
parasite-derived products
physical damage
inflammatory Cells
Cytokines, Chemokines
wound healing
Metabolic oxidative stress
activate signaling pathways
(p53, NF-κB, Jak/Stat, Rb…)
cellular transformation and proliferation
•DNA damage
•Mutation
•Oncogene activation
modification of cell growth, survival, and proliferation
tumor initiation, promotion and progression

Células tumorais como agentes infecciosos





Canine transmissible veneral tumor - CTVT



Prevenção e tratamento

Prevenção

Evitar exposição

Programas de saúde

Vacinas

HPV

HBV

Terapia

HCV – DAA – direct acting antivirals

HIV – HAART – highly active antiretroviral therapy

Vacinas terapêuticas

Antibióticos
(amoxicilina 1g + claritromicina 500 mg 14 dias)

Transplante de fezes