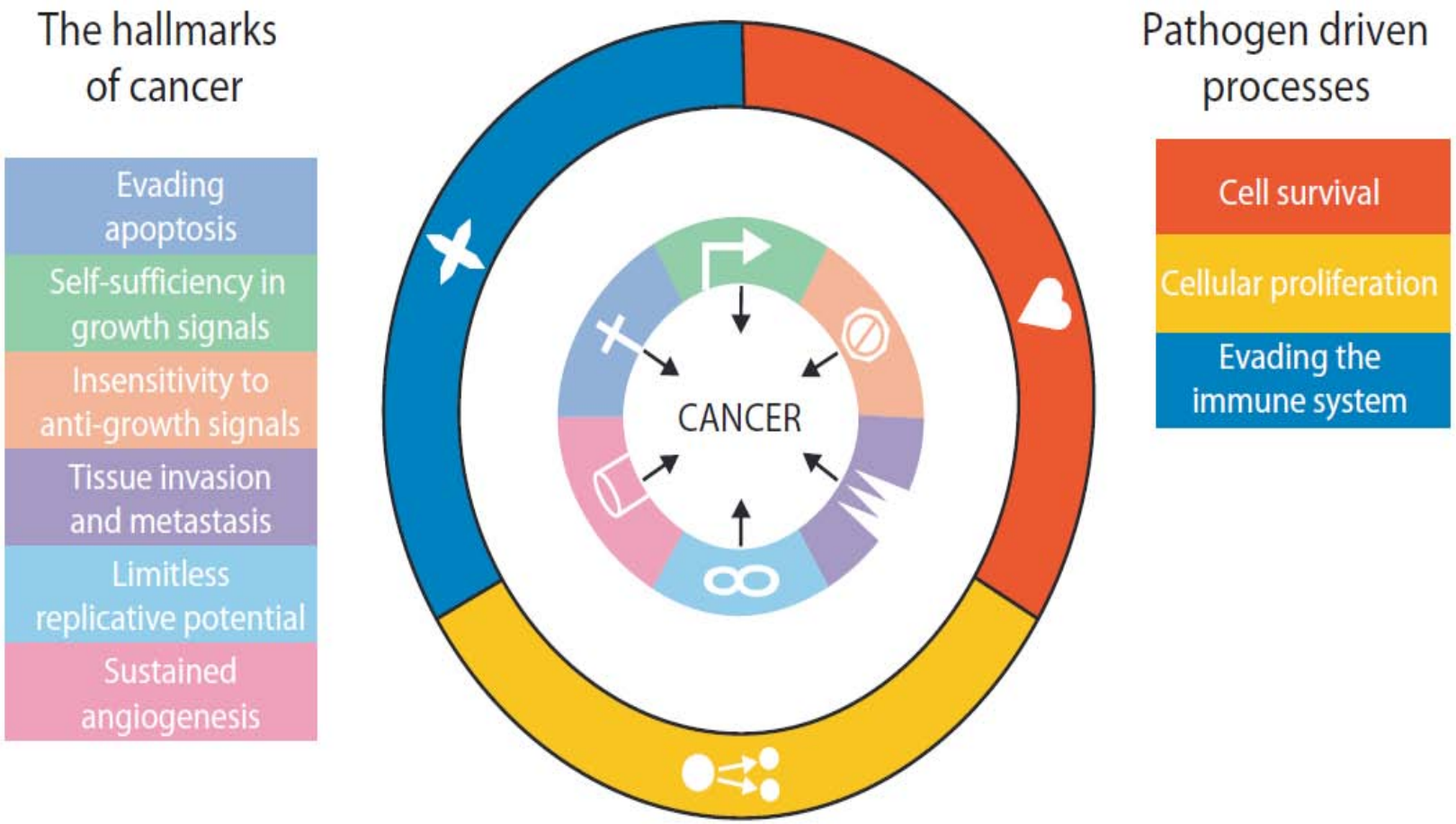
UNG THƯ DO BỆNH TRUYỀN NHIỄM

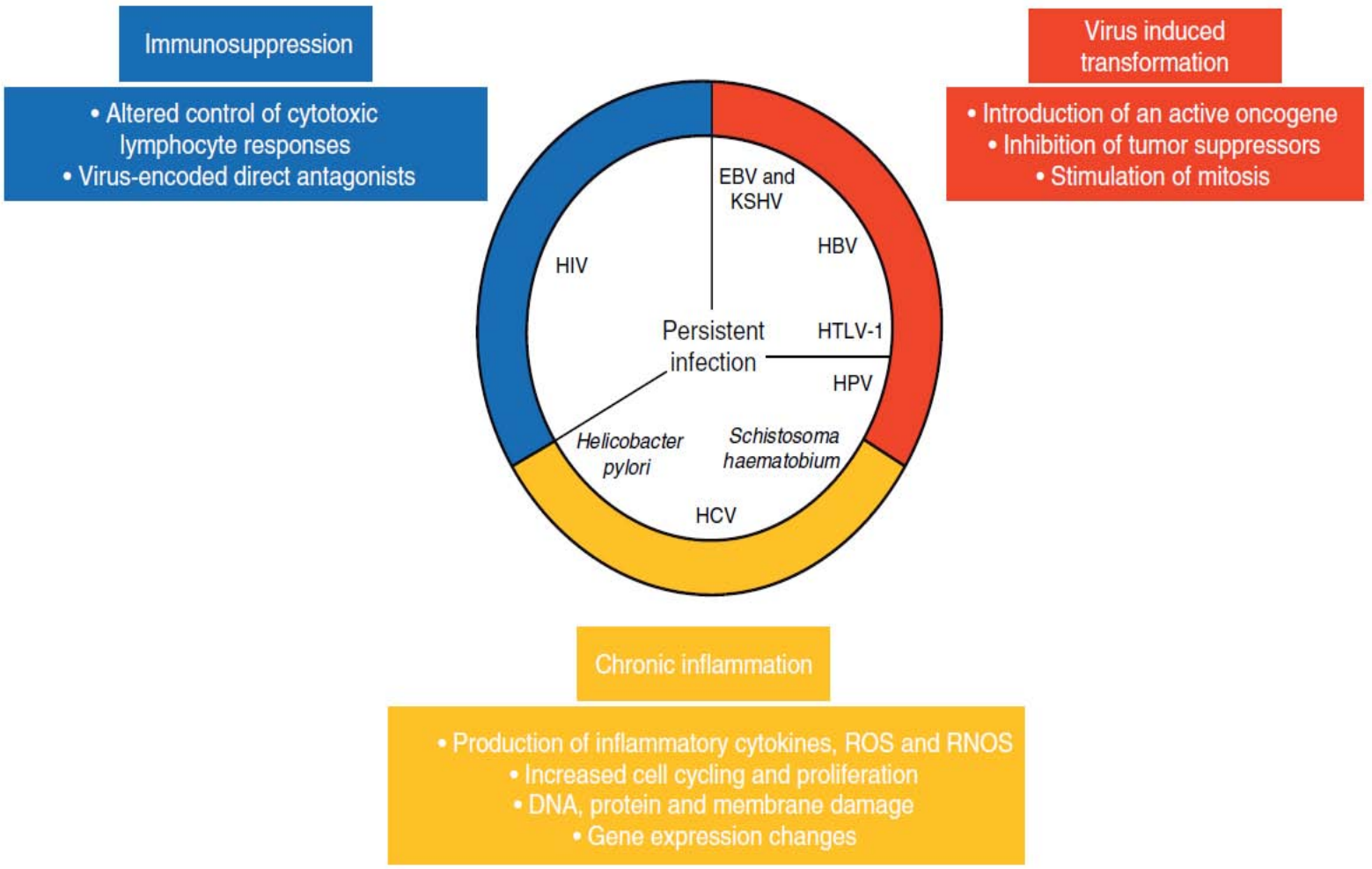
TS. BS Hoàng Anh Vũ
Đại học Y Dược TPHCM

THE DEVELOPMENT OF CANCER IS A COMPLEX MULTISTAGE PROCESS



Continued persistent infection by a pathogen (outer circle) requires host-cell survival (red), host-cell proliferation (yellow), and evasion of the immune system by the pathogen (blue). Alterations in these normally highly regulated pathways can lead to transforming events that have been described as the 'hallmarks of cancer' (inner circle). Accumulation of such events can lead to cancer development. Certain infections may not necessarily cause the infected individual to develop cancer, but may be an associated risk factor (Dalton-Griffin L, *Journal of Biology* 2009)

INFECTIOUS AGENTS CAN CONTRIBUTE TO MALIGNANT TRANSFORMATION BY SEVERAL MECHANISMS.



These can be broadly divided into: chronic inflammation, which drives abnormal levels of cell proliferation (yellow); direct virus-induced transformation of infected cells, leading to increased cell survival (red); and immunosuppression, which allows the pathogen to evade the immune system and persist (blue). EBV, Epstein-Barr virus; HBV, human hepatitis virus B; HCV, hepatitis virus C; HIV, human immunodeficiency virus; HPV, human papillomavirus; HTLV-1, human T-lymphotropic virus 1; KSHV, Kaposi sarcoma-associated herpesvirus

HUMAN VIRUSES ASSOCIATED WITH CANCER DEVELOPMENT

Virus family	Virus	Human tumors	Vaccine
Papillomaviridae	HPV16/18	Cervical, Anogenital and Oesophageus tumors	√
Polyomaviridae	JCV	Brain and Colon tumors	
	SV40	Mesothelioma and Colon tumors	
	MCPyV	Merkel cell carcinoma	
Hepadnaviridae	HBV	Hepatocellular carcinoma	√
Flaviviridae	HCV	Hepatocellular carcinoma	
Herpesviridae	EBV	Nasopharingeal carcinoma, Burkitt's lymphoma, Hodgkin's lymphoma, B-cell lymphoproliferative diseases	
	HHV-8	Kaposis's sarcoma, Primary effusion lymphoma	
Retroviridae	HTLV-1	Adult T-cell leukemia	

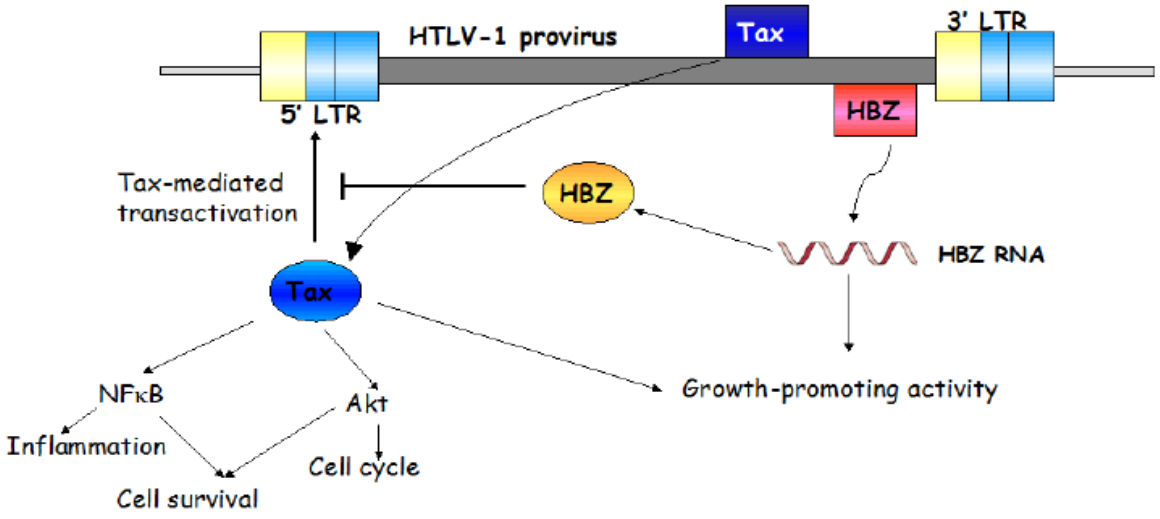
(Bergonzini V, *Infectious Agents and Cancer* 2010)

RNA VIRUS-RELATED ONCOGENIC TRANSFORMATION

A)

Virus	Viral oncoprotein	Cellular targets
HTLV-1	Tax	NFκB, Akt, PDZ protein p300/CBPp53
	HBZ	CREB-2
	p12	MHC-I, STAT-5
HIV	Tat	pRb2/p130
HCV	Core and non structural proteins	hTERT, p53, Rb

B)

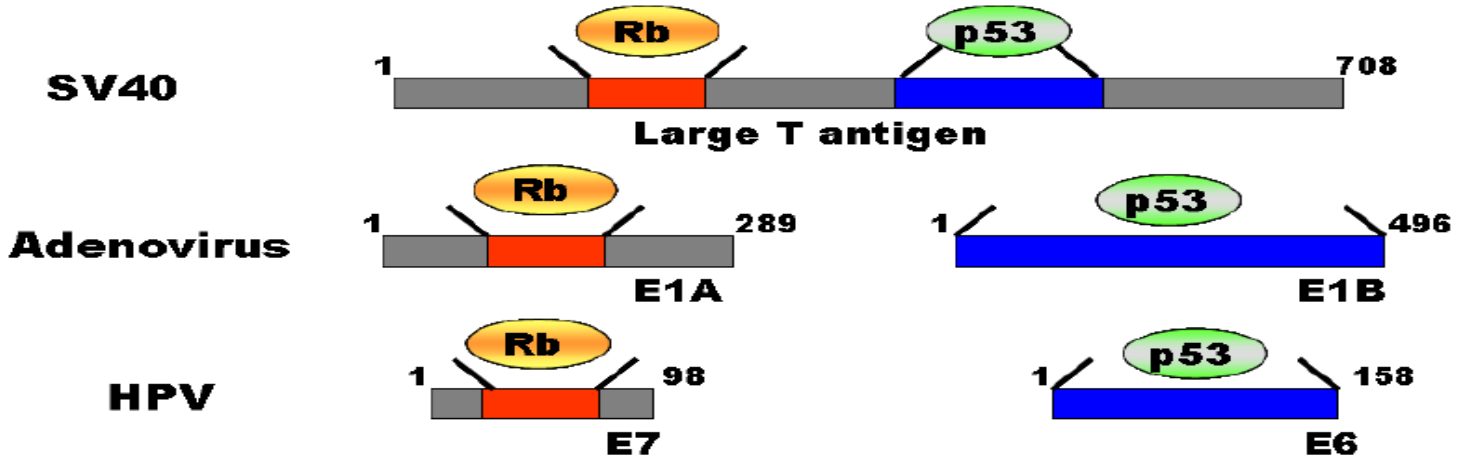


DNA VIRUS-RELATED ONCOGENIC TRANSFORMATION

A)

Virus	Viral oncoprotein	Cellular targets
HPV	E6	p53
	E7	Rb
Adenovirus	E1A	Rb
	E1B	p53
SV40	Large T antigen	p53, Rb
	Small t antigen	PP2A
EBV	LMP1	TRAFs, NF-κB
HBV	X protein	p53

B)

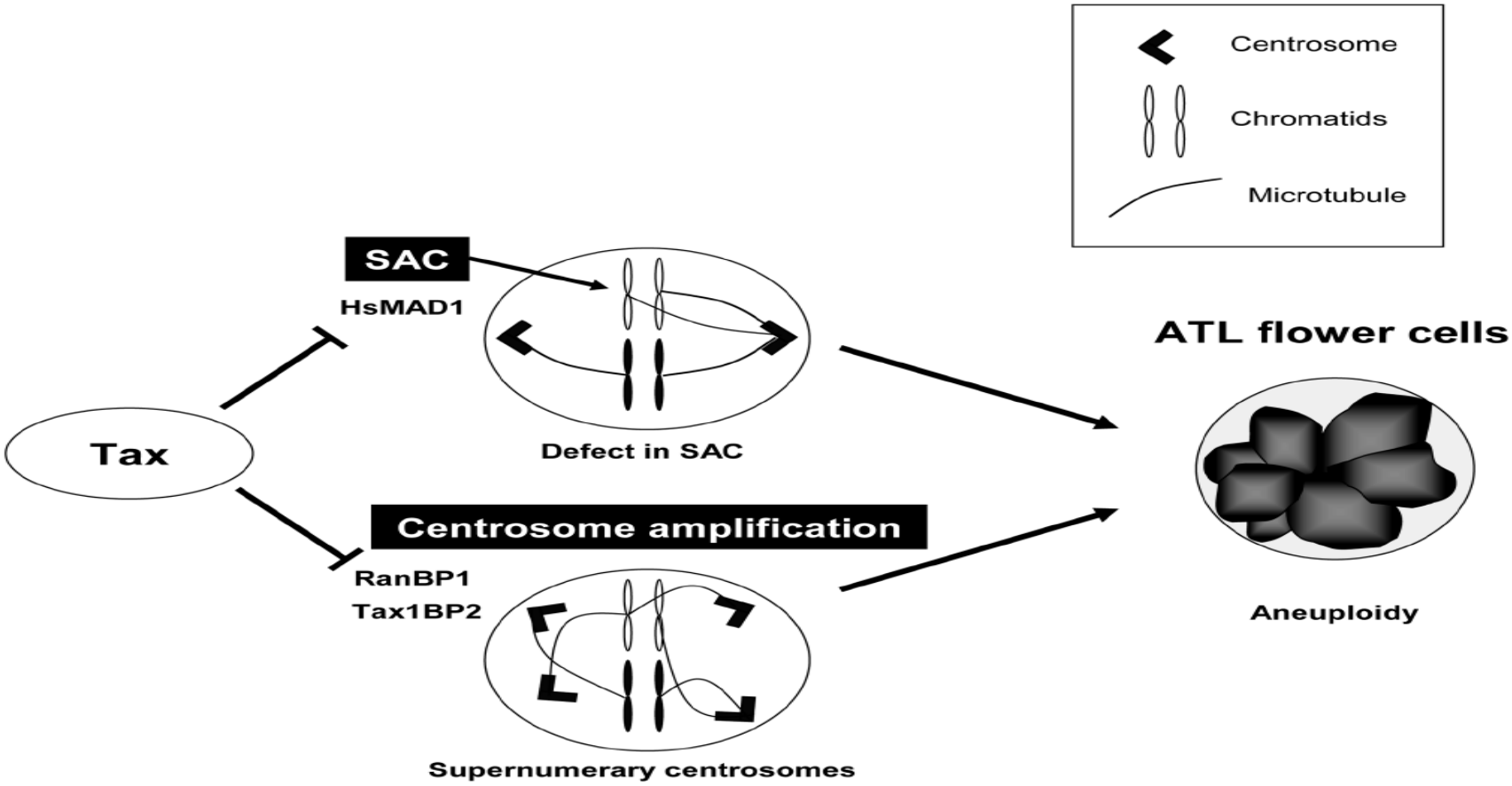


VIRAL PROTEINS ASSOCIATED WITH ANEUPLOIDY

Virus	Malignant diseases	Viral oncoprotein	Induced aberration in mitotic cells	Associated cellular factors
HTLV-I	ATL	Tax	Impairment of SAC	HsMAD1
			Centrosome fragmentation	RanBP1
			Centrosome amplification	Tax1BP2
HPV	Cervical cancer	E6	Centrosome accumulation	p53
	Anogenital cancer			
		E7	Centrosome amplification	pRb
HBV	HCC	HBx	Centriole amplification	Crm1
			Centrosome amplification	Ras-MEK-MAPK pathway
HCV	HCC	NS5A	Centrosome amplification	PKR
				ASPM
EBV	Burkitt's lymphoma	LMP1	Aberrant mitotic spindles	RASSF1A
	Nasopharyngeal carcinoma			
	Hodgkin's disease			
KSHV	Kaposi's sarcoma	K cyclin	Centrosome amplification	CDK6
				NPM1

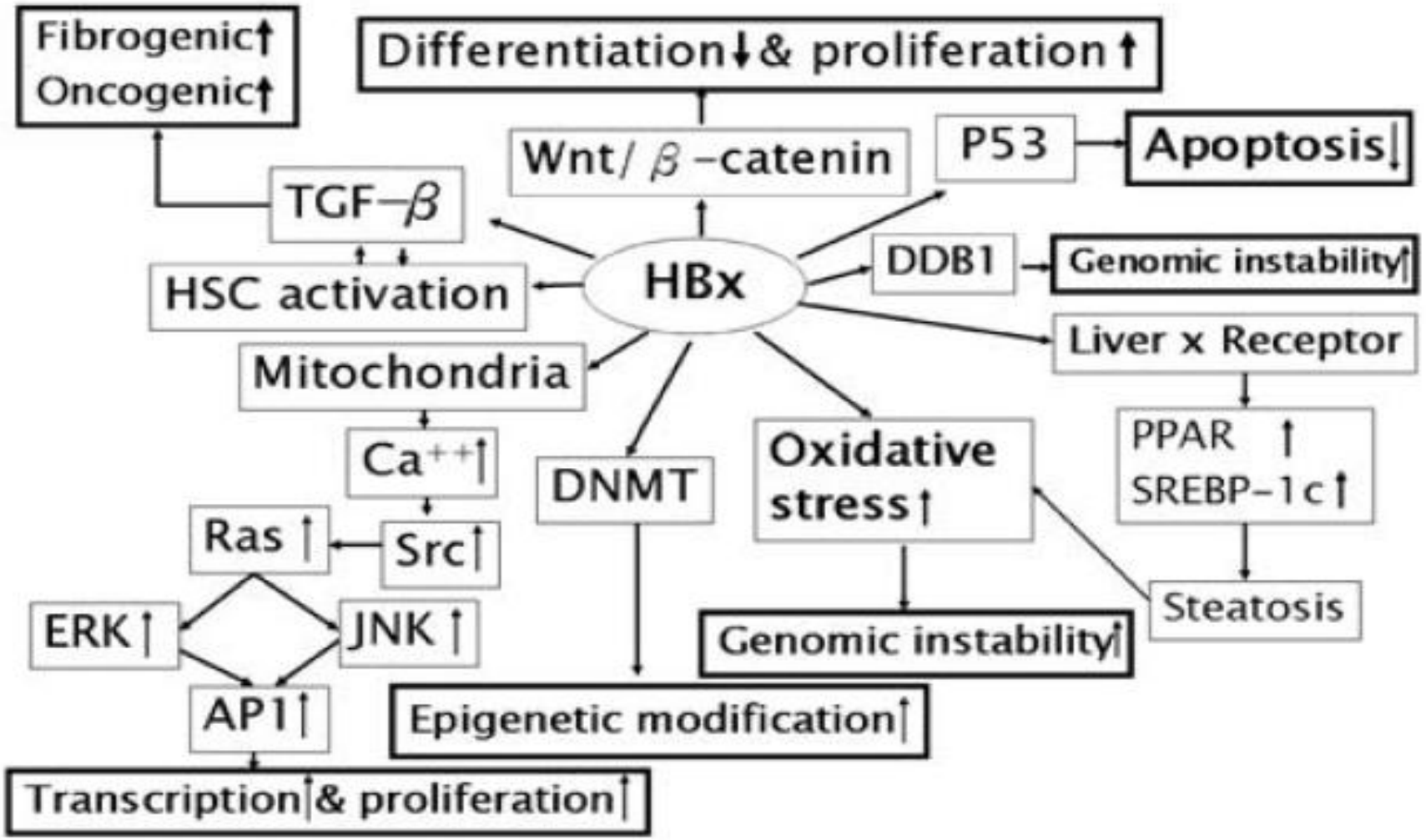
(Yasunaga J, *Environ Mol Mutagen* 2009)

HTLV-I TAX-INDUCED ANEUPLOIDY



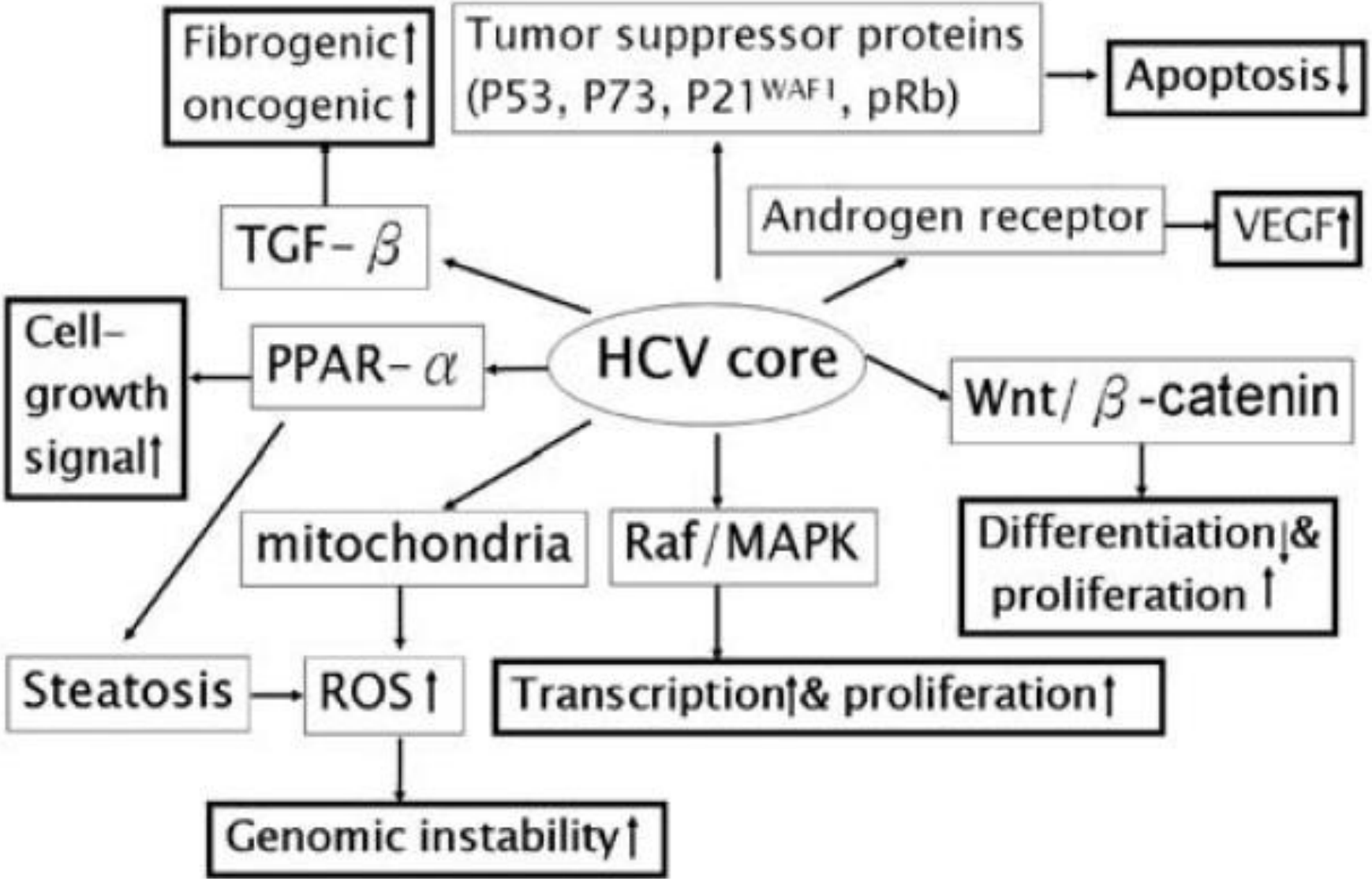
Tax interacts with the spindle assembly checkpoint (SAC) protein, hsMAD1, and inhibits its function. Impairment of SAC permits cells to manifest spontaneous occurrence of unbalanced segregations of chromosomes in mitosis. Separately, Tax can bind RanBP1 and Tax1BP2 which regulate centrosome functions. Tax-induced loss of RanBP1/Tax1BP2 function creates supernumerary centrosomes and multipolar mitotic spindles. A putative result of Tax induced aneuploidy is the presentation of multi-lobulated nuclei in ATL cells, also called “flower cells”.

CELLULAR SIGNALING PATHWAYS IMPLICATED IN HEPATITIS B VIRUS (HBV) X PROTEIN-RELATED HEPATOCARCINOGENESIS.

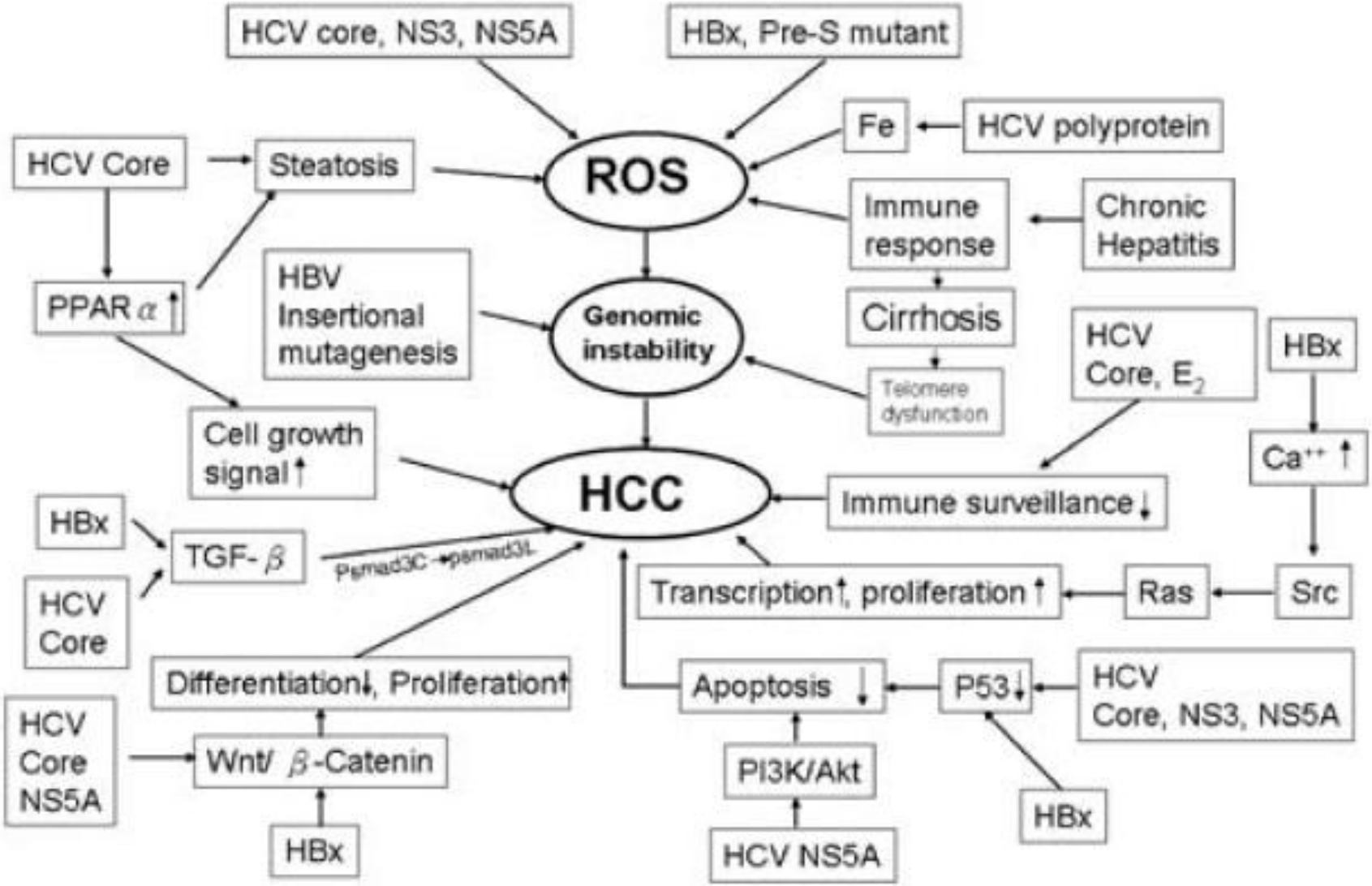


(Tsai W-L, Oncogene 2010)

CELLULAR SIGNALING PATHWAYS IMPLICATED IN HCV CORE PROTEIN-RELATED HEPATOCARCINOGENESIS



A UNIFIED MODEL OF VIRAL HEPATOCARCINOGENESIS



GLOBAL INCIDENCE OF HPV ATTRIBUTABLE CANCER

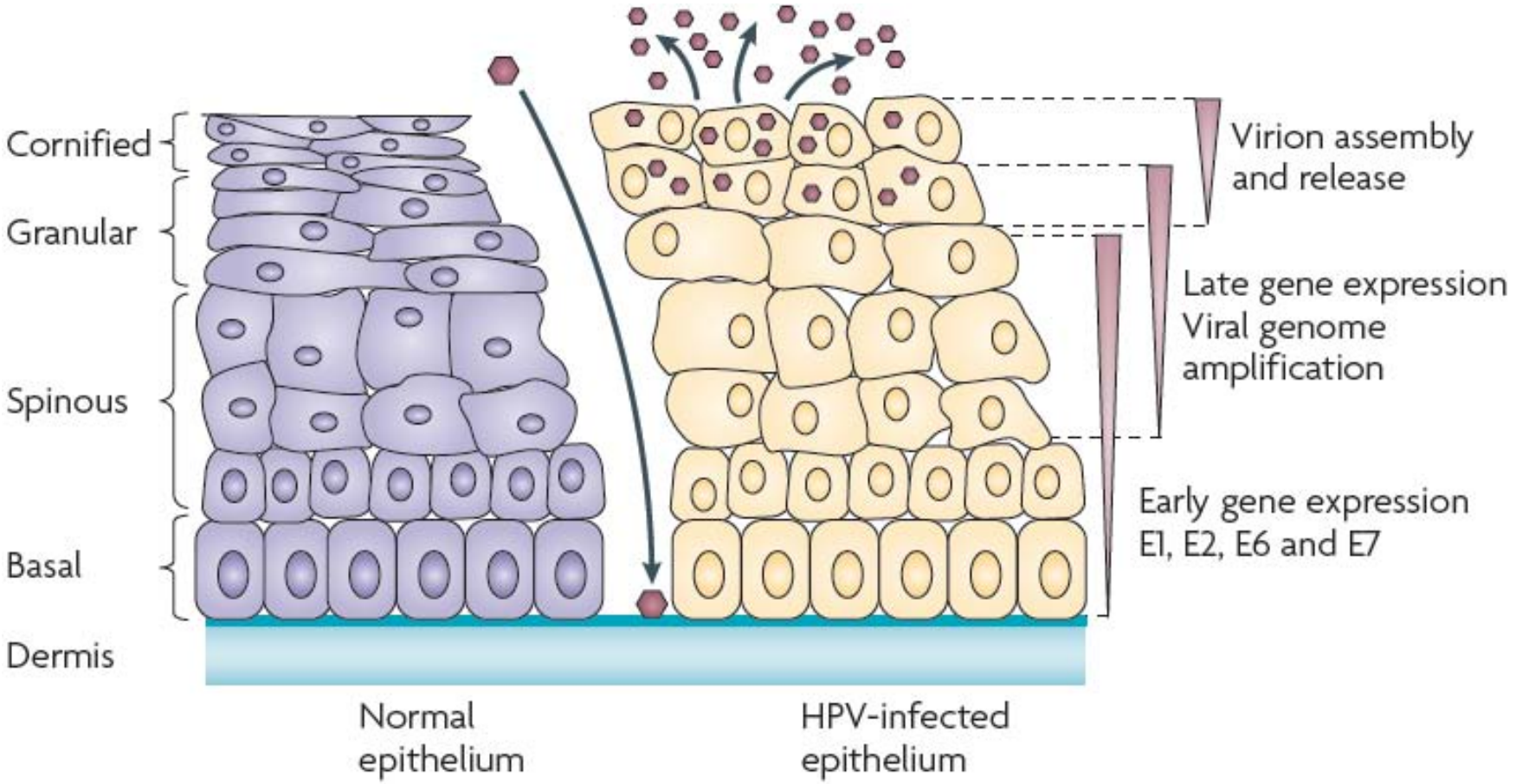
Gender-specific cancers	Human organ site	HPV attribution (%)	Total cancers	Attributable to HPV infection	Per cent of all cancers	HPV 16/18 association (%)	Per cent of all cancers
Females	Uterine cervix	100	492,800	492,800	4.54	344,900 (70)	3.18
	Vulva, vagina	40	40,000	16,000	0.15	12,800 (80)	0.12
Males	Penis	40	26,300	10,500	0.10	6600 (63)	0.06
In both	Anus	90	30,400	27,300	0.25	25,100 (92)	0.23
	Mouth	3	274,300	8200	0.08	7800 (95)	0.07
	Oro-pharynx	12	52,100	6200	0.06	5500 (89)	0.05
	All-sites		10,862,500	561,000	5.17	402,900 (72)	3.71

(Shukla S, Indian J Med Res 2009)

ATTRIBUTION OF HPV INFECTION IN CANCERS OF DIFFERENT ORGAN SITES IN INDIA

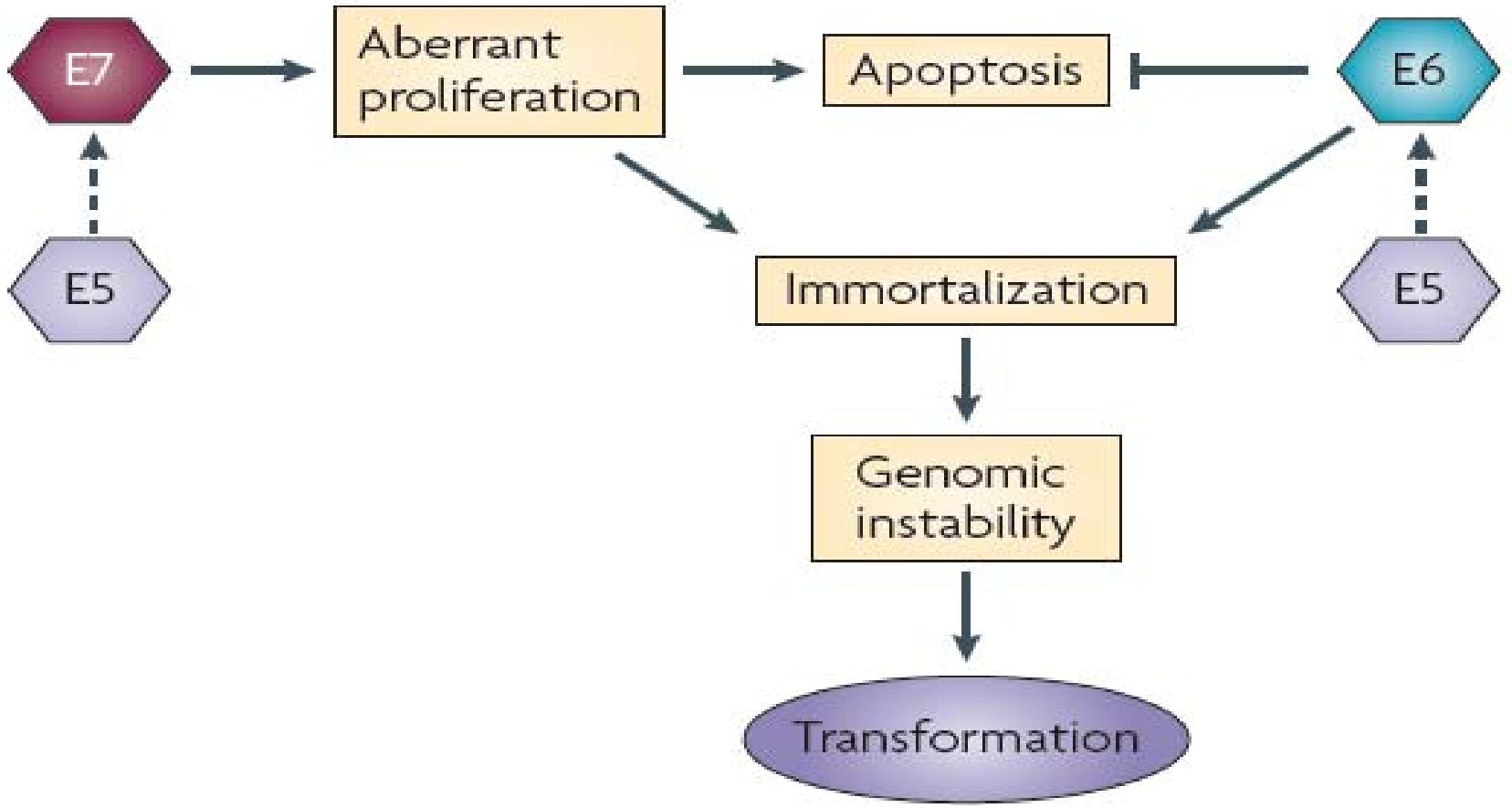
Organ site	HPV prevalence (%)	Prevalence of HPV 16/18 (%)
A. Anogenital cancers		
Uterine Cervix	50-98*	60-90
Anus	0-22	22
Penis	30	30
Ovary	0	0
B. Head and neck cancers		
Oral cavity	15-74	6-47
Esophagus	26.7	18.8
Larynx	30-70	30 (HPV 16),
Naso-pharynx	38.8	ND
C. Other cancers		
Lung	5	5
Urinary bladder	10-20	10-20
Stomach	8.3	8.3 (HPV 16)
Eye	0-17	ND
Breast	0	0

THE LIFE CYCLE OF HUMAN PAPILLOMAVIRUSES



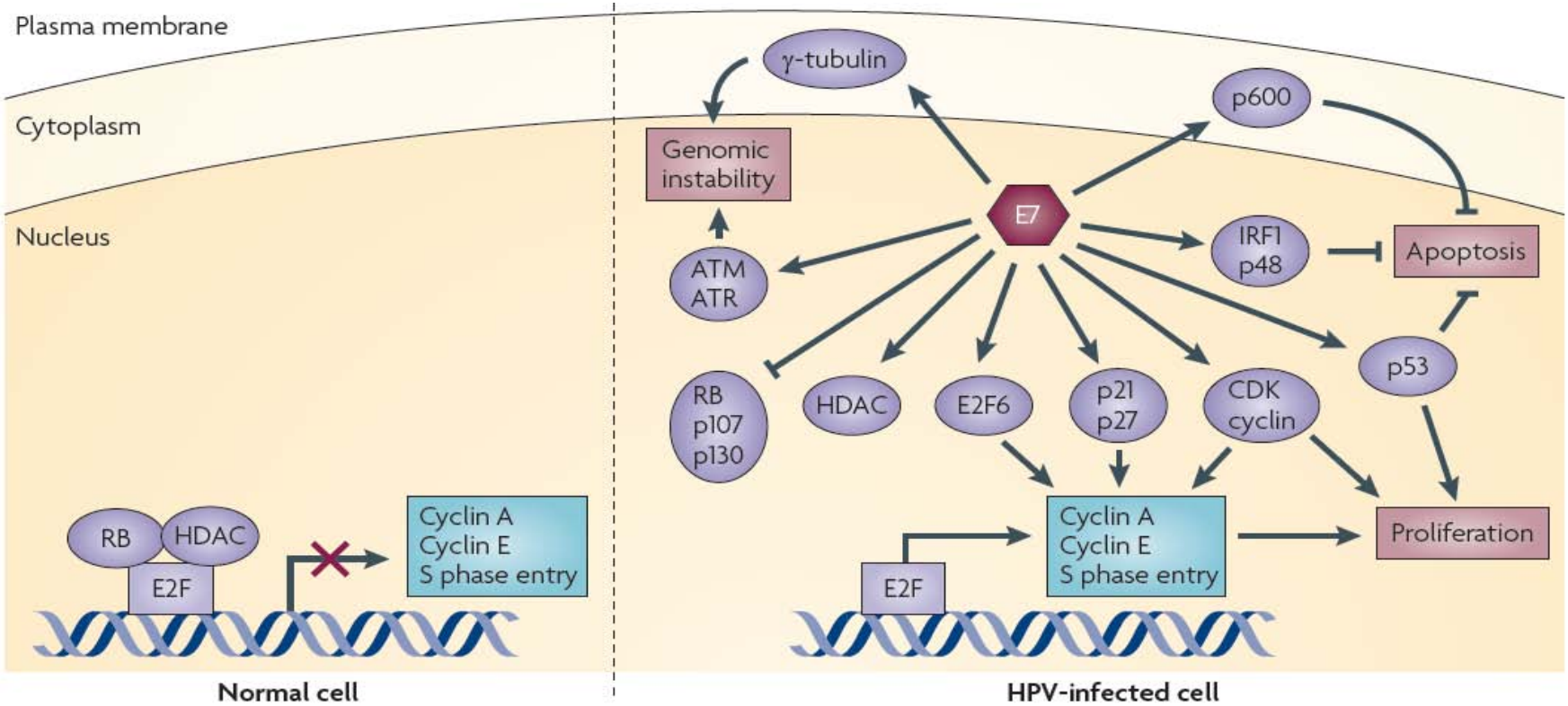
Human papillomaviruses (HPVs) infect keratinocytes in the basal layer of the epithelium that becomes exposed through microwounds. Uninfected epithelium is shown on the left and HPV-infected epithelium is shown on the right. On infection, the viral genomes are established in the nucleus as low-copy episomes and early viral genes are expressed. The viral genomes are replicated in synchrony with cellular DNA replication. After cell division, one daughter cell migrates away from the basal layer and undergoes differentiation. Differentiation of HPV-positive cells induces the productive phase of the viral life cycle, which requires cellular DNA synthesis machinery. The expression of E6 and E7 deregulates cell cycle control, pushing differentiating cells into S phase, allowing viral genome amplification in cells that normally would have exited the cell cycle. The late-phase L1 and L2 proteins encapsidate newly synthesized viral genomes and virions are shed from the uppermost layers of the epithelium (red hexagons). (Moody CA, Nat Rev Cancer 2010)

MOLECULAR MECHANISMS BY WHICH THE HUMAN PAPILLOMAVIRUS ONCOPROTEINS COOPERATE TO INDUCE CERVICAL CARCINOGENESIS



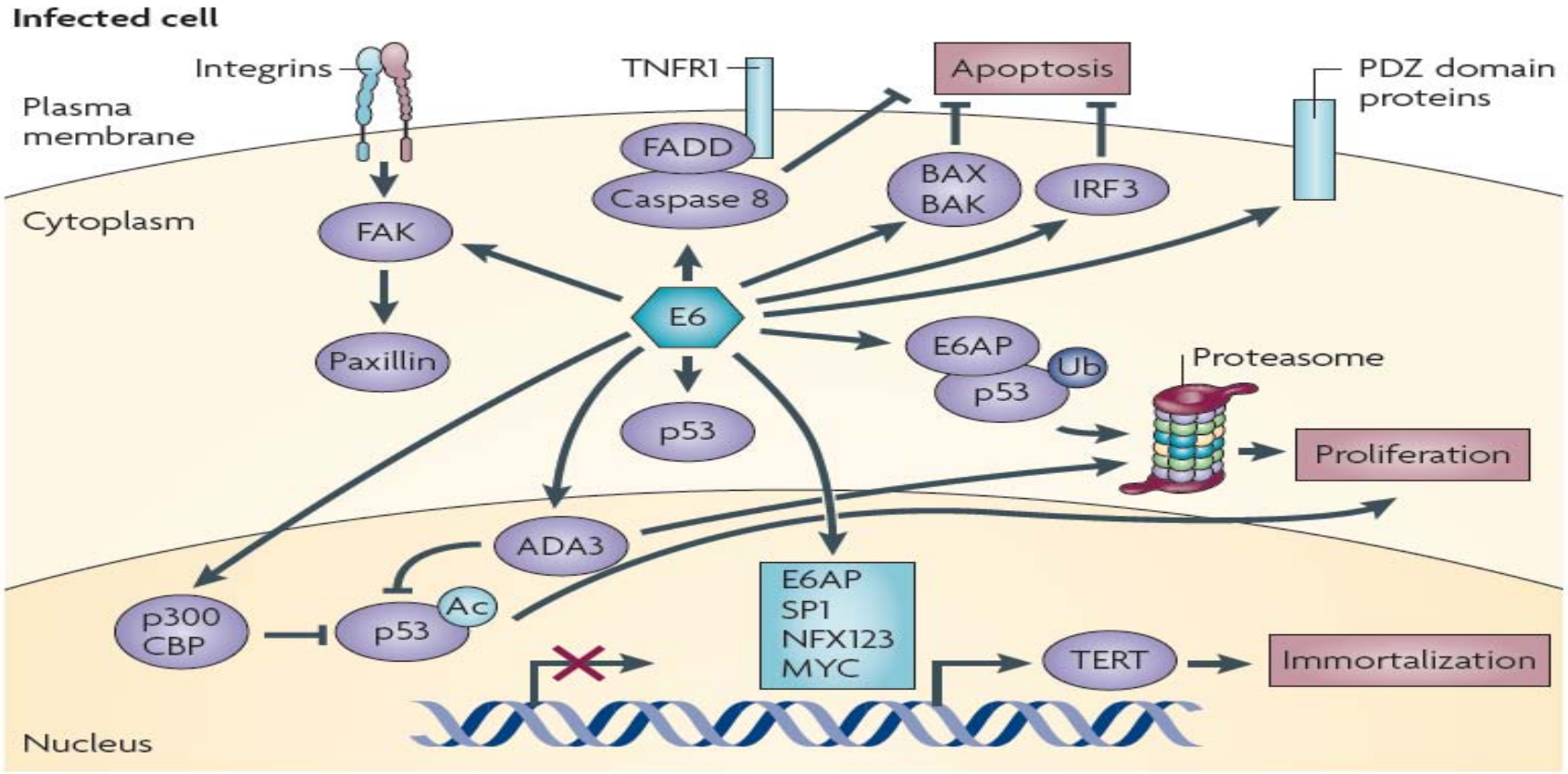
The induction of hyperproliferation by the E7 protein triggers apoptosis, which is blocked by the actions of the E6 protein. The cooperative actions of E6 and E7 efficiently immortalize cells and this process is augmented by the actions of the E5 protein. The ability of E6 and E7 to target crucial regulators of proliferation, apoptosis, immortalization and genomic stability collectively promotes the emergence of a clonal population of cells with a growth advantage and an increased propensity for transformation and malignant progression

THE HPV E7 ONCOPROTEIN AFFECTS NUMEROUS CELLULAR PROCESSES THROUGH INTERACTIONS WITH MULTIPLE HOST CELL PROTEINS



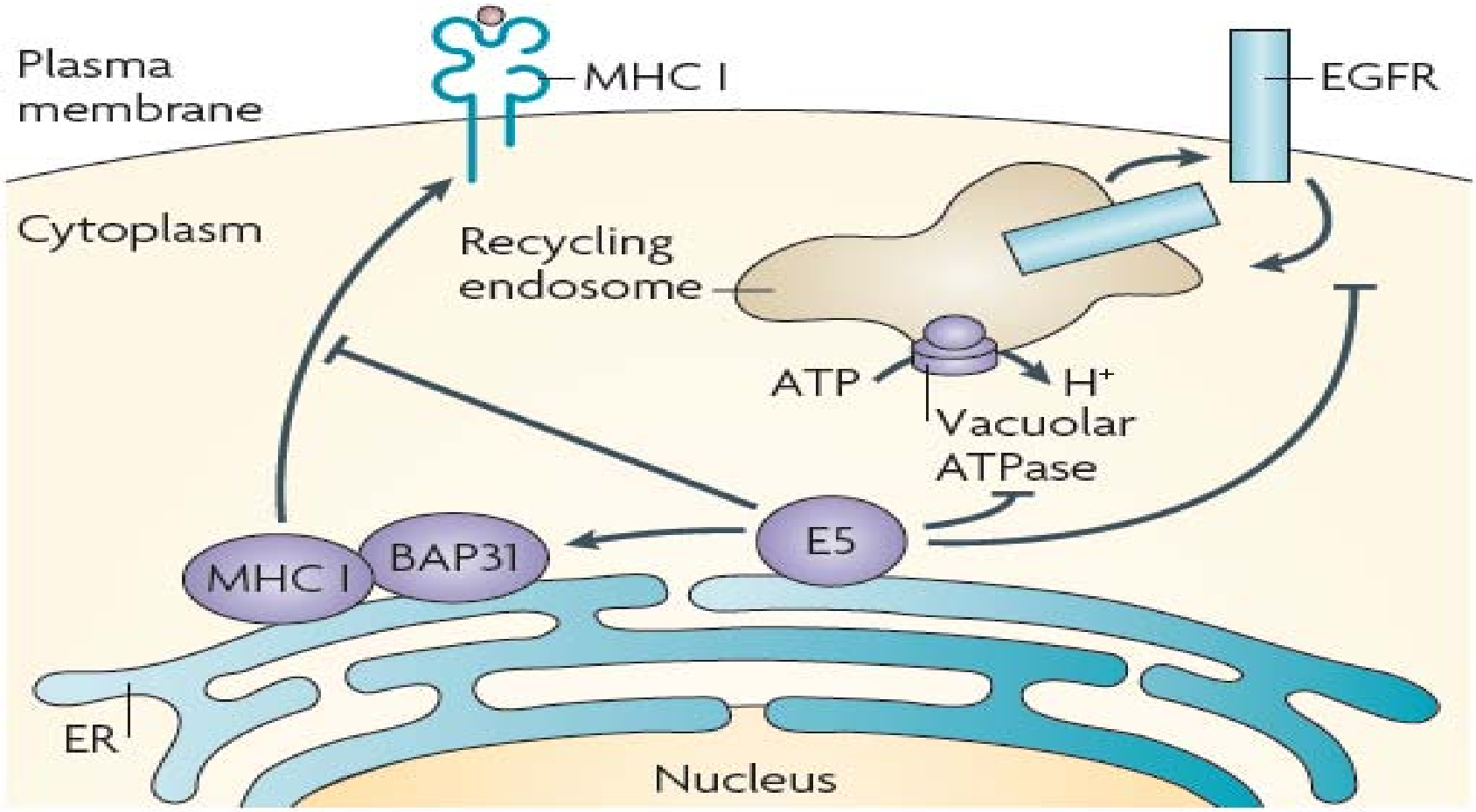
High-risk human papillomavirus (HPV) E7 proteins subvert G1–S arrest and induce hyperproliferation through inhibition of retinoblastoma (RB) family members and constitutive activation of E2F-responsive genes. E7 also affects cellular gene expression through interaction with histone deacetylases (HDACs) and E2F6. E7 further deregulates cell cycle control through inhibition of cyclin-dependent kinase inhibitors (such as p21 and p27), stimulation of cyclins and through direct activation of cyclin-dependent kinase 2 (CDK2). E7 stimulates abnormal centrosome synthesis through increased CDK2 activity and by interacting with γ-tubulin, leading to an increased risk of genomic instability. E7 induces DNA damage and activation of the ATM–ATR pathway (ataxia telangiectasia-mutated–ATM and RAD3-related DNA damage response) which may contribute to the accumulation of chromosomal alterations. Co-expression of HPV E6 with E7 abrogates p53-dependent apoptosis in response to the activities of E7, allowing replication in the presence of DNA damage and increased chromosomal instability. The interaction of E7 with p600 prevents anoikis and allows anchorage-independent growth, promoting malignant progression. E7 interacts with components of the interferon (IFN) response (IFN regulatory factor 1 (IRF1) and p48), contributing to escape from immune surveillance and the establishment of a persistent infection.

CELLULAR PROTEINS AND SIGNALLING PATHWAYS AFFECTED BY THE HUMAN PAPILLOMAVIRUS E6 ONCOPROTEIN



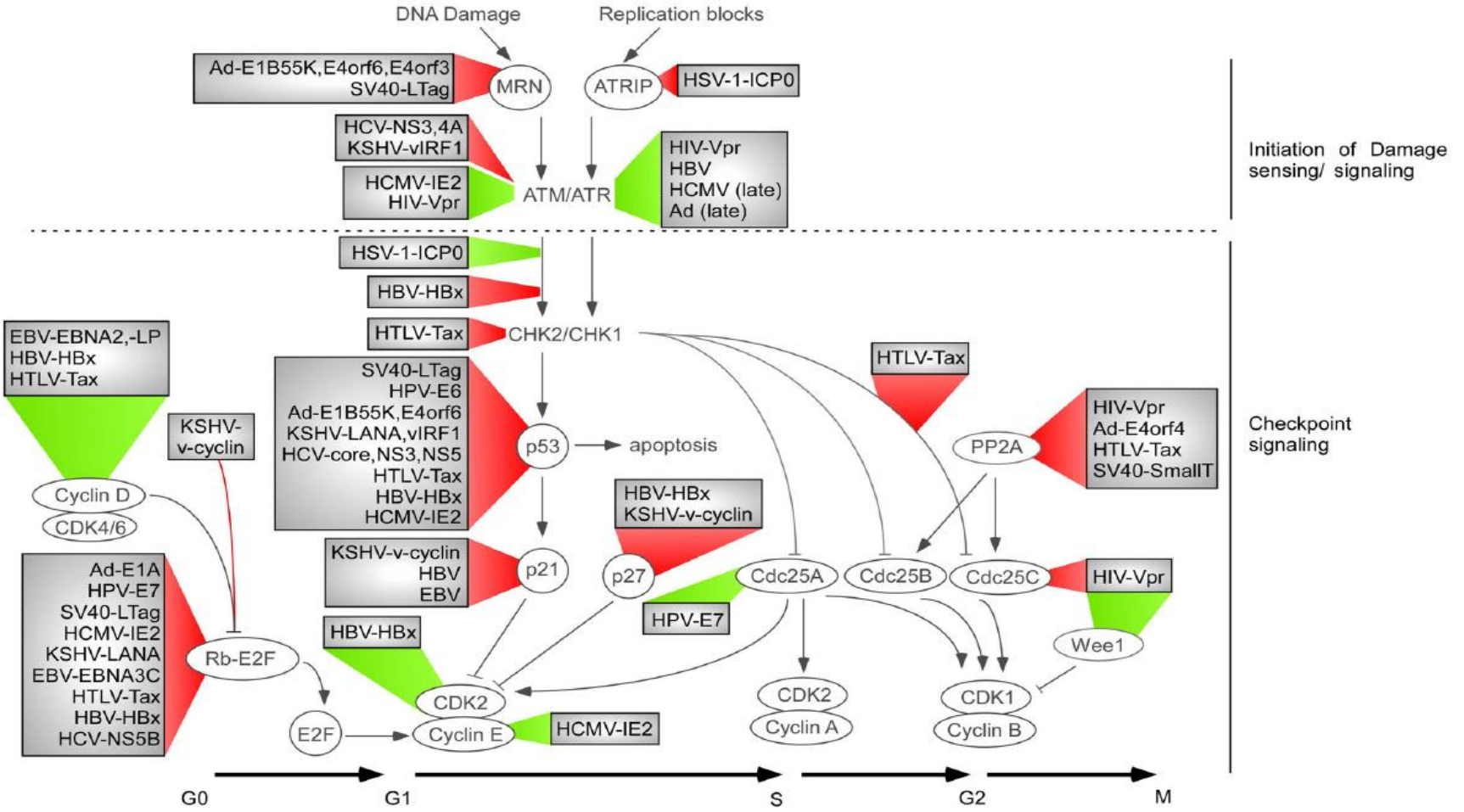
High-risk E6 proteins inhibit p53-dependent growth arrest and apoptosis in response to aberrant proliferation through several mechanisms, resulting in the induction of genomic instability and the accumulation of cellular mutations. Formation of an E6–E6-associated protein (E6AP)–p53 trimeric complex results in p53 degradation, and the interaction of E6 with the histone acetyltransferases p300, CREB binding protein (CBP) and ADA3 prevents p53 acetylation (Ac), inhibiting the transcription of p53-responsive genes. E6 also inhibits apoptotic signalling in response to growth-suppressive cytokines through interaction with the tumour necrosis factor (TNF)-α receptor TNFR1, FAS-associated protein with death domain (FADD) and caspase 8, and through the degradation of pro-apoptotic BAX and BAK. The interaction of E6 with SP1, MYC, nuclear transcription factor, X box-binding protein-123 (NFX123) and E6AP activates telomerase reverse transcriptase (TERT) and telomerase, preventing telomere shortening in response to persistent proliferation and in turn promoting immortalization. E6-mediated degradation of PDZ proteins leads to loss of cell polarity and induces hyperplasia. The interaction of E6 with the focal adhesion protein paxillin and the extracellular matrix protein fibulin prevents anoikis and allows cellular growth in the absence of attachment to extracellular matrix. E6 subverts the interferon (IFN) response through interaction with IFN regulatory factor 3 (IRF3) and through the inhibition of p53 activity. FAK, focal adhesion kinase; Ub, ubiquitin.

HIGH-RISK E5 INTERACTIONS WITH CELLULAR PATHWAYS AND FACTORS



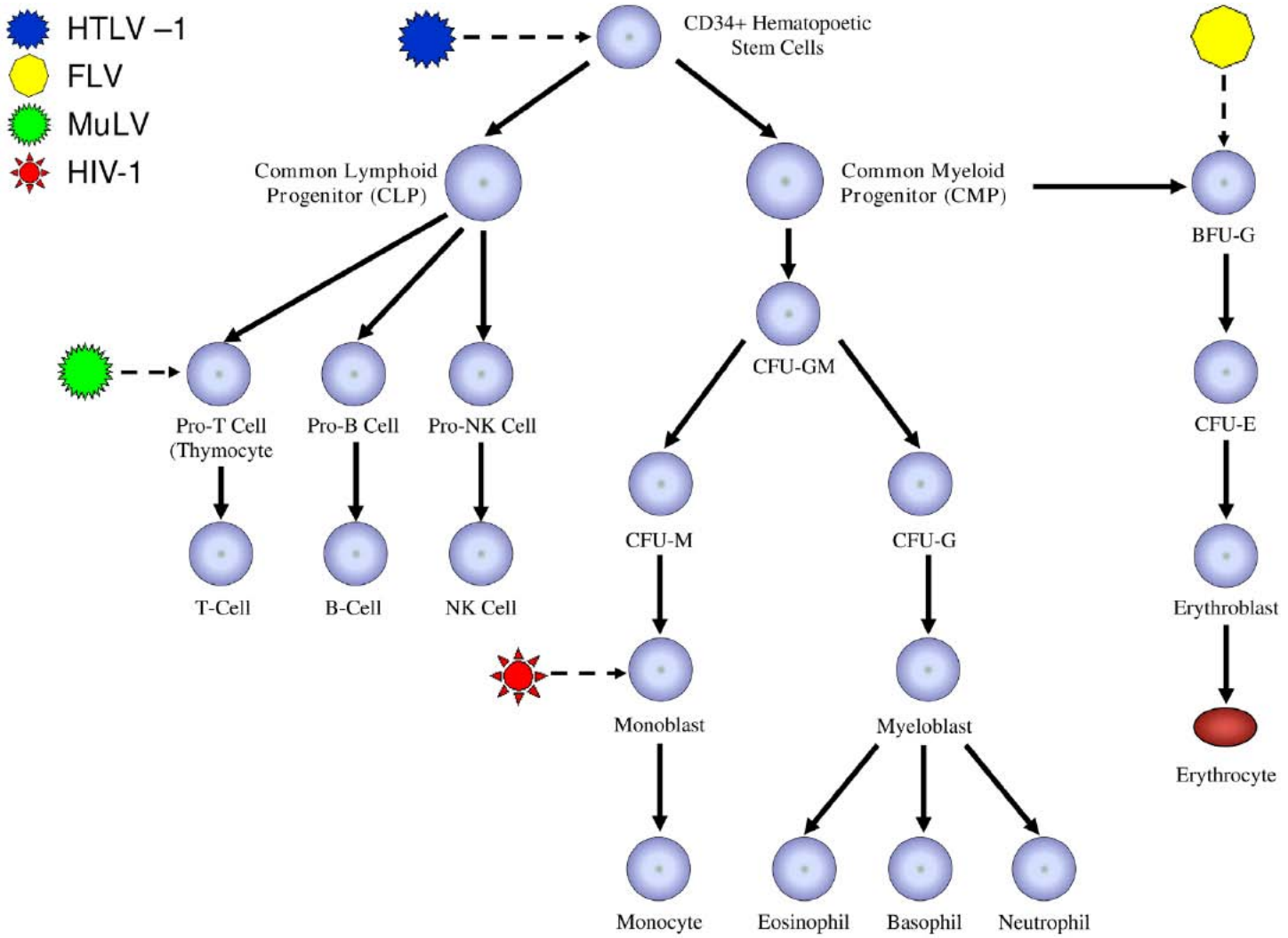
E5 contributes to the actions of E6 and E7 by modulating the transit of signalling proteins through the endoplasmic reticulum (ER) as well as by interacting with factors such as B cell receptor-associated protein 31 (BAP31) and the vacuolar H+-ATPase in endosomes. E5 expression results in increased epidermal growth factor receptor (EGFR) signalling and activation of the MAPK pathway, which augments the activities of E6 and E7, resulting in aberrant proliferation. The interaction of E5 with the vacuolar H+-ATPase may promote recycling of receptors to the cell surface by impairing organelle acidification, resulting in constitutive signalling. E5 has been reported to reduce levels of major histocompatibility complex class I (MHC I) at the cell surface, which may occur through its interaction with the ER protein BAP31, and prevent clearance of infected cells by the immune response.

VIRAL INTERACTIONS WITH ATM/ATR CHECKPOINT PATHWAYS AND CELL CYCLE REGULATORS



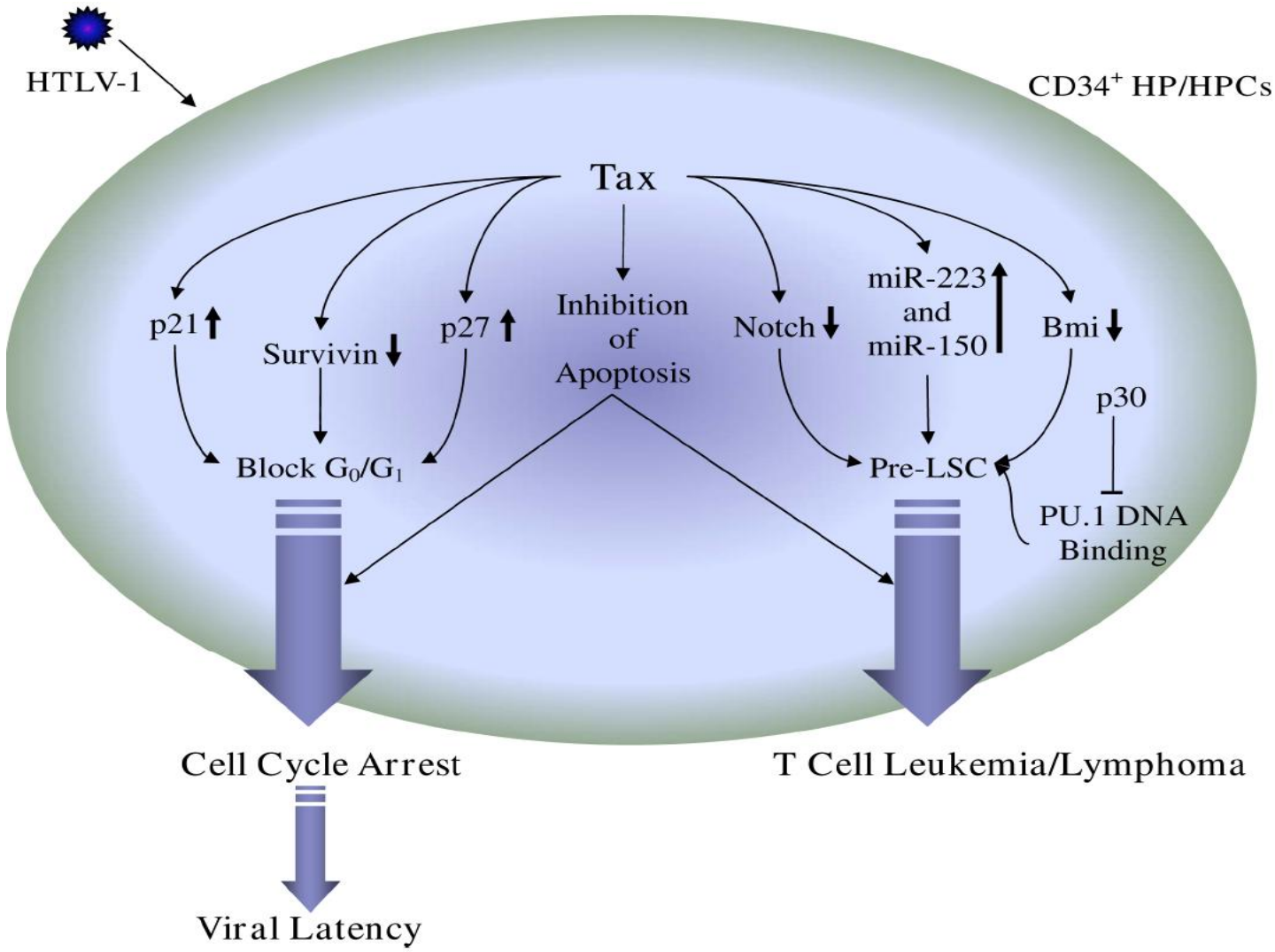
Grey circles and arrows indicate cellular proteins and regulatory networks. Viral proteins boxed in green denote interactions that promote cell cycle progression. Effects of the viral proteins (shaded boxes) on their cellular substrates are indicated by the shaded triangles. Red triangles indicate interactions that are inhibitory to the targeted cellular factors, and green triangles denote interactions that promote activity of the targeted cellular factors. The interactions listed are limited to those covered in this review, and many more viral examples exist that have not been covered here. (Chaurushiya MS, *DNA Repair* 2009)

HEMATOPOIESIS AND RETROVIRAL INFECTION



CD34+ hematopoietic stem cells (HSCs) can undergo self-renewal as well as undergoing maturation to give rise to common lymphoid progenitor (CLP) and common myeloid progenitor (CMP) cells, which serve as precursors to all lymphoid and myeloid cells respectively. HSCs as well as other lineage specific progenitors are permissive for infection by a variety of murine and human retroviruses including HIV-1 and HTLV-1 (Baneriee P, Retrovirology 2010).

THE ROLE OF HTLV-1 INFECTION OF HSC



Potential Mechanisms for Generation of an Infectious Leukemic Stem Cell (ILSC/ICSC). HTLV-1 infection and subsequent Tax1 expression can lead to either cell cycle arrest or generation of pre-leukemic stem cells (pre-LSC/CSC) from infected CD34+ hematopoietic progenitor and stem cells (HP/HSCs).

CHRONIC BACTERIAL AND PARASITIC INFECTIONS AND CANCER

Pathogens	**Main associated cancer**
***Salmonella*Typhi**	Gallbladder carcinoma Hepatobiliary carcinoma Carcinomas in pancreas, lung and colorectum
Chlamydia species 1.*Chlamydia pneumoniae* 2. *Chlamydia trachomatis* 3. *Chlamydia psittaci*	 Lung carcinoma Ovarian carcinoma Ocular lymphoma
Mycobacterium tuberculosis	Lung carcinoma Kaposi's sarcoma
Schistosoma species 1.*Schistosoma haematobium* 2. *Schistosoma mansoni* 3. *Schistosoma japonicum*	 Bladder carcinoma Cervical carcinoma Colorectal carcinoma Liver carcinoma Colorectal carcinoma
Tropheryma whippelii	Lymphoma Gastric adenocarcinoma
Liver flukes 1.*Opisthorchis viverrini* 2. *Clonorchis sinensis*	 Cholangiocarcinoma Cholangiocarcinoma
Various causative agents of Chronic Osteomyelitis	Squamous cell carcinoma of the skin Basal cell carcinoma of the skin Fibrosarcoma Myeloma Angiosarcoma Rhabdomyosarcoma
Various causative agents of Hidradenitis Suppurativa	Lymphoma Squamous cell carcinoma of the skin Liver carcinoma

RISK FACTORS FOR GASTRIC CANCER

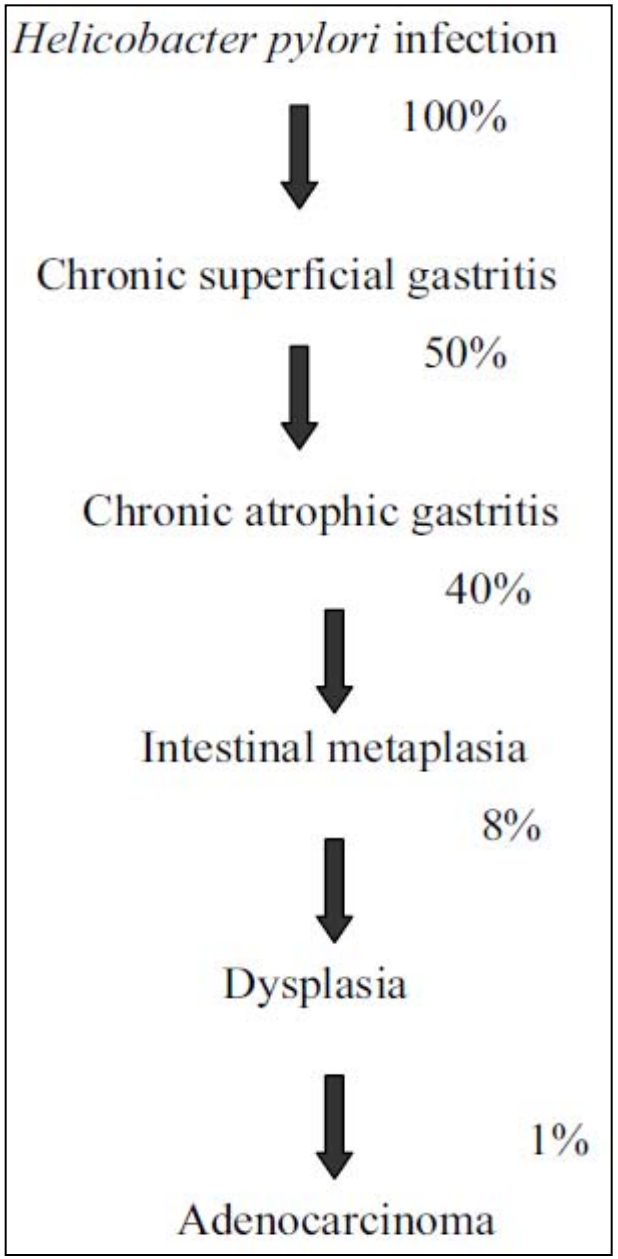
Definite: surveillance suggested
- Familial adenomatous polyposis
- Gastric adenomas
- Gastric biopsy revealing high-grade dysplasia

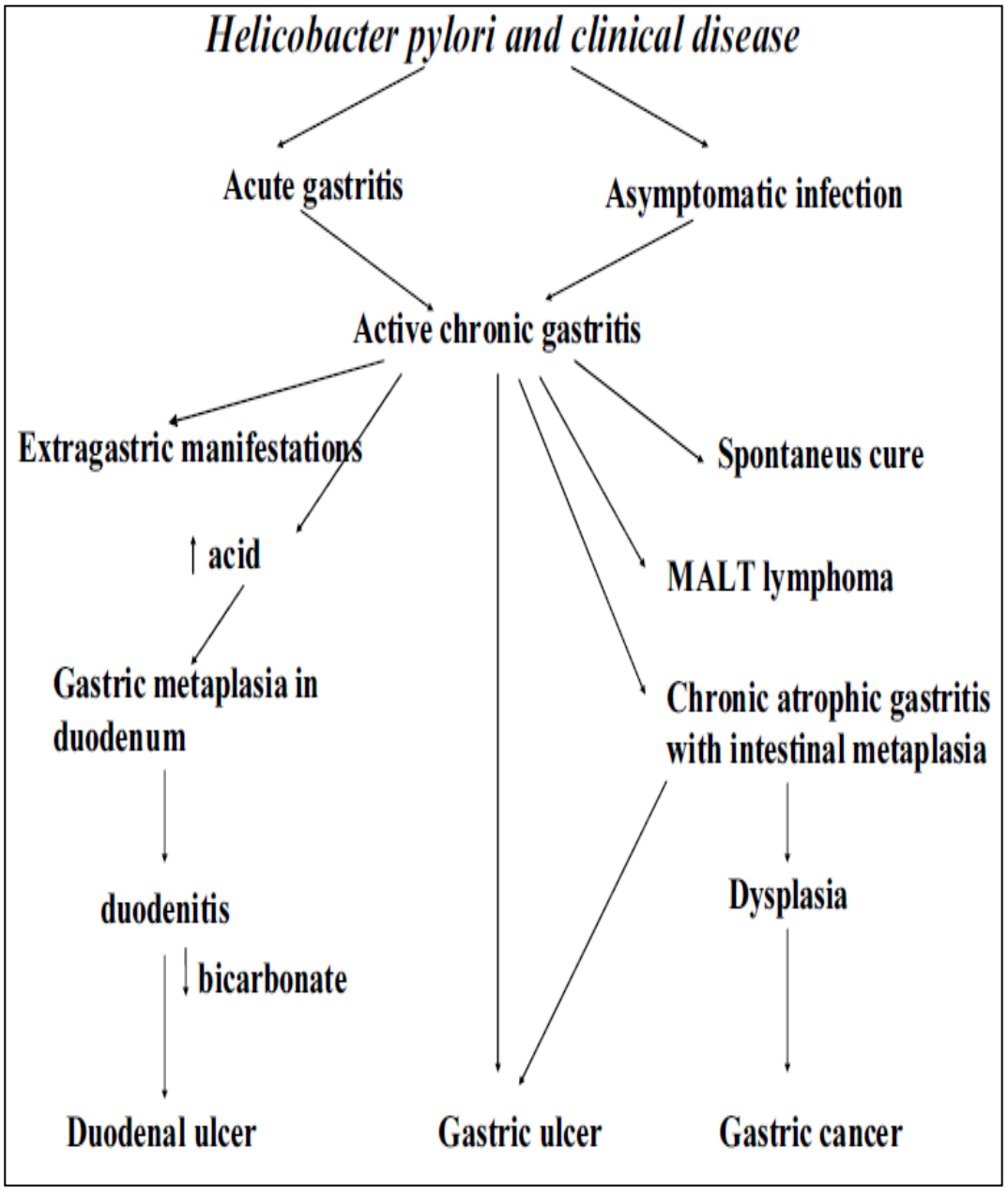
Definite
- Chronic atrophic gastritis
- Gastric metaplasia or biopsy
- *Helicobacter pylori* infection
- Hereditary nonpolyposis colorectal cancer (Lynch II syndrome)

Probable
- History of subtotal gastrectomy (>20 years)
- Pernicious anemia
- Tobacco smoking (adenocarcinoma of cardia)

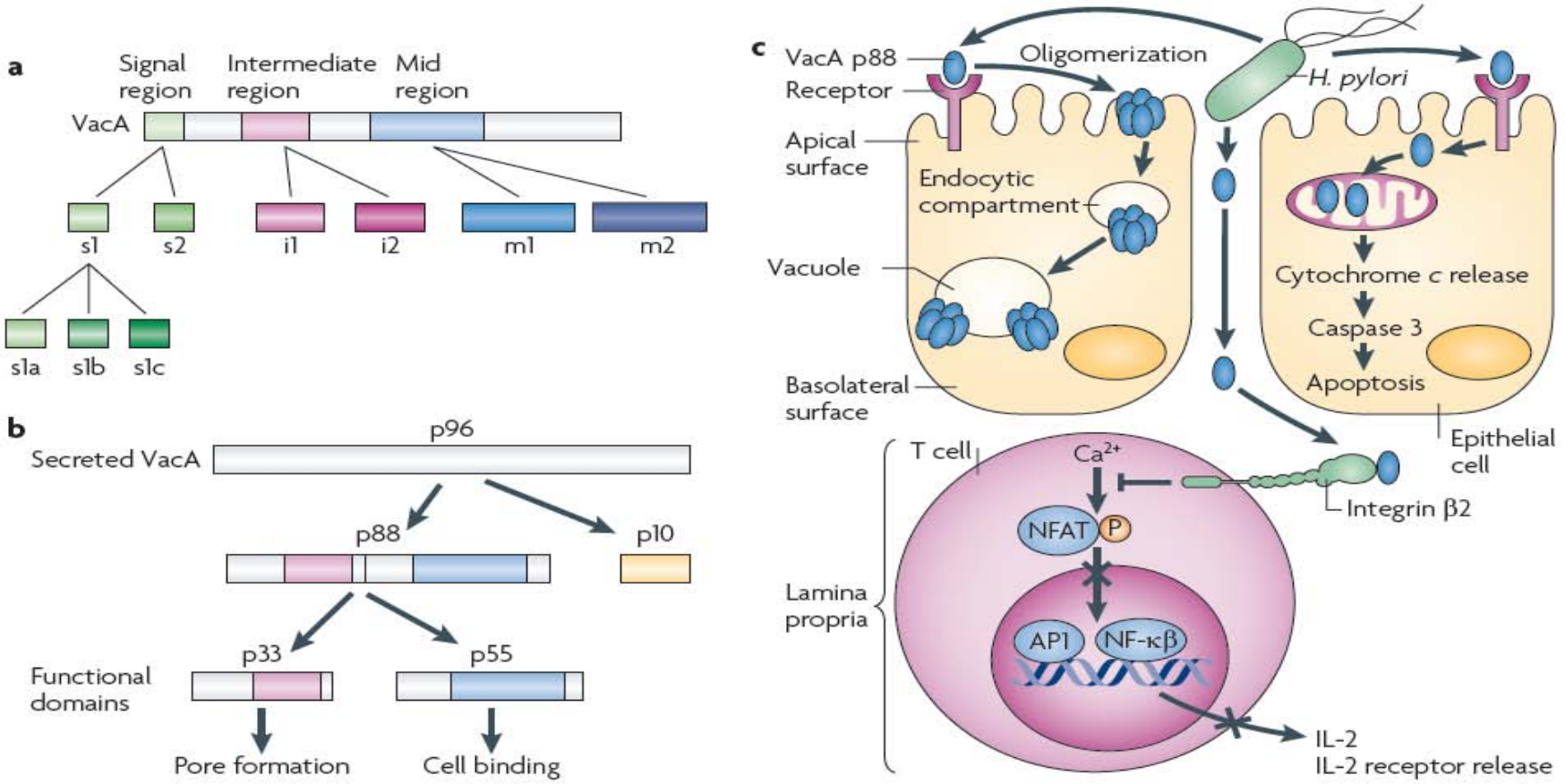
Possible
- Excess alcohol ingestion
- Hamartomas
- High intake of salted, pickled, or smoked foods
- Low intake of fruits and vegetables
- Ménétrier's disease
- Peutz-Jeghers syndrome
- Tobacco smoking

Questionable
- Benign gastric ulcers
- Fundic gland polyps
- Hyperplastic polyps


Helicobacter pylori infection
100%
Chronic superficial gastritis
50%
Chronic atrophic gastritis
40%
Intestinal metaplasia
8%
Dysplasia
1%
Adenocarcinoma


Helicobacter pylori and clinical disease
Acute gastritis
Asymptomatic infection
Active chronic gastritis
Extragastric manifestations
↑ acid
Spontaneus cure
MALT lymphoma
Gastric metaplasia in duodenum
Chronic atrophic gastritis with intestinal metaplasia
duodenitis
↓ bicarbonate
Dysplasia
Duodenal ulcer
Gastric ulcer
Gastric cancer

HELICOBACTER PYLORI VacA STRUCTURE AND FUNCTIONAL EFFECTS.



a | vacA is a polymorphic mosaic gene that arose through homologous recombination. Regions of sequence diversity are localized to the signal (s), intermediate (i) and mid (m) region. The s1 signal region is fully active, but the s2 region encodes a protein with a different signal peptide cleavage site, resulting in a short amino-terminal extension that inhibits vacuolation. The mid region encodes a cell-binding site, but the m2 allele is attenuated in its ability to induce vacuolation. The function of the i region is undefined. **b | VacA is secreted** as a 96 kDa protein, which is rapidly cleaved into a 10 kDa passenger domain (p10) and an 88 kDa mature protein (p88). The p88 fragment contains two domains, designated p33 and p55, which are VacA functional domains. **c | The secreted** monomeric form of VacA p88 binds to epithelial cells nonspecifically and through specific receptor binding. Following binding, VacA monomers form oligomers, which are then internalized by a pinocytic-like mechanism and form anion-selective channels in endosomal membranes; vacuoles arise owing to the swelling of endosomal compartments. The biological consequences of vacuolation are currently undefined, but VacA also induces other effects, such as apoptosis, partly by forming pores in mitochondrial membranes, allowing cytochrome *c release. VacA has also been* identified in the lamina propria, and probably enters by traversing epithelial paracellular spaces, where it can interact with integrin β2 on T cells and inhibit the transcription factor nuclear factor of activated T cells (NFAT), leading to the inhibition of interleukin-2 (IL-2) secretion and blockade of T cell activation and proliferation. AP1, activator protein 1; NF-κB, nuclear factor-κB; P, phosphorylation (Polk BD, *Nat Rev Cancer* 2010)

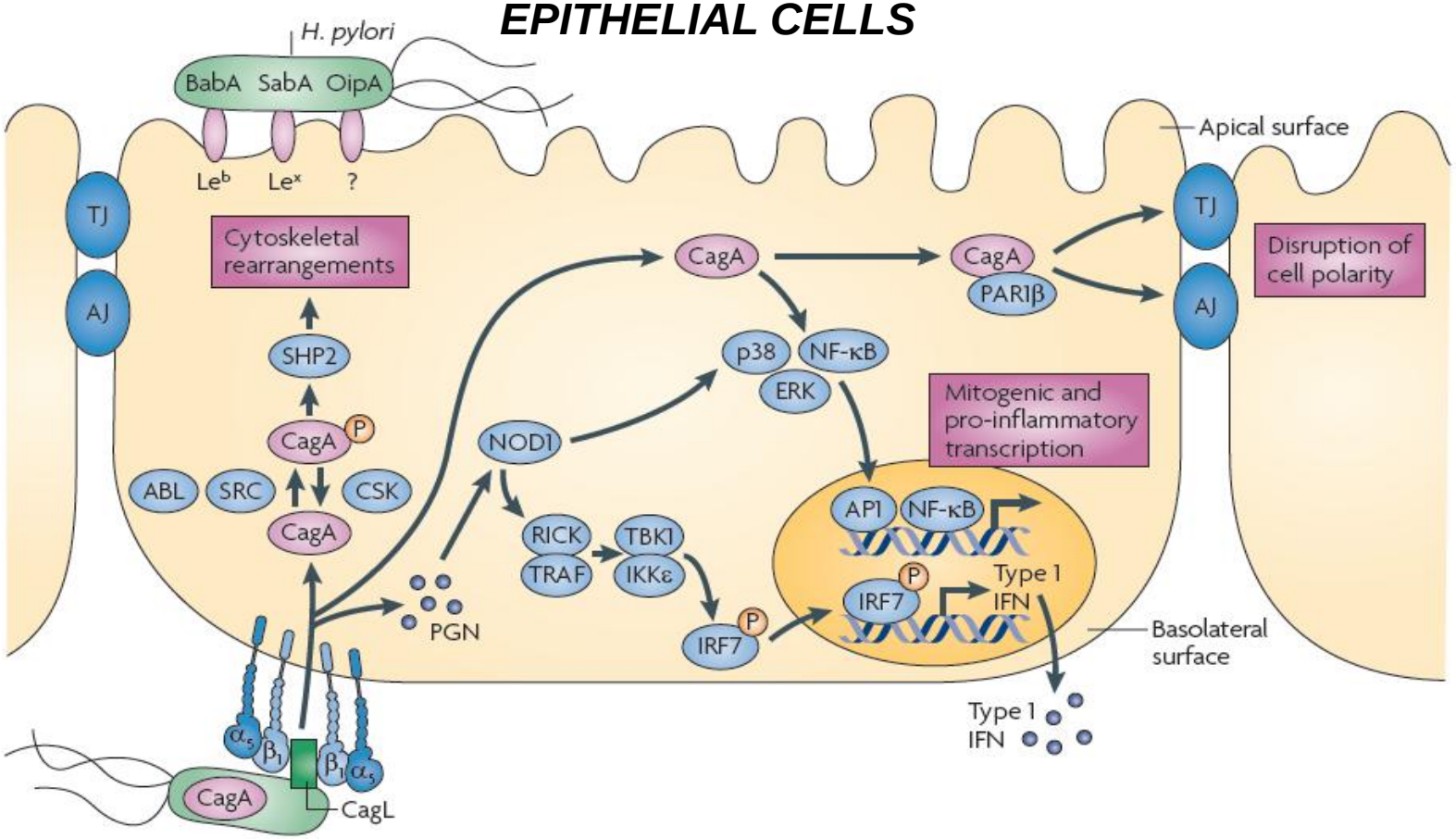
Helicobacter pylori infection and gastroduodenal diseases in Vietnam : a cross-sectional, hospital-based study

BMC Gastroenterology 2010, **10**:114 doi:10.1186/1471-230X-10-114

Table 4. Prevalence of *H. pylori* virulence factors in Hanoi and Ho Chi Minh

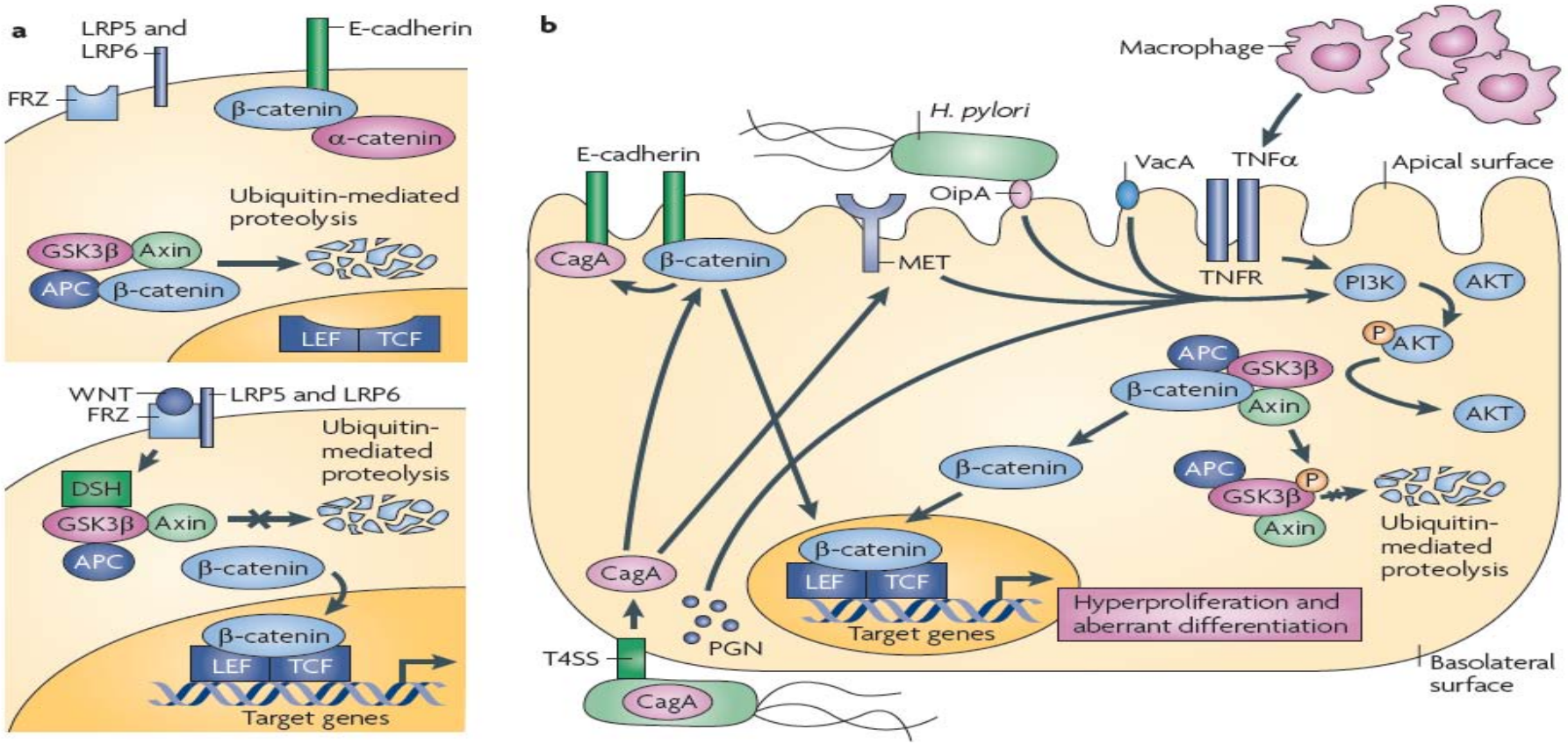
		Hanoi (n=53)	Ho Chi Minh (n=47)	p (Hanoi vs. Ho Chi Minh)
cagA				N.S
	Positive	51 (96.2%)	44 (93.6%)	
	Negative	2 (3.8%)	3 (6.4%)	
cagE				N.S
	Positive	49 (92.5%)	39 (83.0%)	
	Negative	4 (7.5%)	3 (6.4%)	
vacA m				0.034
	m1	31 (58.%)	17 (36.2%)	
	m2	22 (41.5%	30 (63.8%)	
vacA s				N.S
	s1	53 (100%)	48 (100%)	
	s2	0 (0%)	0 (0%)	

INTERACTIONS BETWEEN PATHOGENIC *H. PYLORI AND GASTRIC EPITHELIAL CELLS*



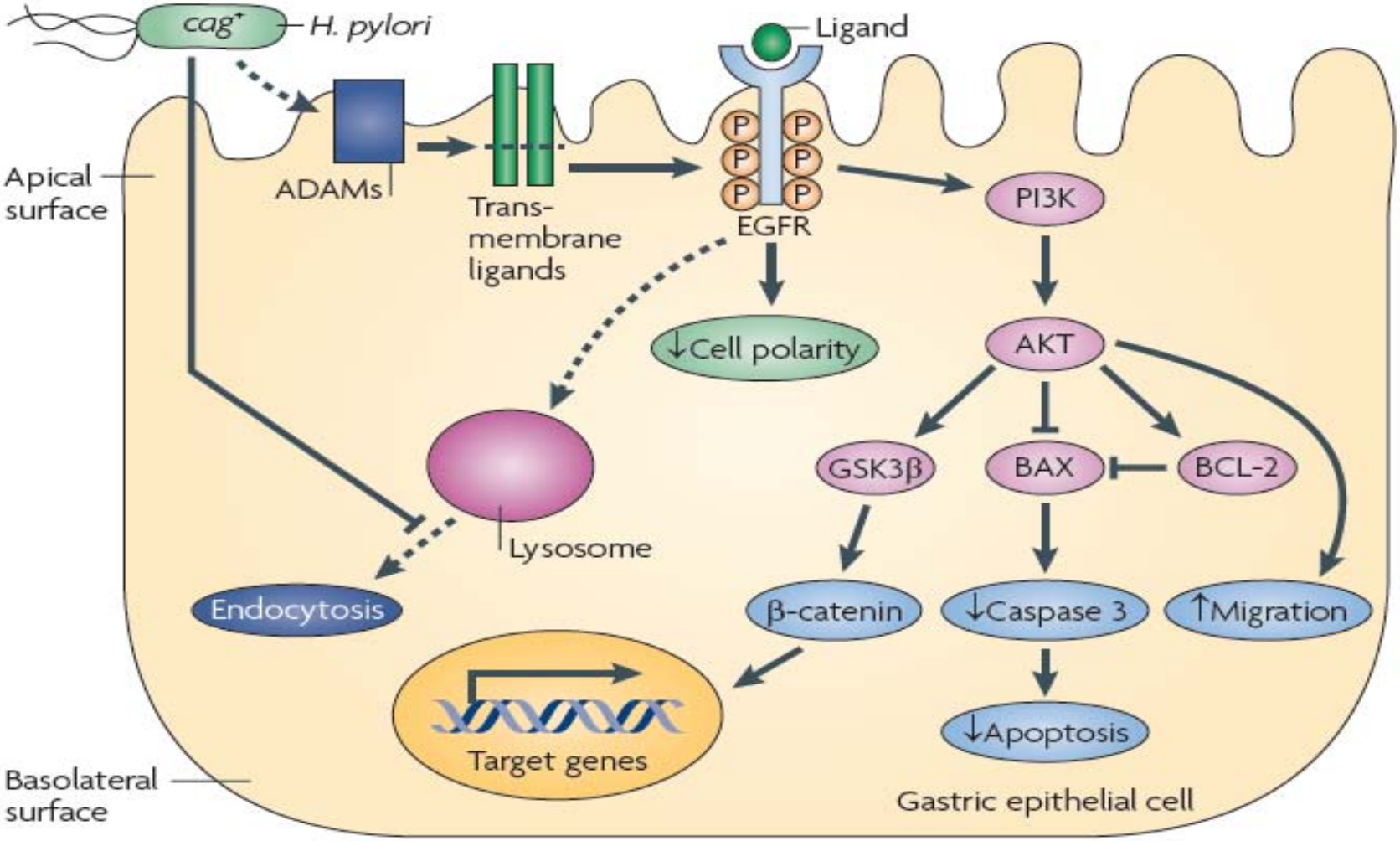
Several adhesins such as BabA, SabA and OipA mediate binding of *Helicobacter pylori to gastric epithelial cells, probably through the apical surface. H. pylori can* also bind to α5β1 integrins, which are located on the basolateral surface of epithelial cells. After adherence, *H. pylori can* translocate effector molecules such as CagA and peptidoglycan (PGN) into the host cell. PGN is sensed by the intracellular receptor nucleotide-binding oligomerization domain-containing protein 1 (NOD1), which activates nuclear factor-κB (NF-κB), p38, ERK and IRF7 to induce the release of pro-inflammatory cytokines. Translocated CagA is rapidly phosphorylated (P) by SRC and ABL kinases, leading to cytoskeletal rearrangements. Unphosphorylated CagA can trigger several different signalling cascades, including the activation of NF-κB and the disruption of cell–cell junctions, which may contribute to the loss of epithelial barrier function. Injection of CagA seems to be dependent on basolateral integrin α5β1. AJ, adherens junction; CSK, c-src tyrosine kinase; IFN, interferon; IKKε, IκB kinase-ε; IRF7, interferon regulatory factor 7; RICK, receptor-interacting serine-threonine kinase 2; TBK1, TANK-binding kinase 1; TJ, tight junction

ABERRANT ACTIVATION OF B-CATENIN BY *HELICOBACTER PYLORI.*



a* | *Membrane-bound β-catenin links cadherin receptors to the actin cytoskeleton, and in non-transformed epithelial cells β-catenin is primarily localized to E-cadherin complexes. Cytoplasmic β-catenin is a downstream component of the Wnt pathway; in the absence of Wnt (upper panel), cytosolic β-catenin remains bound within a multi-protein inhibitory complex comprised of glycogen synthase kinase-3β (GSK3β), the adenomatous polyposis coli (APC) tumour suppressor protein and axin141. Under unstimulated conditions, β-catenin is constitutively phosphorylated (P) by GSK3β, ubiquitylated and degraded141. Binding of Wnt to its receptor, Frizzled (FRZ; lower panel), activates dishevelled (DSH) and Wnt co-receptors, low density lipoprotein receptor-related protein 5 (LRP5) and LRP6, which then interact with axin and other members of the inhibitory complex, leading to the inhibition of the kinase activity of GSK3β141. These events inhibit the degradation of β-catenin, leading to its nuclear accumulation and formation of heterodimers with the transcription factor lymphocyte enhancer factor/T cell factor (LEF/TCF), resulting in the transcriptional activation of target genes that influence carcinogenesis. **b | Injection of CagA** results in the dispersal of β-catenin from β-catenin–E-cadherin complexes at the cell membrane, allowing β-catenin to accumulate in the cytosol and nucleus. CagA, potentially by binding MET or other *H. pylori constituents such as OipA, VacA* and peptidoglycan (PGN) as well as tumour necrosis factor-α (TNFα), which is produced by infiltrating macrophages, can activate PI3K, leading to the phosphorylation and inactivation of GSK3β. This liberates β-catenin to translocate to the nucleus and upregulate genes, leading to increased proliferation and aberrant differentiation; TNFR, TNF receptor.

TRANSACTIVATION OF EGFR BY *H. PYLORI AND INDUCED CELLULAR CONSEQUENCES* WITH CARCINOGENIC POTENTIAL



Helicobacter pylori transactivates epidermal growth factor receptor (EGFR) through cleavage, which is dependent on the a disintegrin and metalloproteinase (ADAM) family proteinases, of EGFR ligands, such as heparin-binding EGF-like growth factor (HBEGF) in gastric epithelial cells. One downstream target of EGFR transactivation is PI3K–AKT, which leads to AKT-dependent cell migration, inhibition of apoptosis and β-catenin activation. BAX, BCL-2-associated X protein; GSK3β, glycogen synthase kinase-3β; P, phosphorylation.