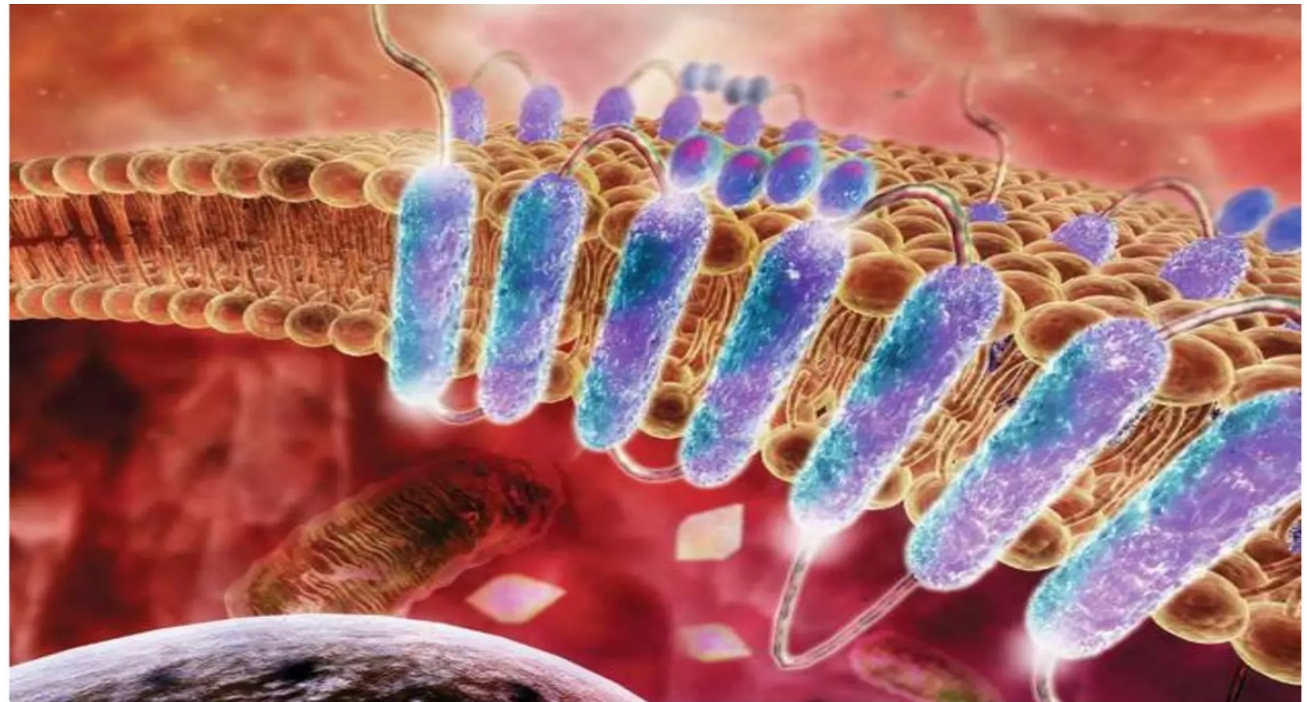


Viral Hijacking of G-protein-coupled-receptor Signaling Pathways

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CONTENT

1 G-protein-coupled-receptor(GPCR) signaling pathway

2 Viral hijacking of GPCR signaling pathway

- *Human papillomavirus(HPV)*
- *Human immunodeficiency virus (HIV)*
- *Kaposi sarcoma-associated herpesvirus (KSHV)*

3 Targeting GPCR for antiviral therapy

1 GPCR signaling pathway

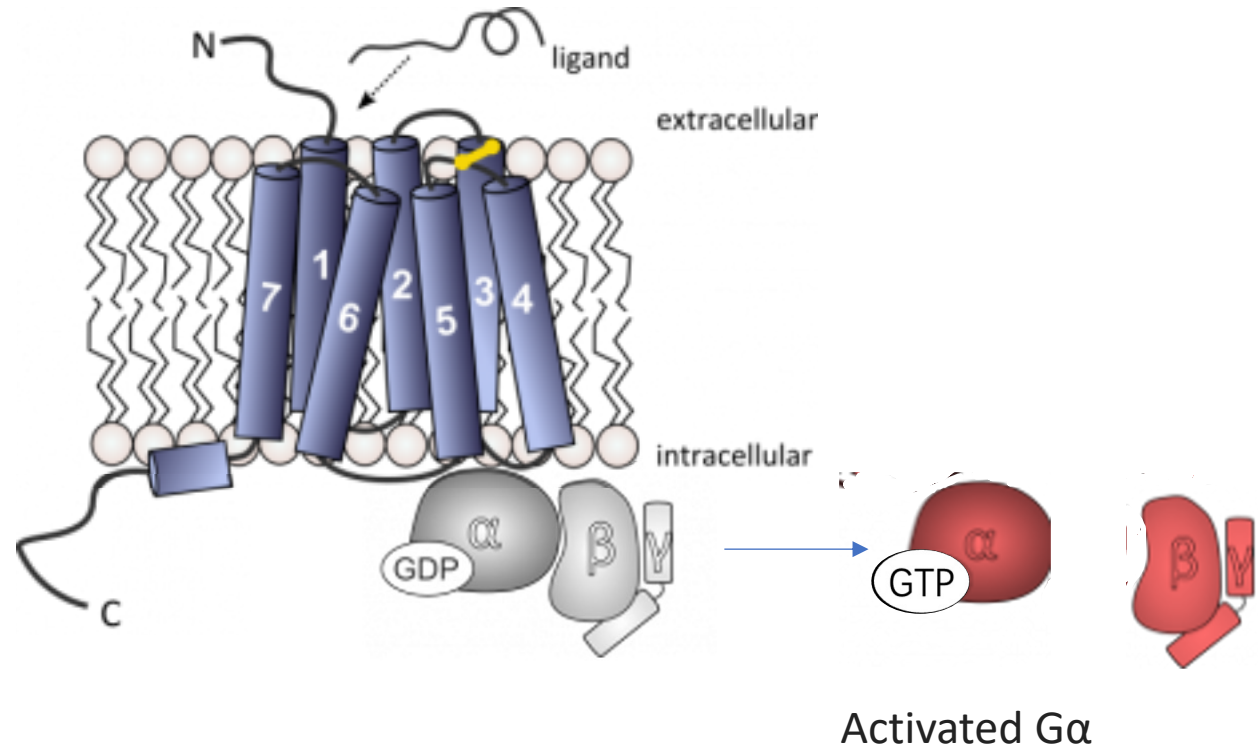
G protein and GPCR

G protein

- Guanine nucleotides binding

GPCR

- 7-transmembrane domain
- Catalyze GDP release from $G\alpha$ to bind with GTP



1 GPCR signaling pathway

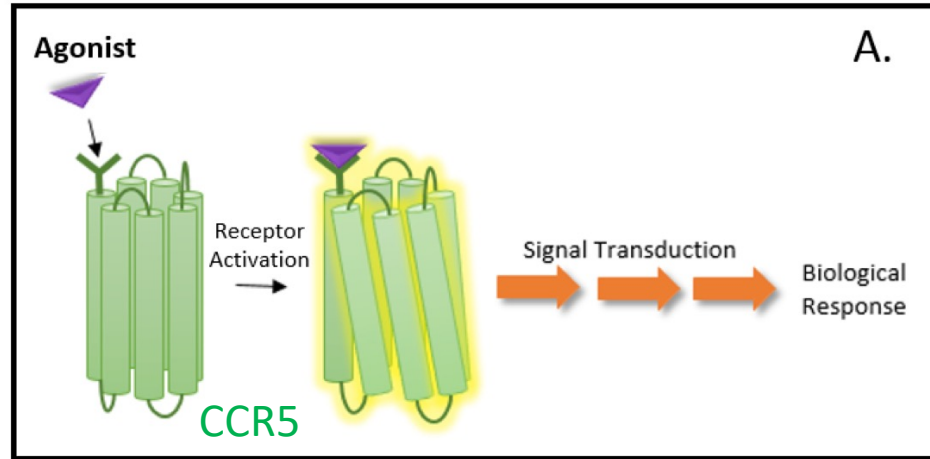
Chemokine for chemokine receptor

Chemokine (~40 members)

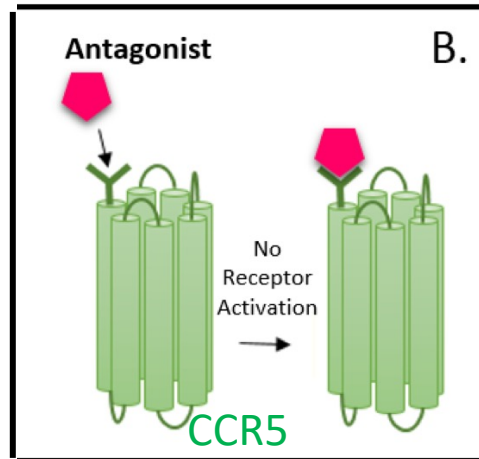
- 8-12 kda
- position of conserved cysteines
- CC-chemokines ligand 1-25
eg. CCL5
- CXC-chemokine ligand 1-18
eg. CXCL12

Chemokine receptor (18 members)

- eg. CC-chemokine receptor-5
CCR5
- CXC-chemokine receptor-4
CXCR4

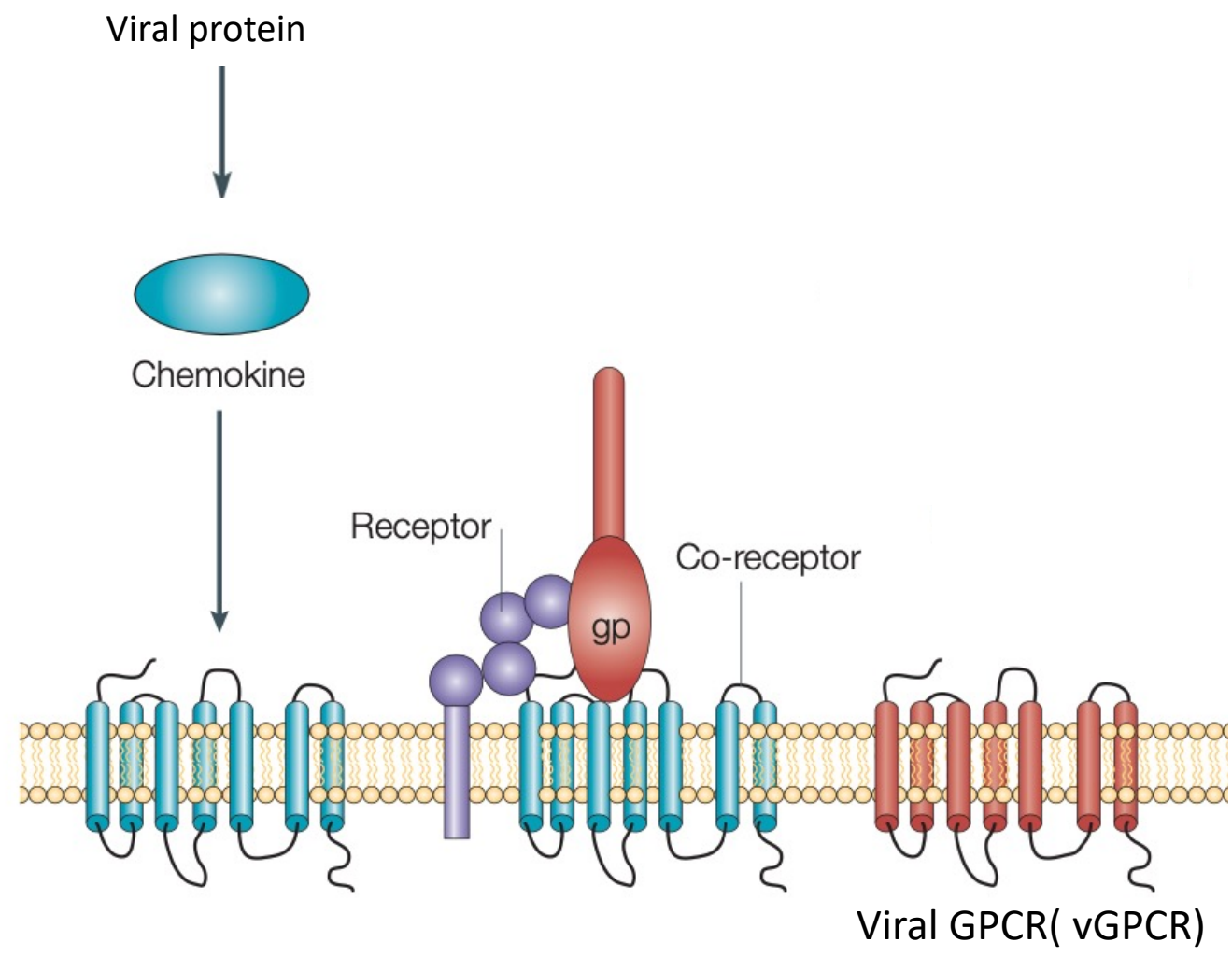


- Activates a receptor to produce a biological response
e.g. CCL3, CCL4 and CCL5



- Block the binding with other ligands
e.g. CCL7

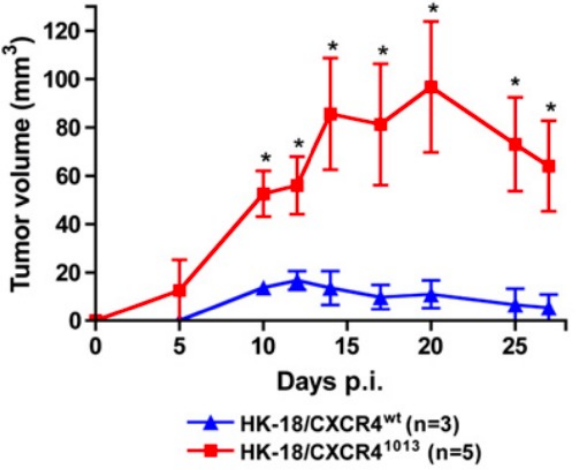
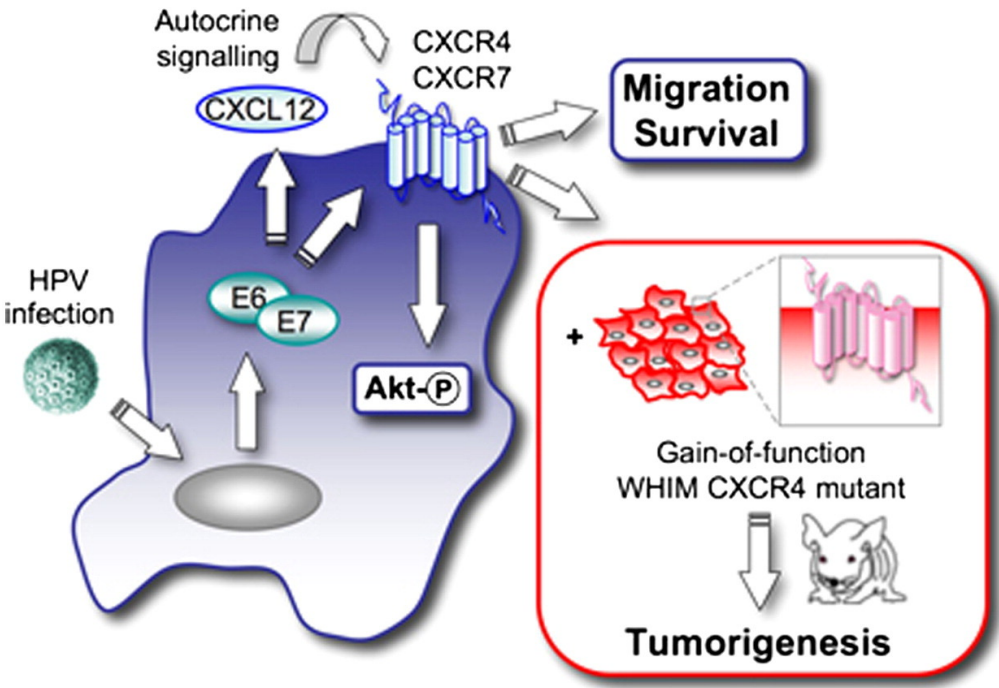
2 Viral hijacking of GPCR signaling pathway



2 Viral hijacking of GPCR signaling pathway

CXCL12-CXCR4 role for HPV-mediated tumorigenesis

CXC-chemokine receptor-4 (CXCR4)



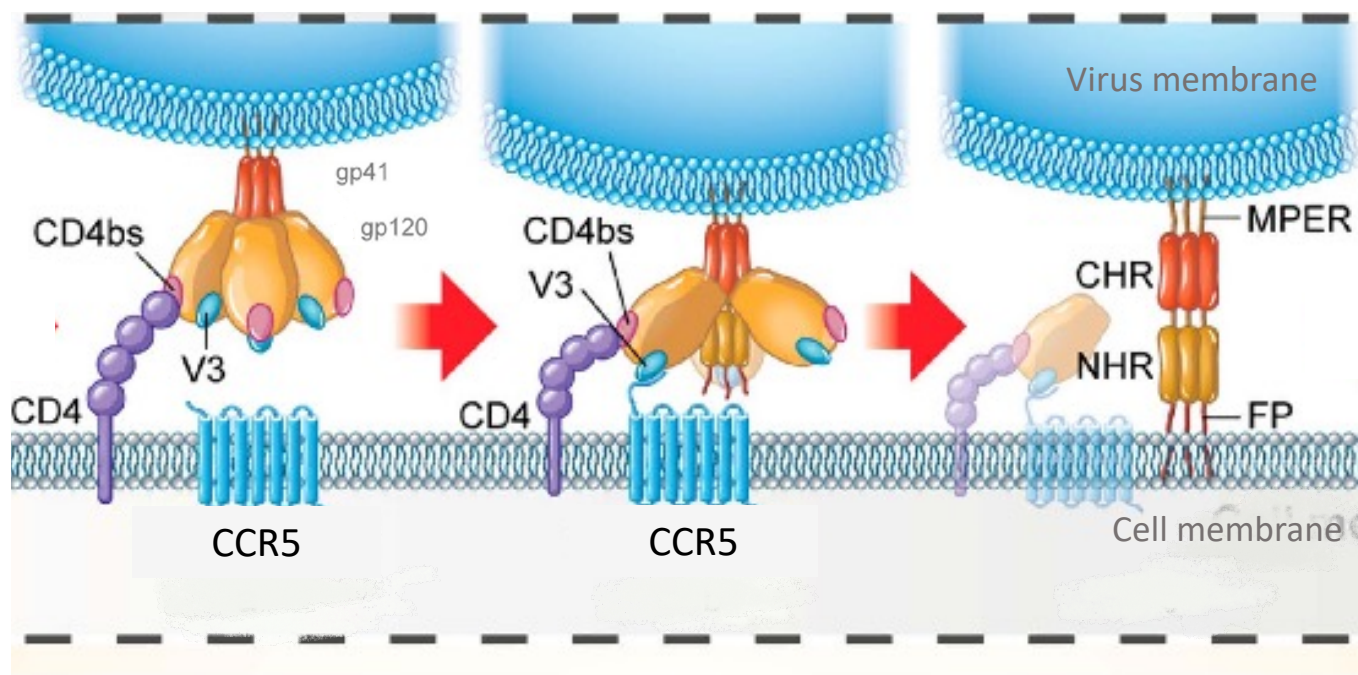
- CXCL12 and its receptors CXCR4 and CXCR7 are up-regulated in HPV-immortalized keratinocytes
- CXCL12-dependent signaling controls the motility and survival of keratinocytes
- Gain-of-function CXCR4 leads to HPV-keratinocytes tumorigenesis

K. Y. C. Chow, Cell Host & Microbe 2010

2 Viral hijacking of GPCR signaling pathway

HIV using CCR5 as co-receptor for entry

- CC-chemokine receptor-5 (CCR5)



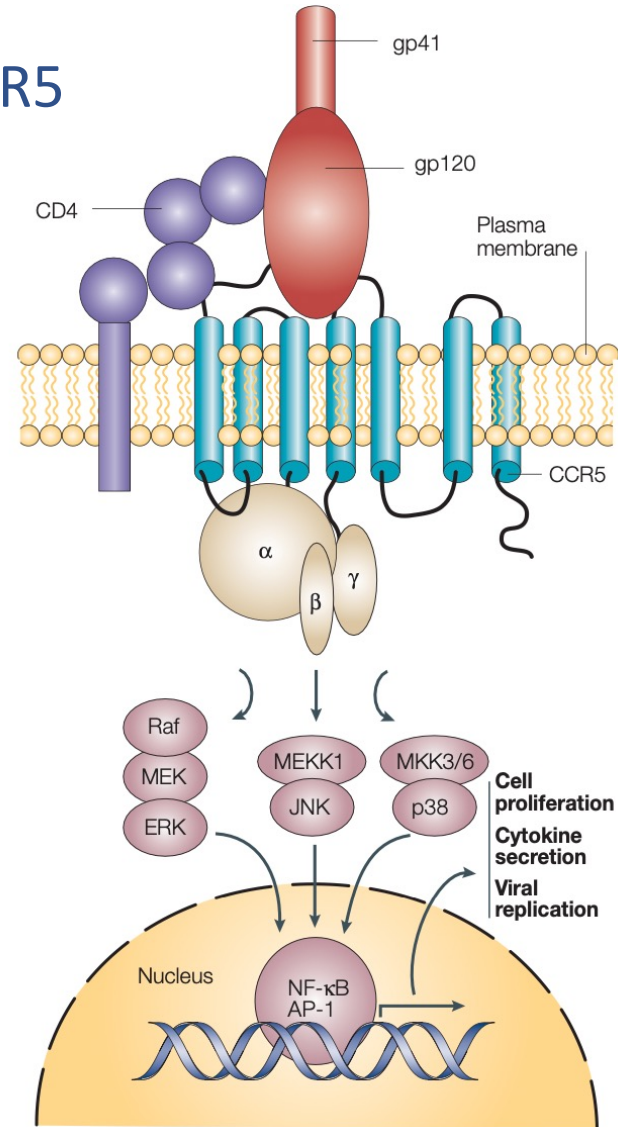
1. Receptor binding 2. Coreceptor binding 3. Membrane fusion

HIV entry into target cell

J. Pu, et al Viruses 2019

2 Viral hijacking of GPCR signaling pathway

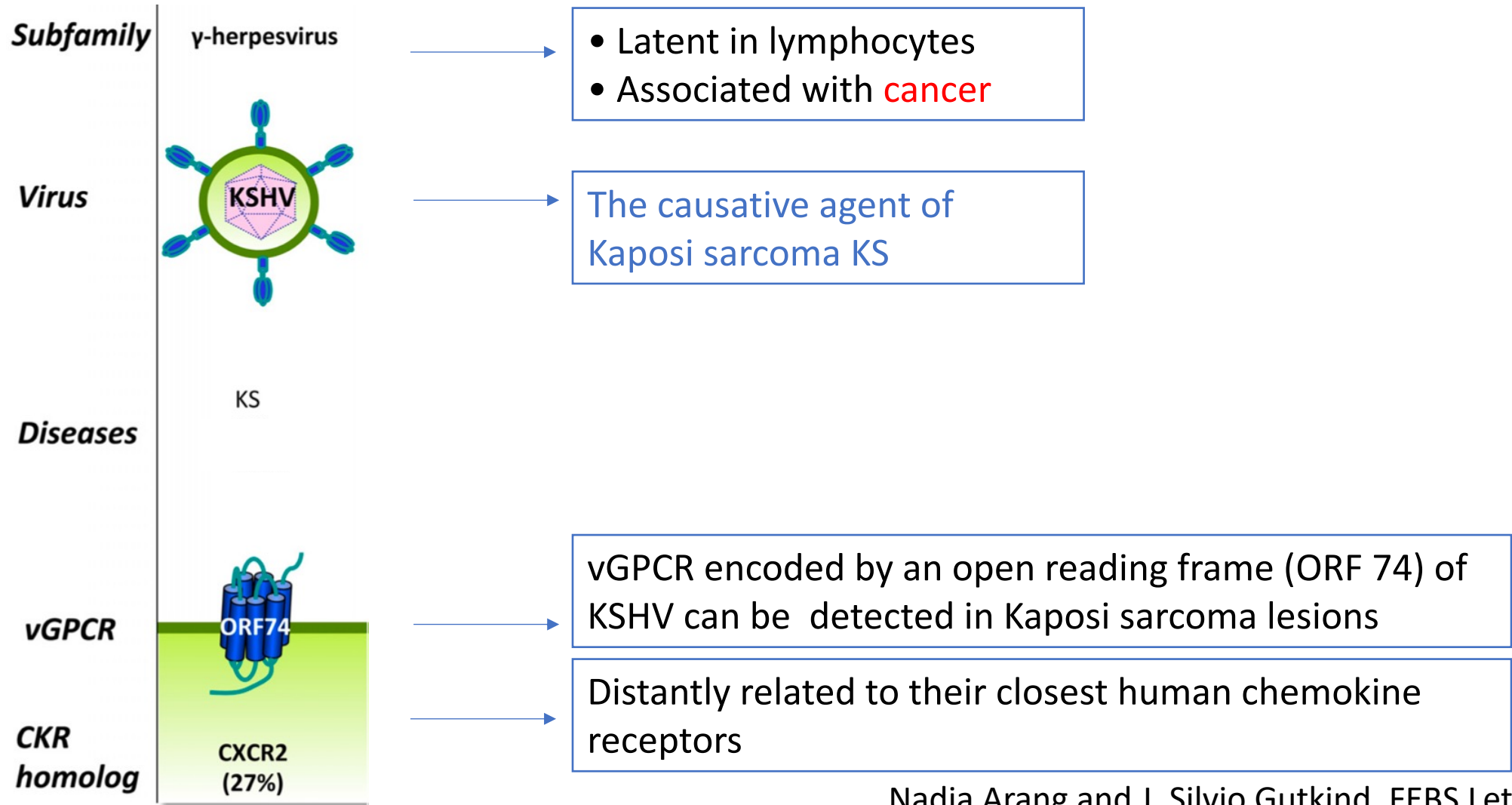
HIV harness the signaling capacity of CCR5



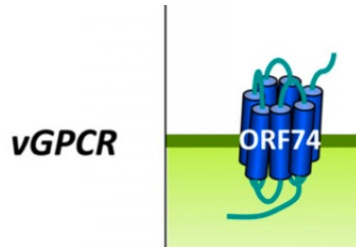
- Induce intracellular mitogen-activated protein kinase MAPKs pathway

2 Viral hijacking of GPCR signaling pathway

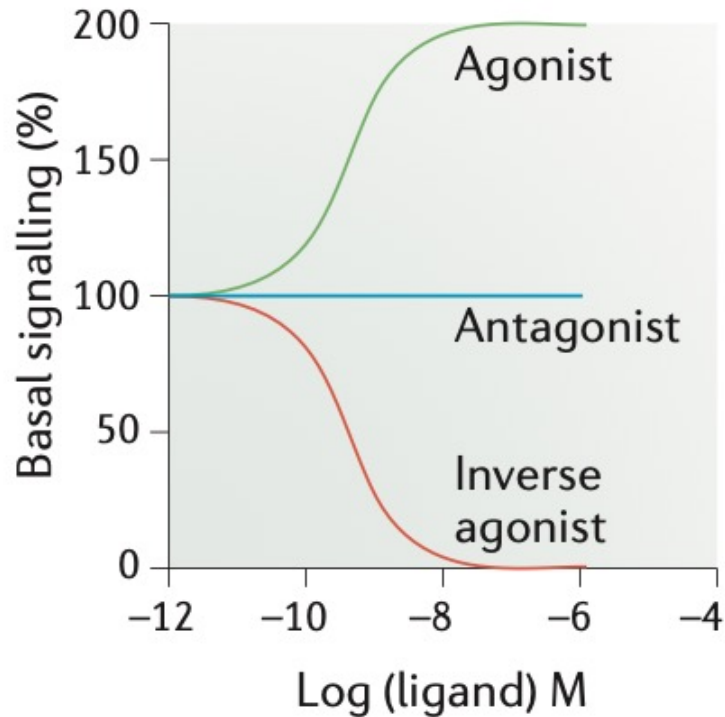
Kaposi sarcoma-associated herpesvirus (KSHV)



2 Viral hijacking of GPCR signaling pathway



- **Constitutive activity**
- What makes ORF74 distinct from human chemokine receptors



- **Agonists**
 - Growth-regulated oncogene α (GRO α , CXCL1)
 - **Angiogenic** chemokines
- **Antagonist**
 - CXC chemokines IL-8 (CXCL8)
- **Inverse agonists**
 - **Inhibit the constitutive activity of the receptor**
 - CXCL10
 - **Angiostatic** chemokines

2 Viral hijacking of GPCR signaling pathway

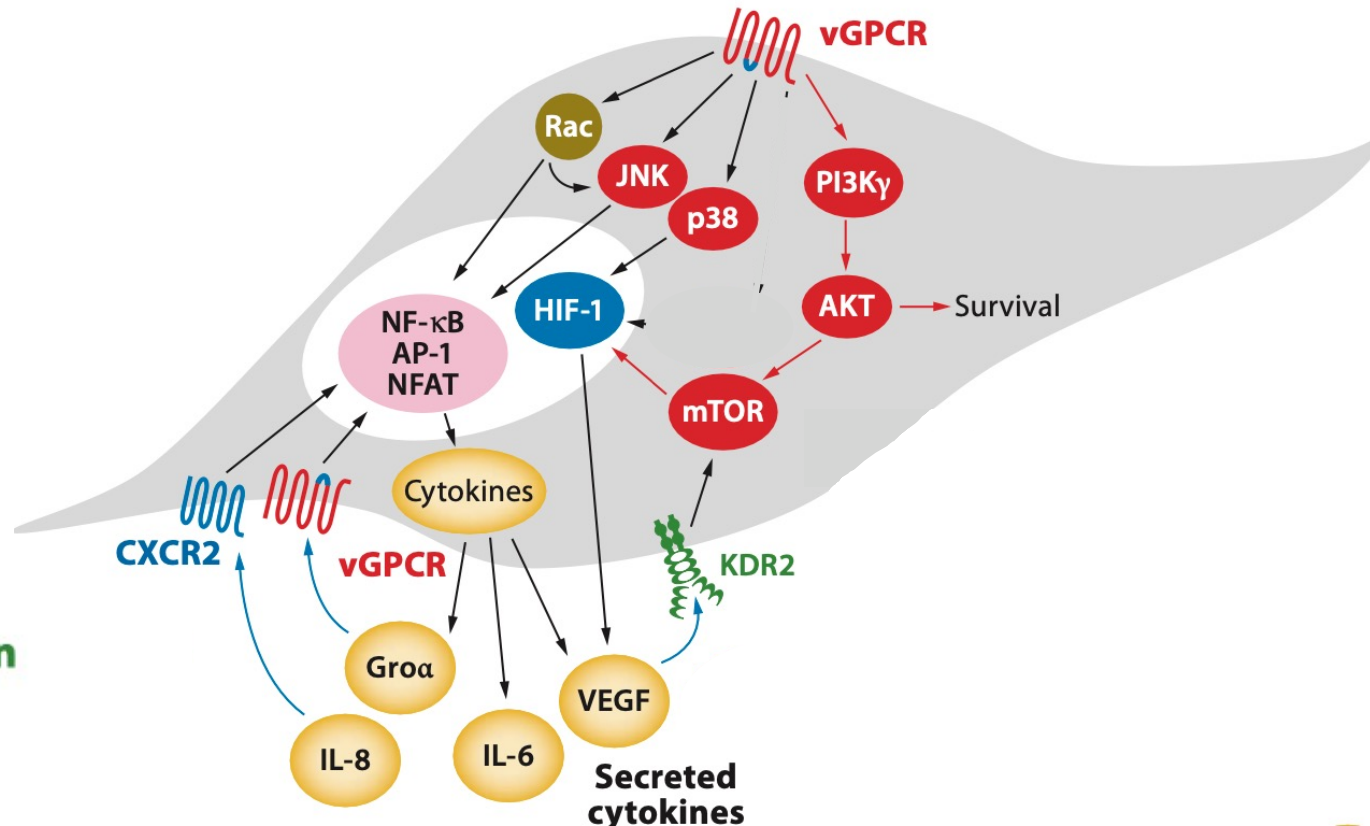
ORF74 receptor stimulates signalling pathways

- Transforming
 - Pro-angiogenic
- Mechanism

1 Direct transformation
of vGPCR-expressing cells

2 Autocrine signaling
of vGPCR-expressing cells

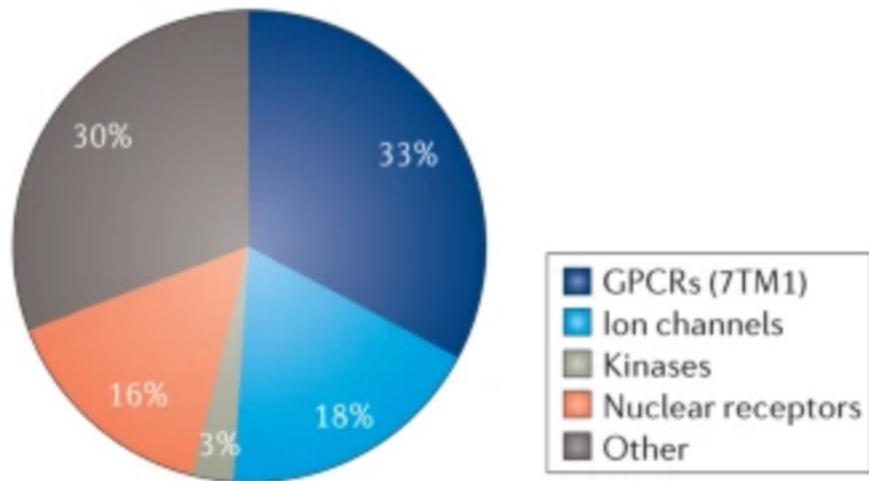
3 Paracrine transformation



- Direct and paracrine AKT activation is necessary and sufficient for ORF74 oncogenesis

3 Targeting GPCR for antiviral therapy

Proportion of small-molecule drugs that target major families



- Targets of ~30% FDA approved small molecule drugs

Table 1. Some drugs acting through GPCRs

Trademark	Generic name	Company	Disease	Target receptor
Claritin	loratadine	Schering-Plough	allergies	H1 antagonist
Zyprexa	olanzapine	Eli Lilly/Tatemo to	schizophrenia	mixed D2/D1/5-HT2
Cozaar	losartan	Merk & Co	hypertension	AT1 antagonist
Risperdal	risperidone	Johnson & Johnson	psychosis	mixed D2/5-HT2A
Leuplin/Lupron	leuprolide	Takeda	cancer	LH-RH agonist
Neurontin	gabapentin	Pfizer	neurogenic pain	GABA B agonist
Allegra/Telfast	fexofenadine	Aventis	allergies	H1 antagonist
Imigran/Imitex	sumatriptan	GlaxoSmithKline	migraine	5-HT1 agonist
Serevent	salmeterol	GlaxoSmithKline	asthma	β2 agonist
Zantac	ranitidine	GlaxoSmithKline	ulcers	H2 antagonist
Pepcidine	famotidine	Merk & Co	ulcers	H2 antagonist
Zofran	ondansetron	GlaxoSmithKline	antiemetic	5-HT3 antagonist
Dovan	valsartan	Novartis	hypertension	AT1 antagonist
Duragesic	fentanyl	Johnson & Johnson	pain	opioid agonist

3 Targeting GPCR for antiviral therapy

Targeting human CCR5



Maraviroc

- CCR5 Antagonist
 - Celsentri sales to reach USD 350m in 2015
- Successful example
 - For the treatment of HIV infection
 - Drugs against **host targets** and blocking the virus-host protein-protein interactions

O Latinovic et al Clinical Medicine: Therapeutics 2009
de Chassey et al. Genome Medicine 2014 ¹⁴

3 Targeting GPCR for antiviral therapy

Targeting ORF74

- Zn²⁺ ions have inverse agonistic effects on an ORF74 mutant receptor
- No **small molecular compounds** against ORF74 have been reported to our knowledge
- Attractive target for Herpesvirus-associated diseases

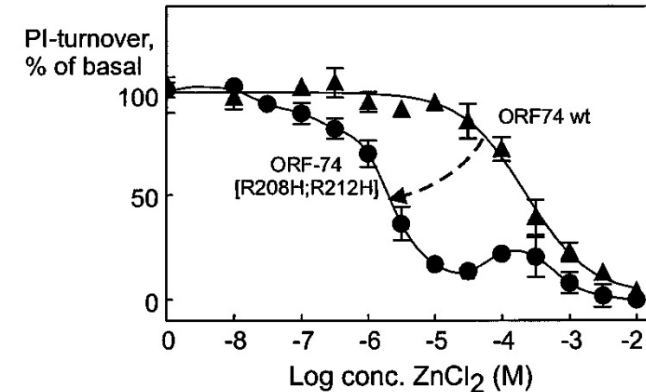


FIG. 6. Inhibition by Zn²⁺ of constitutive phosphatidylinositol turnover induced by ORF-74 with an engineered bis-His metal ion switch. ▲, wild-type ORF-74 (*ORF74 wt*; $n = 5$); ●, R208H,R212H ORF-74 ($n = 7$). In the mutant receptor, His(V:01) (His²⁰⁸) and His(V:05) (His²¹²) are located in i and $i+4$ positions, which in a helical configuration is optimal for binding zinc ions (see Fig. 1). *PI*, phosphatidylinositol.

Conclusion and perspective

- Viruses have their distinct strategy of hijacking of GPCR signaling pathway
 - HPV
 - Upregulating CXCR4 to promote carcinogenesis
 - HIV
 - Using CCR5 as coreceptor for entry and CCR5 signaling enhances viral replication
 - Maraviroc
 - KSHV
 - Encoding ORF74 for transforming and angiogenesis
 - Hitherto no compound
- Targeting vGPCRs by inverse agonists
 - can be considered as attractive targets moving forward in the development of antiviral, cancer disease treatments

Thank you ! Acknowledgment !