

Viruses, bacteria and Hallmarks of Cancer. Self-sufficiency in growth signals

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Abstract

In 2000, Robert Weinberg and Douglas Hanahan proposed the 6 Hallmarks of Cancer, which are found in most if not all cancers. This article describes how 11 viruses and 8 bacteria may stimulate the development of the first hallmark, self-sufficiency in growth signals. For this, viruses and bacteria either stimulate the synthesis of growth factors in the cell, or activate growth factor receptors, or regulate the expression of a gene involved in the transduction of a signal of cell division initiation from growth factor receptor.

Keywords

virus – bacteria- Hallmarks of Cancer

Background

In 2000 Robert Weinberg and Douglas Hanahan published the paper “The Hallmarks of Cancer”[1]. In this paper the authors suggest that most if not all cancers have acquired the same set of functional capabilities during their development, albeit through various mechanistic strategies. This set of functional capabilities was called The Hallmarks of Cancer, which consist of 6 hallmarks: **self-sufficiency in growth signals, insensitivity to growth-inhibitory (antigrowth) signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis**. By this moment, this paper is cited for more than 28 thousand times. It is one of the most highly cited papers in the field of oncology. This can mean that many oncologists agree about the existence of a set of functional capabilities during cancer incidence and development.

At present it is believed that only about 15-20% of all cases of cancer can be caused by viruses and bacteria. We have previously described [2, 3] why and how viruses and bacteria can stimulate cancer development. It seems logical to consider if viruses and bacteria can favor the development of “The Hallmarks of Cancer” and if yes, how they do it. In the present paper the influence of viruses and bacteria (hereafter bacteria will mean intracellular bacteria) on the incidence of the first trait - self-sufficiency in growth signals.

Main text

When considering how viruses and bacteria can stimulate self-sufficiency in growth signals, we base on the assumption that viruses and intracellular bacteria are the beneficiaries of a continuous division of host cells, namely:

- First, S-phase of cell division is the phase when the synthesis of cellular DNA takes place and which is also the perfect time for reproduction of viruses and intracellular bacteria. During this time the cell environment is rich in nutrients necessary for reproduction of viruses and bacteria. That is why viruses and bacteria will aim for the cell spending as much time as possible in the S-phase of cell division.
- Second, cell division means expansion of life space for intracellular

bacteria and viruses. This way of expansion does not require the release of viruses and bacteria from the cell, and does not jeopardize them with immune system attack. Unlimited division of the host cells means unlimited expansion of the living space and possibility for unlimited multiplication of viral and bacterial particles. To initiate cell division, viruses and bacteria must be able to affect the **Activating system**

Activating system

A cell found in G0 phase, can be forced out of the G0 phase by the external stimulating (mitogenic) influences, e.g. the effect of growth factors on the cell (growth factors mean any factors - growth factors, growth hormones, growth cytokines, Wnt etc., which effect on a corresponding receptor results in the appearance of Cyclin D and CDK4/6 in the cell). Growth factors through the receptors send the signal for division start to the cell through Ras, Jak/Stat and other signaling pathways, which, in turn, activate sufficient amount of genes for starting cell division. As a result of this activation, together with other gene products, Cyclins D and CDK4/6 proteins appear in the cell. In short, for further discussion it is necessary to understand, that the outcome of the stimulation of activating system is the appearance of Cyclins D and CDK4/6 in the cell. It is the occurrence of Cyclins D and CDK4/6 that triggers cell division (Figure 1).

Cell division stimulation

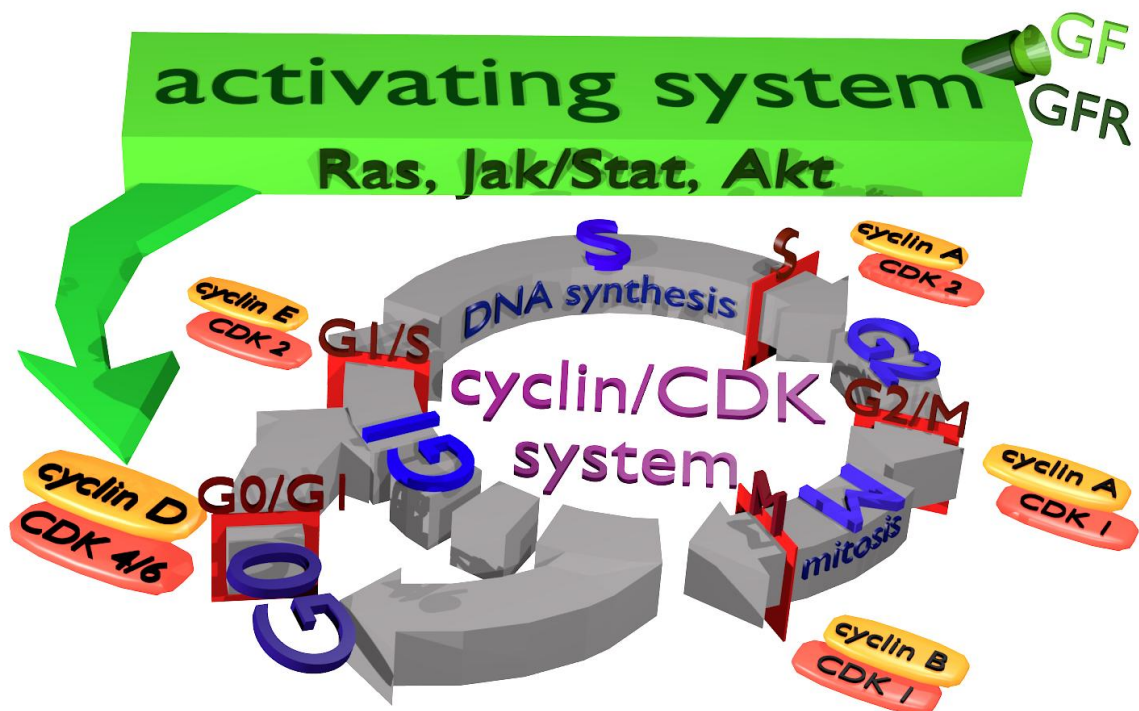


Figure 1. Cell division stimulation. The action of growth factors (GF) on a corresponding receptor (GFR) results in the appearance of Cyclin D and CDK4/6. Cyclin D and CDK4/6 complex initiates the process of cell division, which consists in sequential transitions to the cell division phases (G0-G1-S-G2-M).

Stimulation of activating system

For a cell to enter S phase (phase of cellular DNA synthesis) viruses and bacteria must be capable of stimulating **activating system**. Theoretically, viruses can affect any of the genes involved in the transmission of the signal of activation (Ras, Raf, Myc etc) downstream the growth factor receptors until cyclins D и CDK4/6 proteins appear in the cell.

However, the best would be to affect a growth factor or a growth factor receptor. This case is similar to the normal stimulation of cell division, and it results in the suppression of the function of the genes of controlling system and suppression of apoptosis. In general, the ideal case of cell division initiation for viruses and bacteria is the case when a virus or bacteria can activate the synthesis of both growth factor and its receptor. In this case the receptor will be embedded into the cell membrane, and the synthesized growth factor, binding to its receptor, will stimulate cell division. Probably, using this last case, the virus can trigger division of any cell, no matter which growth factor used to control the division of this cell earlier (in this case the direction of cell differentiation can be changed). During stimulation of growth factor synthesis or stimulation of growth factor receptor, the controlling system is less likely to “suspect” a failure in the system function or external (viral or bacterial) interference.

Tables 1 and 2 summarize the information, how different viruses and bacteria can stimulate and maintain cell proliferation.

Table 1. Sustaining proliferative signaling in the cell by viruses.

Virus	Virus gene	Impact on the cell	Human gene	Proliferation, as a consequence of the impact on the cell
adenovirus	E4-ORF1	Adenovirus E4-ORF1 dysregulates EGFR and IGFR to mediate constitutive Myc expression [4]	EGFR, IGFR	EGF receptor is involved in WNT3a-mediated proliferation ... via ERK pathway activation [5]
	E1A	Adenoviral E1A function through Myc [6]	Myc	c-Myc recruits P-TEFb for ... cellular proliferation ... [7]
hepatitis B virus	HBx	Trans-activation of epidermal growth factor receptor gene by the hepatitis B virus X-gene product [8]	EGFR	Role of epidermal growth factor receptor ... in autonomous proliferation of ... human breast cancer cells [9]
	HBx	The human hepatitis B virus transactivator X gene product regulates ... transcription of an insulin-like growth factor II ... [10]	IGFR II	Insulin-like growth factor II stimulates cell proliferation through the insulin receptor [11]
	HBx	Hepatitis B virus X protein is essential for the activation of Wnt/beta-catenin signaling ... [12]	Wnt/beta-catenin	Wnt signaling promotes proliferation ... [13]
	HBx	Activation of Src family	Src	Src family kinases are

		kinases by hepatitis B virus HBx protein [14]		required for... induction of cell proliferation [15]
Hepatitis C virus		Hepatitis C virus induces epidermal growth factor receptor activation...[16]	EGFR	Epidermal growth factor receptor-directed enterocyte proliferation... [17]
	core	Hepatitis C virus core protein transactivates insulin-like growth factor II gene [18]	IGF II	Insulin-like growth factor-1 and -2 stimulate osteoprogenitor proliferation [19]
	core	Hepatitis C virus core protein upregulates transforming growth factor-beta 1 transcription [20]	TGF beta 1	Transforming growth factor beta 1 induces proliferation in colon carcinoma cells... [21]
	core	Hepatitis C virus core protein activates Wnt/ β -catenin signaling... [22]	Wnt/ β -catenin	Wnt signaling promotes androgen-independent prostate cancer cell proliferation... [23]
herpes simplex virus		Induction of transforming growth factor-beta 1 production in human cells by herpes simplex virus [24]	TGF- β 1	Transforming growth factor-beta 1 differentially regulates proliferation... [25]
HIV-1	Tat	HIV-1 Tat-mediated induction of platelet-derived growth factor in astrocytes... [26]	PDGF	Platelet-derived growth-factor requirements for in vitro proliferation of normal and malignant mesenchymal cells [27]
	gp160	HIV-1 gp160 induces transforming growth factor-beta production in human PBMC [28]	TGF-beta	Transforming growth factor-beta regulates basal transcriptional regulatory machinery to control cell proliferation... [29]
	gp120	HIV-1 gp120 Upregulates Brain-Derived Neurotrophic Factor (BDNF) Expression ...[30]	BDNF	Brain-derived neurotrophic factor stimulates proliferation and differentiation of neural stem cells... [31]
Epstein-Barr virus	LMP 1	Epstein-Barr virus latent membrane protein 1 induces expression of the epidermal growth factor receptor [32]	EGFR	The epidermal growth factor receptor is required to maintain the proliferative population... [33]
	LMP 1	Epstein-barr virus latent membrane protein 1 induces and causes release of fibroblast growth factor-2 [34]	FGF-2	Basic fibroblast growth factor stimulates the proliferation of human dermal fibroblasts... [35]
	small RNA	Epstein-Barr virus-encoded small RNA	IGF-1	Insulin-like growth factor 1 and oestradiol promote

		induces insulin-like growth factor 1 ... [36]		cell proliferation... [37]
	EBV	Binding of the Epstein-Barr virus to human platelets causes the release of transforming growth factor-beta [38]	TGF-beta	Transforming growth factor-beta differentially regulates oval cell and hepatocyte proliferation [39]
human herpesvirus-8	vIL-6	Kaposi's sarcoma-associated herpesvirus (KSHV) vIL-6 promotes cell proliferation ... [40]	IL-6	Interleukin-6 enhances growth factor-dependent proliferation of the blast cells ... [41]
	v-cyclin	The cyclin encoded by Kaposi's sarcoma-associated herpesvirus stimulates cdk6 ... [42]	cdk6	Cdk6-cyclin D3 complex ... uniquely controls cell's proliferation competence [43]
	miR-K12-11	Kaposi's sarcoma-associated herpesvirus-encoded microRNA miR-K12-11 attenuates transforming growth factor beta signaling... [44]	TGF-beta	Transforming growth factor-beta enhances the M-CSF and GM-CSF-stimulated proliferation of macrophages [45]
	vIRF4	Kaposi's Sarcoma-Associated Herpesvirus Viral Interferon Regulatory Factor 4 (vIRF4) Perturbs the G1-S Cell Cycle Progression via Deregulation of the cyclin D1 Gene [46]	cyclin D1	Nuclear cyclin D1 overexpression is a critical event associated with cell proliferation... [47]
human T-cell leukemia virus	Tax	Human T-cell leukemia virus type-I Tax induces expression of interleukin-6 receptor (IL-6R)... [48]	IL-6R	Signaling through interleukin-6 receptor supports blast cell proliferation... [49]
	Tax	Direct trans-activation of the human cyclin D2 gene by the oncogene product ... [50]	cyclin D2	Cyclin D2 is an FSH-responsive gene involved in gonadal cell proliferation... [51]
	Tax	The tax protein of human T-cell leukemia virus type 1 mediates the transactivation of the c-sis/platelet-derived growth factor-B promoter... [52]	PDGF-B	Platelet-derived growth factor causes pulmonary cell proliferation and collagen deposition in vivo [53]
papillomavirus	E6 and E7	Human papillomavirus type 16 E6 and E7 cooperate to increase epidermal growth factor receptor (EGFR) mRNA levels... [54]	EGFR	Stimulation of cell proliferation by endosomal epidermal growth factor receptor... [55]
	E6 and E7	E6 and E7 oncoproteins from human papillomavirus type 16	TGF-beta	Transforming growth factor beta modulates phosphorylation of the

		induce activation of human transforming growth factor beta1 promoter... [56]		epidermal growth factor receptor and proliferation of A431 cells [57]
<i>polyomavirus</i>	large T antigen	The SV40 large T antigen-p53 complexes bind and activate the insulin-like growth factor-I promoter ... [58]	ILGF-1	Insulin-like growth factor-I promotes proliferation and migration of cavernous smooth muscle cells [59]
	Middle-T antigen	Middle-T associates with and thereby activates p60c-src, a cellular tyrosine kinase homologous to the oncogene product of Rous sarcoma virus [60]	SRC	Src stimulates insulin-like growth factor I (IGF-I)-dependent cell proliferation ... [61]
	Middle-T antigen	Middle T interacts with a number of the proteins used by tyrosine kinase associated receptors to stimulate mitogenesis... [62]	tyrosine kinase	Simultaneous targeting of Src kinase and receptor tyrosine kinase results in synergistic inhibition of renal cell carcinoma proliferation and migration [63]
	small T antigen	Induction of cyclin D1 by simian virus 40 small tumor antigen [64]	cyclin D1	A cyclin D1/microRNA 17/20 regulatory feedback loop in control of breast cancer cell proliferation [65]
poxvirus	A49	Vaccinia virus protein A49 activates Wnt signalling by targetting the E3 ligase β -TrCP [66]	Wnt	Wnt3a is critical for endothelial progenitor cell-mediated neural stem cell proliferation and differentiation [67]
	A52	Poxviral protein A52 stimulates p38 mitogen-activated protein kinase (MAPK) activation...[68]	MAPK	A p38 MAPK-MEF2C pathway regulates B-cell proliferation [69]

Table 2. Sustaining proliferative signaling in the cell by bacteria.

Bacteria	Impact on the cell	Human gene	Proliferation, as a consequence of the impact on the cell
Chlamydia	... Chlamydia trachomatis increases the phosphorylation of EGFR [70]	EGFR	Epidermal growth factor receptor (EGFR) signaling promotes proliferation... [71]
	... C. pneumoniae activates endothelial cells to produce bFGF ... [72]	bFGF	Basic fibroblast growth factor induces cell migration and proliferation ... [73]
Escherichia coli	Enteropathogenic Escherichia coli-induced epidermal growth	EGFR	Epidermal growth factor receptor transactivation is implicated in IL-6-

	factor receptor activation... [74]		induced proliferation and ERK1/2 ... [75]
Helicobacter pylori	Activation of beta-catenin by carcinogenic Helicobacter pylori [76]	beta-catenin	β -Catenin and p120 mediate PPAR δ -dependent proliferation induced by Helicobacter pylori ... [77]
	Helicobacter pylori activate epidermal growth factor receptor... [78]	EGFR	Epidermal growth factor receptor mediates increased cell proliferation... [79]
Mycobacterium leprae	Mycobacterium leprae induces insulin-like growth factor... [80]	ILGF	Insulin-like growth factor induces the survival and proliferation of myeloma cells... [81]
Mycobacterium tuberculosis	Activation of the Wnt pathway by Mycobacterium tuberculosis... [82]	Wnt	Notch and Wnt signals cooperatively control cell proliferation and tumorigenesis in the intestine [83]
	Induction of transforming growth factor beta 1 by purified protein derivative of Mycobacterium tuberculosis [84]	TGF-beta 1	Transforming growth factor beta activation of p44mapk in proliferating cultures of epithelial cells [85]
Mycoplasma	Mycoplasma fermentans-derived high-molecular-weight material induces interleukin-6 release... [86]	IL-6	Intracellular interleukin 6 mediates platelet-derived growth factor-induced proliferation of nontransformed cells [87]
Staphylococcus	Pore-forming Staphylococcus aureus alpha-toxin triggers epidermal growth factor receptor-dependent proliferation[88]	EGFR	Epidermal growth factor induces bladder cancer cell proliferation through activation of the androgen receptor [89]
Toxoplasma	Toxoplasma gondii induces granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor secretion [90]	G-CSF, GM-CSF	Effects of granulocyte-colony-stimulating factor and granulocyte/macrophage-colony-stimulating factor administration on T cell proliferation...[91]

Conclusions

The above data indicate that the capability of viruses and bacteria of sustaining self-sufficiency in growth signals is rather common. What can this capability of viruses and bacteria indicate?

As viral particles reproduce, high frequency of mutations in genomes of viruses will result in the increased divergence of virus genomes, forming a cloud of quasispecies. The occurrence of such a cloud of mutant viruses can favor rapid adaptation of the virus to changing environment and improve its resiliency. On the other hand, considering that during millions of years of evolution of viral genomes, the nucleotide sequences for each gene of a virus were optimized, one can expect that the mutations appearing during replication of viruses will reduce the efficacy of the mutated genes and reduce competitiveness of viral particles. This may not be crucial as long as the viruses are inside the same cell, since the “correct” versions of the genes co-reside in the same cell. If the viruses are released from the cell, the viral particles with the minimal changes to the genomes will have the highest competitiveness. They will force the

mutated viral particles out of further replication. Besides, due to continuing mutagenesis, the survived viral particles will tend to have the ideal nucleotide sequence. Natural selection allows preserving the optimal nucleotide sequence of viral genome even during extended (long-term) reproduction in different habitats. The similarity of sequenced regions of genomes of viruses of the same species supports such assumption. Sequenced sequences only slightly vary from some “consensus” sequence. This variation is smaller in the genes crucial for the virus, for example, polymerase-coding genes, and is higher in the genes, not essential for the survival of the virus (for example, genes of envelope), or even favoring the survival of the virus.

However, this may mean that viruses, especially viruses with relatively small genome, are unlikely to retain in their genome unessential sequences which are not important for virus survival. Therefore, the presence in the viral genome of the genes, capable of keeping self-sufficiency in growth signals in the cell can mean that viruses need such genes, that these genes offer additional advantages for species maintenance to the viruses. Considering that along with the viruses, a number of bacteria is capable of inducing self-sufficiency in growth signals (see table 1, 2), such ability apparently gives them significant advantages. Since growth signals initiate cell division, it can mean that viruses and bacteria are interested in cell division and that they benefit from this process.

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