Oncogenome model of cancer development.

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Abstract

The goal of the present work is to describe the Oncogenome model of cancer development, according to which viruses and intracellular bacteria benefit from continuous cell division. Unlimited division of the host cells means unlimited expansion of the living space and possibility for unlimited multiplication of viral и bacterial particles. We call oncogenomes those viruses and bacteria, which could evolve to acquire an ability to affect the System of regulation of cell division. We discuss which genes and systems have to be affected by viruses and bacteria to trigger the unlimited proliferation of the host cells. Data regarding the effect of 9 viruses and 8 bacteria on cell are given. It is suggested that the main reason of cancer development is oncogenome microevolution, which takes place during chronic infection. This microevolution allows oncogenomes to overcome cell resistance and gain the control over cell division, leading to cancer incidence and development.

Keywords

Cancer - virus - bacteria

Introduction

The first draft of Oncogenome model of cancer development was described earlier[1], suggesting that it is viruses and intracellular bacteria that is the main cause of cancer. The model is based on the assumption that viruses and intracellular bacteria are the only 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.

The present work summarizes most of the contemporary ideas of this model.

Taking into account that the main goal of viruses and bacteria, like that of any living organism, is to maintain their species, viruses and bacteria could acquire, during evolution, the ability to stimulate the host cell division. This ability would give them an advantage during reproduction. By now many viruses and bacteria are known to have the capability of causing host cell division (see the text). These viruses and bacteria will be called oncogenomes hereafter. To stimulate host cell division, viruses and bacteria must be capable of affecting the System of regulation of cell division. At first we will briefly analyze, how the System of regulation of cell division works.

System of regulation of cell division.

To understand how viruses and bacteria (hereafter bacteria will mean intracellular bacteria) can

affect the system of regulation of cell division, we consider it helpful to restructure the current knowledge of the process of cell division. According to our knowledge, a number of systems are involved in regulation of cell division, including **activating system**, **cyclin/CDK system**, **differentiation system**, **supporting system** (which stimulates synthesis of proteins, ribosomes, transport, provides energy for cell division) and **controlling system** (a part of which can be **verifying system**, which checks the readiness of the cell to continue cell division at each checkpoint). Without such restructuring it can be difficult to understand how viruses and bacteria can affect the cell to stimulate uncontrolled cell proliferation. The evaluation of the work of activating system, cyclin/CDK system, controlling system and capability of viruses and bacteria of affecting the work of these systems can facilitate the observation of the effect of viruses and bacteria on the control of cell division (Figure 1)

Figure 1. Some systems participating in cell division regulation. GF is growth factor, GFR - growth factor receptor.

of Cyclin D and CDK4 in the cell). Growth factors through the receptors send a 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. For further discussion it is necessary to understand, that the result of 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.

Cyclin/CDK system

Fine tuning, including subsequent division stages, and, consequently, subsequent turning on and off of different genes, characteristic for each division stage, is, apparently, performed by cyclin/CDK system (Figure 2). Cyclin/CDK system, probably, can be considered a central

Cell division

Below is the brief description of the function of some of the above-named systems during cell division, and some ideas of how viruses and bacteria can initiate cell division by affecting these systems.

Activating system

A cell found in G0 phase, can be forced out of the G0 phase by the external stimulating (mitogenic) influences, e.g. as a result of the action of growth factors on the cell (growth factors mean any factors - growth factors, growth hormones, growth cytokines, Wnt etc., the

action of which on a corresponding receptor results in the appearance

system of cell division, and it is triggered with the appearance of Cyclins D and CDK4/6 in the cell.

Figure 2. Activation of cyclin/CDK system

cyclin-dependant kinases (CDK4/6, CDK2, CDC2 etc.) After formation of a complex with cyclins, cyclin-dependant kinases can activate the expression of genes, necessary for transition to the next phase of cell division. For transition through each phase of cell division, a different set of enzymes is necessary, so each checkpoint (G0, G1/S, G2/M and M) has a particular cyclin/CDK complex activating the expression of a particular gene set.

Controlling system

Cell division is directed not only by activating system, cyclin/CDK complexes and other stimulating genes (Figure 3). More controlling genes, influencing cell division progress, exist. Such genes include genes of CIP/KIP families (p21, p27, p57), genes of INK4 families (p16, p15, p18 and p19), as well as p53 and RB.

Figure 3. Scheme of the work of controlling system

It is this system that directs the successive transition from one checkpoint to another (from G0 to G1 and later to S phase, during which cell DNA synthesis takes place, then to G2 and M-phase of mitosis) and during these transitions cell division occurs. The control is carried out by the action of complexes of different cyclins (A, B, E, D etc.) with corresponding

CIP/KIP family.

All proteins of the family ($p21^{Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$) interact with all cyclin/CDK complexes, thus interfering with the function of these complexes.

Apparently, $p21^{Cip1}$ protein, under the control of p53 gene, arrests cell division in stress situations (including mutations or under the influence of viruses and bacteria on the cell), and the function of p27(KIP1) and p57(KIP2) genes,

is probably related to the control of accuracy of cell division process. Besides, p27 is capable of

arresting cell division in contact inhibition.

All these proteins interact with different cyclin/CDK complexes, suppressing their ability to phosphorylate corresponding targets. In other words, p21 and p27 proteins, interacting with different cycling/CDK complexes, are probably responsible for global division arrest during all check points, regardless of cell division stage in the situation when continuation of cell division is not desirable.

INK4 family.

Proteins of the INK4 family (p16, p15, p18 and p19) specifically bind to Cdk4 and Cdk6, but not to other Cdk, preventing their interaction with the three different D-type cyclins, D1, D2 and D3 and thus preventing pRB phosphorylation. Such scenario prevents termination of G0 phase and cell transition to S phase. As the increase in concentration of some INK4 proteins takes place during G2/M phase[2], one of the possible functions of INK4 family may be prevention of repeated cell transition to S-phase after completion of DNA synthesis, before cell division process is completed. On the other hand, p16 (Ink4a), p15 (Ink4b) and p18 (Ink4c) are highly stable proteins. This can mean that most part of the life-time these proteins will function in new cells, formed after mitosis. And the main goal of these proteins will be cell transition to G0 phase and blockage of the new division in these newly-formed cells. In this case, the organism is given time to decide the fate of these cells, it can be either further division, or differentiation. Only following egg cell fertilization, when almost no expression of these genes is detected, the cell can enter new cell division cycle directly after mitosis.

This is probably due to the need for a more precise control of cell division process, and a new cell division is possible only after a new stimulating signal appears (appearance of cyclins D and CDK4/6 in the cell), so the division will be a one step process.

p53 protein is one of the regulators, addressed by different cell systems in case of need of cell division arrest. p53 gene product can, through p21 gene (WAF/CIP), suppress the activity of cyclin/CDK complexes, arresting cell division process. For instance, DNA mutations lead to the increase in p53 protein concentration, which in turn activates p21 gene transcription, and the increase of p21 protein concentration results in cyclin/CDK complex inactivation. It stops cell division process and let cell DNA repairing system repair DNA damage. In case the mutation cannot be corrected, further increase in p53 protein concentration results in apoptosis, programmed cell death. The main role of p53 gene in the cell division is apparently cell division arrest in a stressful situation, including viral and bacterial infection, and directing the cell to apoptosis, if the stressful situation fails to be resolved.

pRB protein can apparently be referred to as a part of the controlling system as well. The final result of any division stimulation must be the increase of the concentration of E2F transcription factor, and its concentration is in inverse relation with pRB concentration. There are no more intermediate regulators of E2F other than *pRB* proteins, so in case of pRB inactivation, for instance in a result of a mutation (normally such mutations should result in apoptosis) or action of viruses or bacteria, E2F concentration is increased, and the process of DNA synthesis, i.e. S phase of the cell cycle may start.

How viruses and bacteria can stimulate cell division?

For viruses and intracellular bacteria to be able to stimulate cell division, they must be able to:

- ✓ Trigger the function of activating system
- ✓ Limit the function of controlling system
- ✓ Forbid apoptosis (at least the part of it controlling the accuracy of cell division processes)
- ✓ Restrain the activity of the immune system which will tend to prevent excessive reproduction of viruses and bacteria

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** (Figure 4). 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.

Figure 4. Implementation of viral and bacterial control over cell division processes

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 as a result of it a suppression of the function of the genes of controlling system and apoptosis takes place as well. 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.

Suppression of controlling system

However, the stimulation of activating system alone is not enough for gaining the control over cells division. **The controlling system** needs to be suppressed as well. However, this problem is a lot more complicated than the stimulation of the activating system. If in case of activating system affecting either of the alleles involved in the gene activation is enough, in case of controlling system each of the alleles of the gene and each of the homologous gene alleles has to be suppressed. For viruses and bacteria, the most attractive target for suppressing the functions of controlling system can be retinoblastoma (RB) gene, though in this case each of RB gene alleles and each of the homologous gene p107 and/or p130 alleles have to be suppressed. But in case of RB gene inactivation (and inactivation of its homologues) other genes of the controlling system (p53, SIP/KIP, INK4) will not be able to prevent the transition of the cell to cell division initiation.

It is also desirable to suppress the function of p53 gene; otherwise the increase of the

number of viruses during their reproduction will lead to p53 activation followed by cell division arrest and apoptosis. P53 suppression is more preferable than p21 suppression, since in this case p53-dependent apoptosis will be suppressed as well.

However, stimulation of activating system and suppression of controlling system alone is not enough for gaining the control over host cell division.

Suppression of Immunity

Uncontrolled reproduction of viruses and bacteria during cell division stimulation should result in the activation of immune system, followed by the transition of the viruses from reproduction to survival. So, immune system suppression (global or local) is another priority for cell division stimulation. This is achievable, since the ability to suppress the immune system is essential for viruses and bacteria to solve the problem of survival during all their life in the human organism, and they are capable of solving it.

Suppression of Apoptosis

In case of any failure in cell division process caused by incorrect regulation, mutation, viral or bacterial interference etc, if the situation cannot be corrected by other means, the cell must be directed to apoptosis (programmed cell death). This situation is very undesirable for the reproduction of viruses and bacteria. It means that viruses and bacteria must as well have a mechanism to block apoptosis, which can be activated because of some defects in cell division. The suppression of apoptosis, as well as the suppression of immunity, is essential for all viruses and intracellular bacteria during all the time they are located in human organism. At least some of them, those which can turn the illness to chronic stage, could solve these tasks during evolution.

Now we can give a more exact definition of an **oncogenome**. **Oncogenomes** are viruses and intracellular bacteria (as well as some other microorganisms) which, during evolution, gained the ability to either **stimulate the activating system or suppress the controlling system**, as well as to affect Cyclin/CDK system in a way that would allow the stimulation of cell division. If the oncogenome is capable of suppressing apoptosis and immune system as well, then such virus or bacterium can already have an ability to induce uncontrolled cell proliferation.

Other viruses and bacteria, not capable of affecting the system of regulation of cell division, but capable of suppressing **Apoptosis** and **Immunity**, can be called **helper genomes**. Having additive or cooperative effect on apoptosis and immunity, helper genomes can make it easier for oncogenomes to gain the control over cell division.

How do viruses and bacteria affect the cell to stimulate its division?

The data describing how oncogenomes can initiate cell division uncontrolled by the organism are shown in tables 1 and 2.

Table 1. Effect of the viruses on cell division regulation and stimulation of cells for division.

viruses	Activating system		Controlling system		Apoptosis		Immunity system	
	viral gene	human gene	viral gene	human gene	viral gene	human gene	viral gene	human gene
adenovirus	E1A	EGF[3]	E1A E1B-55K	RB [4] P53[5]	E1B	FAS[6]	E1A	effectors of cellular immunity[7]
EBV	LMP1 LMP 2A	EGFR[8] Wnt/beta-catenin [9]	BZLF1	P53[10]	BZLF1	TNF[11]	BNLF2a	T cell immunity[12]
HBV	HBx HBx	Src[13] Wnt/beta-catenin[14]	HBx	P53[15]	HBx	Wnt/beta-catenin[16]	HBx	IFN-beta[17]
HCV	Hepatitis C virus core protein	EGFR[18] Wnt/beta-catenin[19]	NS3	P53[20]	NS5A	lineage kinase 3[21]	core protein	immune evasion[22]
HHV6	HHV6	E2F1[23]	HHV6U14	RB[23] P53[24]	U19	p53-dependent apoptosis[25]	HHV6	molecular mimicry[26]
HHV8	vIL-6 vGPCR v-cyclin	IL-6R[27] Wnt/beta-catenin[28] E2F[29]	LANA microRNA v-cyclin	P53[30] p21[31] RB[32]	microRNA FLICE	caspase 3[33] Fas[34]	vIRF3	interferon[35]
HPV16/18	E6 and E7 E6 and E7 E5	TGFB1[36] EGFR[37] EGFR[38]	E7 E6	RB[39] P53[40]	E6 E7	Fas[41],Bac[42] TNF[43]	E7 E5	interferon regulatory factor-1[44] CD1d[45]
HTLV	Tax Tax Tax	IL-2[46] IL-2R[47] IL-6R[48]	Tax Tax	RB[49] P53[50]	Tax	Fas[51]	Tax	IFN[52]
Polyomavirus	Py/T	Shc[53]	Py/T Py/T	RB[54] P53[55]	Py/T	Fas[56]		

Table 2. Effect of bacteria on cell division regulation and stimulation of cells for division.

bacteria	Activating system		Controlling system		Apoptosis		Immunity system	
	<i>bacterial gene</i>	<i>human gene</i>	<i>bacterial gene</i>	<i>human gene</i>	<i>bacterial gene</i>	<i>human gene</i>	<i>bacterial gene</i>	<i>human gene</i>
Chlamydia	Chlamydia pneumoniae	bFGF, IL-6[57]			Chlamydia trachomatis	Bcl-2[58]	Chlamydia	IFN[59]
Escherichia coli	E.coli	EGFR[60]			Inhibition of apoptosis	BclXL[61]	E.coli	Immune evasion [62]
Helicobacter pylori	H. pylori H. pylori	Wnt/beta-catenin[63] EGFR[64]	CagA	P53[65]	CagA	Bad[66]	VacA, CagA	immune systems manipulation[67]
Mycobacterium leprae	M. leprae	IGF[68]			M. leprae	Bad, Bak, Mcl-1[69]	M. leprae	Immune evasion[70]
Mycobacterium tuberculosis	M. tuberculosis	TGF[71]			MPT64	Bcl-2[72]	SecA2	inhibits the host immune response[73]
Mycoplasma	Mycoplasma	IL-1b, IL-2, IL-2R, IL-6[74]			Mycoplasma	c-Myc[75]	divergent vaa genes[76]	
Staphylococcus	alpha-toxin	EGFR[77]			Peptidoglycan	inhibitor of apoptosis protein-2[78]	Staphylococcus aureus	IgA[79]
Toxoplasma	Toxoplasma gondii	c-Myc[80]			Toxoplasma gondii	caspase[81], Bax[82]	Toxoplasma gondii	Modulation of innate immunity[83]

Under normal conditions, the natural reaction of the organism to an attempt of viruses and bacteria to interfere with the process of cell division is the suppression of the genes of activating system, activating the controlling and immune systems, and stimulation of apoptosis. Tables 1 and 2 contain the data regarding the infection agents being able in certain cases to overcome this natural reaction and suppress apoptosis, controlling system and immune system. Besides, viruses and bacteria are capable of stimulating activating system, irrespective of the organism's needs.

Retention of oncogenes in genomes of viruses and bacteria can mean that they use these oncogenes during their life span. Otherwise (if these oncogenes were not used and were not beneficial for the oncogenomes), these genes would be lost due to high frequency of mutations in viruses. Retention of oncogenes can also mean, that such genes give viruses and bacteria additional advantages during evolution and species conservation.

Full control of cell division

If a virus or a bacterium can take control over the 4 systems described above (activating system, controlling system, apoptosis and immunity), then it can take cell division process under control, and make cell divide (Figure 5).

Figure 5. Cancer incidence is the result of the execution of the full control of oncogenomes over the system of cell division regulation.

During such full control of cell division, the viral genotypes that could force the cell to divide start to reproduce in favorable for them conditions. So, together with the increase of the number of dividing host cells, the number of adapted viruses and bacteria, capable of inducing cell division of a particular organism, also grows exponentially. Later, such adapted

oncogenomes can migrate to adjacent or remote cells of the organ and stimulate division of new cells. This assumption is hardly surprising, since intracellular pathogens are known to have mechanisms for both entering and leaving host cells. Such oncogenomes will be able to migrate in the organism, get in the cells of other organs and also stimulate them for division. The only additional condition is that the new cells must also contain the respective receptors through which viruses can get inside the cell (it also means that each oncogenome has a particular set of organs in which it will be able to trigger cell division). This will lead to the situation that other cells of the organ (or another organ) will also join the process of uncontrolled cell division. And uncontrolled cell division and ability to spread the division to neighboring cells and cells of other organs is the main feature of all types of cancer. It should also be understood that transition of a growing number of differentiated cells to dividing cells will result in a fewer number of differentiated cells in the organ, and at some point the organ may no more be able to carry out its function, resulting in a lethal outcome.

Apparently, there is an alternative way of oncogenome distribution. It can be expected, that during interaction of a growth factor with its corresponding receptor, besides activation of cell division, cell fate (differentiation pathway) of the newly formed cells is decided (for instance, together with cell division, synthesis of the differentiation receptor(s) is triggered, which in future will activate the process of differentiation). There may be different ways how oncogenomes can affect growth factor-growth factor receptor set. The main result of such effect must be cell division. The oncogenomes are unlikely to care if the cell is differentiated or not, and they are unlikely to push the cell to a correct differentiation pathway. In case of incorrect differentiation or no differentiation, the pattern of the receptors necessary for contact of the cells with the adjacent cells of the same tissue will be different in the new cells. Thus, these cells will not be recognized as the same cell type by the neighboring cells. This will lead to inability of new cells to attach to the neighboring cells; they will be detached and gain the ability to spread in the organism. In the new place such cells will continue to divide and be a source of adapted oncogenomes for the cells of other organs. However, in this case the cells must have on their cell membrane receptors, allowing viruses and bacteria to get inside the cells.

Partial control of cell division

The case of the full control of cell division by oncogenomes, resulting in cancer development, is described above. Apparently, some alternative cases of cell division uncontrolled by the organism are possible, when the control over the 4 systems is not full, for example, if either the immunity, or apoptosis, or some genes of controlling system are suppressed, terminal differentiation is impossible, genes opposing oncogenome effect are mutated etc. In these cases cell division is also possible, though this division can still be limited by increasing the organism's resistance to such division, or in a result of immune system activation followed by decrease in number of viruses and bacteria. This will be partial control of cell division. It is not perfect for viruses and bacteria, but can still give some opportunities for their reproduction. Some of the possible cases of partial control are shown in Figure 6.

It is easier to arrange such partial control (as well as full control) in the tissues consisting of normally intensively dividing cells, for example epithelium cells, blood cells etc. In such cells activating system is stimulated by the organism itself, and oncogenomes only need to correct such division, so that it does not cease too soon.

Figure 6. Partial control of oncogenomes over the system of cell division regulation can result in a number of alternatives of host cell division uncontrolled by the host organism.

Koch's postulates

Four criteria that were established by Robert Koch to identify the causative agent of a particular disease include:

- ✓ A specific microorganism is always associated with a given disease.
- ✓ The microorganism can be isolated from the diseased animal and grown in pure culture in

the laboratory.

- ✓ The cultured microbe will cause disease when transferred to a healthy animal.
- ✓ The same type of microorganism can be isolated from the newly infected animal.

Nowadays these postulates look somewhat different, but at present, there is hardly anyone doubting their validity. It means that if some infection agent (pathogen-associated nucleic acid sequences) causes a certain disease, it must comply with these postulates.

It is not the case for cancer. For example, the suspected agent can be found in the organism, but not the cancer itself. Or in case of a similar cancer type, a different infection agent is found in the organism. The transmission of the infection agent from cancer tumor to another organism does not necessarily result in cancer development, or the disease develops after a big lapse. So, it is concluded, that this disease (these diseases) does not comply with Koch's postulates, thus the infection agent cannot be the cause of cancer.

Why cancer, main cause of which is viruses and bacteria, does not comply with Koch's postulates?

- First, cancer incidence and development is a 3-stage process (Figure 7), with only the first stage –infection process- complying with Koch's postulates. The second stage – microevolution – is not an infection process, and thus does not comply with Koch's postulates. As a result, the whole process itself (cancer development) does not comply with these postulates.
- Second, a large number of viruses and bacteria can stimulate uncontrolled cell division (ability to stimulate uncontrolled cell division can be one of the main direction of evolution of viruses and bacteria, not surprising, giving the advantages they gain by obtaining such ability), which is the main feature of cancer. In other words, the effect of different types of viruses and bacteria on a cell results in the common feature - cell division. This also does not comply with Koch's postulates.
- Besides, quite possibly, in most cases cooperative or additive effect of several oncogenomes or oncogenomes and helper genomes is necessary to stimulate cell division and cancer development. These cases are not described in Koch's postulates either.
- The transmission of oncogenomes from cancer tumor of one organism to the cells of another organism is unlikely to cause cancer in the new organism. Oncogenomes will have to go through all stages of cancer development in new organism, including survival, transition to chronic stage and oncogene evolution. Genome evolution is necessary since the new organism will have different gene alleles, not the ones to which the oncogenomes got adapted in the first organism. But the probability of cancer incidence in the new organism will

Figure 7. Three stages of cancer development.

increase. Such mode of disease development does not comply with Koch's postulates either.

An example of the uncontrolled proliferation of host cells under the effect of a bacterium is leprosy. Though *Micobacterium leprae* is considered the main

causing agent of leprosy, this disease does not comply with Koch's postulates either.

Microevolution

If viruses could arrange perfect conditions, those would probably be: host cell is eternal, continuously dividing, and no immune system exists. It looks like cancer cell. Can viruses favor those conditions and what must they do for it? They must be able to stimulate activating system, and suppress the functions of controlling system, as well as to suppress apoptosis and immunity for gaining the control over cell division. It is not a simple task. All this must be done in a single cell, and in many cases different genes (including different alleles) of different systems need to be simultaneously suppressed. How can they solve this task?

One of the adaptive mechanisms of the viruses and bacteria to the host organism are the mutations. Mutation frequency of viruses is significantly higher than that of humans, and can reach 10^{-3} - 10^{-4} per base in case of retroviruses, i.e. one mutation per every reproduction cycle. It means that the rate of evolution of viruses is very high. Some viruses are found in human organism for 50 years and longer. It is a very long time for viral evolution. And in many cases it is enough for viruses and bacteria to solve the task of stimulation of cell division.

The oncogenomes found in the cells of constantly renovating tissues, for example, epithelium or blood cells, have a big advantage. In such conditions they can reproduce and evolve in the absence of forced cell division regulation. In such tissues the evolution rate of oncogenomes and the probability of gaining the control over cell division increase. In case of epithelium it means elevated risk of carcinoma incidence.

Conclusion

According to oncogenome's model of cancer development, **the main cause of cancer incidence is oncogenome microevolution, which takes place during chronic infection process.** In other words, oncogenome-induced chronic infection process is a pathway to cancer. It can be either long, or short, or may not end within organism's lifespan. Chronic infection process gives the oncogenes of oncogenomes a chance to adapt to a particular genotype and evolve to an extent that viral and bacterial oncogenes could gain the control over cell division. Presence of several oncogenomes, or oncogenomes and helper genomes in the cell, can significantly decrease the time the oncogenomes need to stimulate cell division. Oncogenome genotypes, that could overcome cell or organism resistance in one cell, will get an opportunity to stimulate its division, opportunity to reproduce and gain an evolutionary advantage over other genotypes. The ability of oncogenomes to both enter and leave host cells can be one of the explanations, how cancer cells can spread to other cells of the organ, or cells of another organ. The diversity of cancer types is thus determined by the diversity of oncogenomes and combinations of oncogenomes and helper genomes.

This can also be true in other cases of stimulation of host cell division, including the case when oncogenomes can only partially overcome cell resistance (adenoma etc). In other words, in cases of cell division uncontrolled by the organism, viruses and intracellular bacteria are the first to be suspected in stimulation of such division. They are the beneficiaries of such processes.

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