Cancer is a side effect of evolution of viruses and bacteria.

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Abstract

Any human organism is home to viruses and bacteria. However, viruses (as well as other intracellular parasites) are interested in continuous division of the host cells. Unlimited division of the host cells means unlimited expansion of the living space and possibility for unlimited multiplication of viral particles. For this, human Cell Cycle Regulation System has to be affected in such a way to induce unlimited division of host cells. The present work describes oncogenome`s model of cancer development, according to which, in order to stimulate cell division, viruses affect a gene (or several genes) during transduction of a signal for cell division from growth factor to cyclin/CDK system. At the same time, controlling gene (p53, RB etc.) function and switch to apoptosis are suppressed. Cell switch to cell division implies inability of the cell to carry out the functions of a differentiated cell. Spreading of viruses (bacteria) to the adjacent cells and forcing them into division, with simultaneous loss of differentiated cell functions, will become evident as the formation of malignant tumor or cancer.

Introduction

Viruses and bacteria accompany humans during all human evolution and during life of every human being. Viruses and bacteria have evolved with humans. The main goal of viruses and bacteria, like any living organism, is to maintain their species, and they can reach this goal through reproduction and expansion. Nevertheless, their urge for reproduction often comes in conflict with the goals of the host organism, and in this case host (human) immune system, including early nonspecific responses, immune responses mediated by cells, humoral immune responses, comes into play. However, viruses and bacteria too have evolved ways to regulate and evade the host's immune defense. Sometimes they succeed, and infection process gets into chronic stage, during which the confrontation of viruses and immune system continues. In some cases, viruses succeed to suppress the immune system up to the stage that it can no more interfere with viral reproduction. Finally, multiplication of the viruses can reach the point when they themselves inhibit further multiplication. This is a dead-lock situation, but there is a way out of it. Unlimited division of the host cells means unlimited expansion of the living space and possibility for unlimited multiplication of viral particles. For this, human Cell Cycle Regulation System (CCR System) has to be affected in such a way to induce unlimited division of host cells, and viruses and bacteria, that could evolve to acquire an ability to affect CCR System, will be called oncogenomes hereafter.

Oncogenome`s model of cancer development

One of the adaptive mechanisms of the viruses 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. 24 hours later every base in viral genome can be mutated, and a year later a virus can construct a new gene. However, such calculations can be true only for viruses with high frequency of mutations, and for the case when viruses can multiply freely. In the real world the immune system will suppress multiplication of viral particles and slow down evolution of the virus. Nevertheless, under decreased immunity, the frequency of multiplication of the virus can remain fairly high.

Apparently, mutations take place relatively uniformly in viral genome, but if a mutation takes place in functionally important genes (e.g. polymerase) and decreases viral ability for

reproduction and surviving, then the newly formed quasispecies will be eliminated from the viral pool. At the same time, if the mutation does not lead to a significant deterioration of virus's competiveness, it can be kept. Different genes, apparently, allow for a different amount of relatively neutral for virus vital functions mutations. Thus, some regions with formally more frequent mutations then others (hypervariable regions) can appear in viral genome. Often such genes are viral coat genes. In this case, quasispecies with different antigenes are formed, and such mutations help the virus to escape immune pressure and favor its surviving. Such hypervariable genes may as well be genes that do not directly participate in the reproduction of viruses, but are needed by the virus to influence the host organism.

High mutation frequency of the viruses implies that if a virus has a gene which remains unchanged during a prolonged period of time, this gene is actively used by a virus and gives additional advantages for virus surviving and spreading. This can be attributed to viral oncogenes as well.

When a virus gets in a cell of some specialized organ, it gets in a cell in G0 phase. Cells cycle is divided into stages: G1- is a phase prior to DNA synthesis. S-phase is the period of DNA synthesis (replication). G2 phase is the period between DNA synthesis and mitosis, M phase is cell division[1]. G0 is the stage of the cell when it acts as a specialized cell, in other words, G0 is the price the cell has to pay for the chance to divide and transfer its genes to the progeny as a part of a multicellular organism. In the end of the M-phase, the decision whether the cell continues to divide, and thus be directed to G1 phase, or the cell goes back to its functions as a specialized cell, and thus be directed to G0 phase is made. The vast majority of cells of a specialized organ are specifically in G0 phase and normally divide quite rarely. The process of division itself takes about 24 hours, while, for instance, liver cells remain in G0 phase for about a year. Nerve cells do not divide during the lifetime, and epithelium cells divide continuously. That is the reason why the cells of such organ as liver are normally in G0 phase. But this implies that the environment for viral reproduction in such an organ is rather unfavorable. The only thing that can interest the viruses is species maintenance and expansion, and for that reproduction of viruses is needed. Best conditions for the reproduction of the viruses are when host cell is in S-phase, the phase when cell DNA synthesis occurs. Possibly, to keep the cell in S-phase and prolong these favorable conditions, human immunodeficiency virus-1 (HIV-1), through structural virion protein vpr, arrests cell division in G2 phase[2]. Other viruses also try to coordinate their reproduction with S-phase of the cell cycle. This can be one of the ways to explain that for viral DNA synthesis cell proteins appearing in S-phase, for instance polymerase, need to be available. However, in order to direct the host cell to S-phase, viruses must affect the Cell Cycle Regulation system (CCR system).

A cell 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 through the receptors send a signal for division start to the cell and further through Ras, Raf and MEKK, activate MAP (Mitogen Activated Protein) kinase cascades, which, in turn, transmit the division signal through Myc protein to cyclin/CDK system. Such kinases as Raf, MAP and Myc activate sufficient amount of genes for starting cell division, but 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. Cyclin/CDK system consists of a number of cyclins (A, B, C, D, H etc.) and cyclin-dependent kinases (Cdk2, Cdk3, Cdk4, Cdk5, Cdk6 etc.). Cyclins are specific activators of a family of cyclin-dependent protein kinases and belong to the proteins with a rapid turn-over and a short half-life. CDK activating kinases (i.g. CDK7 with cyclin H) can also be referred to this system. It is different cyclin/CDK complexes that regulate the cell transition through the cell division phases. During cell division process, the cell needs to overcome several checkpoints, in which CCR system verifies that the conditions necessary to continue the process exist at every division stage. For instance, during G1/S checkpoint it is checked whether the cell must exit G0 phase and start DNA synthesis. The impulse for cell division start can be the presence of growth factor and normal gene expression during all the way of signal transition from growth factor to

cyclin/CDK. In this case cyclin D and E gene, normally referred to as G1 cyclins, expression increases, their intracellular concentration is raised. Cyclins D1, D2 and D3 form complexes with CDK4 and CDK6 kinases. Such cyclin/CDK complexes phosphorylate RB protein (the product of retinoblatoma Rb gene), which promotes releasing E2F transcription factor from E2F/RB complex. pRB phosphorylation is completed under the action of CDK2, activated by cyclin E. In other words, the main function of cyclin D/CDK4/6 complex and cyclin E/CDK2 complex is the activation of E2F transcription factor, which activates a number of genes necessary at the first stage of cell division i.e. cell entrance to the S stage, including DNA polymerase. Signal for S-phase completion and cell transition to G2 phase is the activation of another kinase CDK1 by cyclin A, with simultaneous termination of CDK2 activation. Signal to the cell division (mitosis) start proceeds from M phase promoting factor, posing a complex of CDK1 kinase with activating cyclins A or B, stimulating M-phase of the cell cycle. Consequently, it is the subsequent activation of different cyclin/CDK complexes that leads to the subsequent transition of the cell to different division stages, and the absence of the necessary cyclin/CDK complexes at some cell division stages can result in division arrest.

However, cell division is directed not only by cyclin/CDK complexes and other stimulating genes. More controlling genes, influencing cell division progress, exist. First of all it is p53 gene, which protein can, through p21 gene (WAF/CIP), suppress the activity of cyclin/CDK complexes, arresting cell division process. Such scheme apparently works during stress situation, including mutations or viruses. Similar to p21 properties are possessed by p27(KIP1), p57(KIP2) proteins. These proteins interact with different complexes comprised of CDK1 and CDK2, B, A and E cyclins, suppressing their ability to phosphorylate corresponding targets. p27 concentration drops when Ras and Myc genes are activated. Overexpression of cmyc can induce a heat-labile factor that binds p27 and inhibits its association with cyclin E/cdk2 [3]. Overexpression of mitogen-activated protein kinase (MAPK) in fibroblasts increased p27 degradation [4]. RAS is required for p27 degradation at G1 to S phase entrance [5; 6]. Simultaneous activation of Ras and Myc genes occurs during signal for cell division start transduction from growth factors to cyclin/CDK. In this case p27 concentration drops, and, correspondingly, cell transition to S phase is permitted. In case when only Myc or cyclins are activated, p27 concentration decrease may not be sufficient for the cell transition to S phase. It possibly means that p27 belongs to a verifying system, that checks if the conditions for cell division start exist. Besides, p27 is capable of arresting cell division in contact inhibition. 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. Proteins of the INK4 family (p16, p15, p18 and p19) specifically bind to Cdk4 and Cdk6, but not to other Cdks, preventing their interaction with the three different D-type cyclins, D1, D2 and D3 and thus preventing pRB phosphorylation. Such scenario prevents cell transition to S phase. As the increase in concentration of INK4 proteins takes place during G2/M phase [7], one of the possible functions of INK4 family may be prevention of repeated cell transition to S-phase afer completion of DNA synthesis, before cell division process is completed. Thus, all these proteins (p21, p27, p57, INK4) can inhibit cyclin/CDK complex activity, arresting cell division. Through these proteins CCR system regulates cell division process, activating in the proper time either cyclin/CDK complexes, or proteins suppressing division. p53 protein is one of the regulators, addressed by different cell systems in case of need of cell division arrest. For instance, DNA mutations lead to the increase in p53 protein concentration, which in turn activates p21 gene transcription, and the increase of p21protein concentration results in cyclin/CDK complex inactivation. It stops cell division process and let cell DNA repairing system repair DNA damage. In case if the mutation cannot be corrected, further increase in p53 protein concentration results in apoptosis, programmed cell death.

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. As all the controlling proteins act through cycling/CDK complexes on pRB activity, this protein can be

called «last guardian» in the system of controlling genes. Behind this gene there are no more intermediates before E2F, so in case of pRB inactivation, for instance in a result of a mutation (normally such mutations should result in apoptosis), E2F concentration is increased, and the process of DNA synthesis, i.e. S phase of the cell cycle may start.

But this is only applied to G1/S checkpoint transition. G2/M and M checkpoint transitions can demand activation of other genes, not associated with E2F activation, and thus, pRB inactivation only may not be necessary for cell division progress.

Nevertheless, in case of pRB gene mutations, p53 protein, also called "genome guardian", cannot stop cell division process acting upon cyclin/CDK complex through p21. This action is meaningless in this situation, since it cannot transmit the signal of division termination through pRB. However, apoptosis which can be initiated by p53 can be used as an alternative for elimination of RB gene mutation. In case of either viral action upon p53 gene, or mutation in this gene, as well as in case of apoptosis inactivation, the cell has no choice but S phase transition. Since in this situation p53 is not capable of terminating cell division initiation, the arising mutations will remain in cells of following generations. Moreover, CCR system will tend to return the cell to normal state, and to do that, will increase the expression of such genes as p53, RB etc. However, it is known [8], that increased expression of some gene results in the increased probability of mutations in this gene. Moreover, increased mutation frequency will be observed in all genes, which expression was increased. It can be genes stimulating cell division, expression of which increases under the growth factor action, it can be controlling genes, when they try to normalize or suppress cell division. In other words, increased expression of the genes, resisting external factors including mutations, will result in the increased mutation frequency precisely in these genes. Such "gene specific" mutagenesis will further disrupt CCR system abilities to normalize cell regulation and lead to avalanche increase in mutation number.

Such system, in which disruption of function of one gene can result in unpredictable effect, seems unbalanced. Increase in gene copy number will improve gene reliability, at least in case of mutations. In case of homologous (orthologous) genes, such system must be more resistible not only to mutagenesis, but also to the action of other factors, including viruses. Indeed, every gene of CCR system seems to have a homolog. For example, these are p63 and p73 for p53, p107, p130 for RB gene, E2F1, E2F2, E2F3 for E2F family, p15 , p16 , p18 and p19 for INK4 family, some homologues for cyclins and CDKs were described above, etc. CCR system reliability could be enhanced by additional verification of the process. For example, an increase in E2F protein concentration should normally be correlated with activation of a number of genes (RAS, MAP kinases, Myc etc.). If such correlation is missing, it may argue for cell division termination or even apoptosis.

However, let us consider viruses. As mentioned above, when a virus gets into a cell of a highly specialized organ, it gets into a G0 cell, unfavorable for viral multiplication. But the virus must multiply, it is a demand of its genetic program. The solution is to affect the CCR system to force the cell to divide. In the beginning it may be enough to transfer the cell to S phase. Then, as the viruses multiply, and inhibition because of their concentration increase or competition for nutrients starts, S phase transition only may not be enough. Transfer to other division stages and, finally, cell division must be stimulated. Cell division means expansion of living space for the virus.

How can a virus do that? Acting upon the CCR system, using pre-existing mechanisms of cell division stimulation. Cell division is induced by growth factors, and the signal for cell division is transferred through growth factor receptor to the cell and further activates a number of gene cascades, like RAS/RAF, MAP kinases, P13K/AKT, Jak/Stat etc. Activated genes perform all cell division process through proteins. Action upon any gene involved in cell division can be expected to affect to a certain extent the division process. However, the degree of the effect of different genes may not necessarily be the same. For instance, genes, affecting the energy of the process, protein synthesis, transport etc. may speed up or slow down cell division, but division initiation is impossible without G1/S checkpoint transition induction.

For such an action, either growth factors, or action upon genes, transmitting signal to

cyclin/CDK complexes (Ras, MAP, Myc kinases etc.) are necessary. Since on the way of the division signal transduction RAF, MAP, Myc kinases in turn activate a large number of genes, it can be assumed that the earlier upstream the action occurs, the larger number of genes participating in cell division is activated, and the closer the process to normal cell division is. It can be expected, that cell division of different organs is initiated by different growth factors, which promote activation of different gene cascades. But apparently, these cascades will be different only in the beginning, when genes responsible for cell differentiation have to be activated, since these have to be different groups of genes for each organ. Downstream the cascade of the signal transduction, when genes necessary for the division of all cell types (all organs) are activated, these different cascades will presumably combine. If the virus affects the genes upstream the cascade, genes responsible for differentiation may also be activated. If the virus acts upon the downstream genes, cell division can take place, but cell differentiation might fail. Cell differentiation might also fail in case of virus producing or stimulating the production of growth factors, not specific for a given organ. Cell division can be stimulated, however, a conflict may occur during differentiation, resulted from contradictory signals of gene activation, different from the activated genes of the surrounding cells.

However, effects on the cascade, even very upstream, for example, through growth factors, may not be sufficient for neutralizing the action of controlling genes. It is not impossible, that CCR system checks if growth factor genes are indeed activated. Besides, during cell division, besides G1/S checkpoint transitions, G2/M and M checkpoint transitions should be made, and other genes, including genes favoring checkpoint transition and controlling genes (p53, RB etc.) should be affected. How can viruses achieve that? For instance, viruses may acquire or construct a gene homologous to a cell gene involved in cell division. However, such gene can only be useful if increased gene expression stimulates cell division. In this case, additional protein, especially protein not subjected to sell signals, will favor division. In case of controlling genes (p53, RB etc.), additional protein will no more favor cell division, thus such genes are useless for the virus if acquired. At the same time, viral genes, which will somehow inhibit the function of cell controlling genes will also favor host cell division, and presence of such genes in viral genome can give an additional evolutionary advantage to such viruses. It can be the explanation to the fact that v-ras, v-myc etc., but not p53 and RB homologous genes are found in viruses.

Can viruses really have such an effect upon CCR system and induce cell growth? Epstein-Barr virus (EBV) can serve as an example. Its LMP-1 gene is a viral oncogene that resembles a cell-surface receptor and can induce anti-apoptotic proteins such as BCL-2, A20 and MCL-1. LMP1 activates the NF-κB transcription factor in B-lymphocytes and modulates epidermal growth factor receptor in epithelial cells. LMP-1 is also implicated in three other signaling pathways, c-Jun N-terminal kinase (JNK)-AP-1, mitogen activated protein kinase (p38/MAPK) and Janus kinase (JAK-STAT), which regulate cell proliferation and apoptosis. EBNA-LP function allows the cell to re-enter the cell cycle by stimulating the activation of cyclin D2. Another well-known DNA tumor virus is Human papilloma virus (HPV). Its protein E6 binds with the tumor suppressor gene p53, inducing its degradation. E7 interacts with retinoblastoma suppressor protein (Rb), disrupting the pRb/E2F and releases E2F. E5 protein binds with the platelet-derived growth factor ß receptor, promoting a sustained mitogenic signal. Human herpes virus 8 (HHV-8), also referred to as Kaposi's sarcoma-associated herpes virus (KHSV) and its K1 protein can induce VEGF expression. Viral v-cyclin can replace human cyclin and induce pRB phosphorylation and v-Bcl-2 proteins may inhibit apoptosis. Viral proteins activate pathways controlling cellular growth, angiogenesis and inhibition of apoptosis such as the PI3K MAPK family Jak/STAT and nuclear factor-κB (NF-κB) signaling pathway. More detailed information about the effect of these and other viruses on CCR system can be found in numerous reviews for example [9]. All this indicates that viruses apparently can induce cell division.

A little more difficult is the situation with bacteria. Apparently, the reason for this is primarily smaller amount of information about bacterial genes and ability of bacteria to stimulate

host cell division. However, the bacteria that can develop inside the cell, i.e. can act as intracellular parasites, are not very different from viruses. Though they depend on the cell state to a smaller extend than viruses, cell in the S phase will favor bacterial nutrient supply and stimulate their reproduction. Besides, host cell division will also mean to them increase in living space. To date, it is acknowledged that Helicobacter pylori can induce cancer, besides, Salmonella typhi, Streptococcus bovis, Chlamydia pneumoniae and Mycoplasma are suspected to have this ability[10]. By the way, practically all of them can exist as intracellular parasites. As for bacteria that are not intracellular parasites and exist in intercellular space, at least such bacteria can be interested in angiogenesis (the physiological process involving the growth of new blood vessels from pre-existing vessels). Besides, Gardnerella vaginalis[11] are known to be able to destroy epithelial layer, when anchoring on an organ wall. It can make oncogenome penetration to G0 cells considerably easier, i.e. in this case bacteria will play a role of helper (for example, viruses not directly involved in the regulation of CCR System, but capable of, for instance, reducing immunity, thus favoring oncogenomes reproduction, can act as helpers. Changing the environment from habitual to constraining which restricts bacterial reproduction or even existence (G0 phase) can have an unexpected outcome, including the bacteria becoming intracellular parasite and oncogenome. Time and microevolution can favor this process.

An example of a possible role of bacteria in oncogenesis can come from some research on Mycoplasma [12], done in cell culture. The cell culture can only partially be considered similar to in vivo situation, since cells divide continuously and do not enter G0 phase (are not differentiated). It is possible, that these cells have compromised apoptosis (since they are immortal). So, these cells are on their way to become cancer cells. But some functions, like contact inhibition, are retained. It may mean that CCR system of these cells can terminate division through a controlling system (apparently p27). Incubation of such cells with Mycoplasma resulted in the cells no longer growing in a flat monolayer, and piling up and forming foci with multiple cell layers . Thus contact inhibition is disrupted under the action of Mycoplasma, and this may mean that bacteria, as well as viruses, are capable of affecting cell CCR system. Moreover, cDNA microarray technology showed increased expression level of, among others, RAB17 и RAB24 (member RAS family) and decreased expression level of p107 (Retinoblastoma-like) under the action of Mycoplasma. Besides, authors note reversible и irreversible forms of transformation. Apparently, the initial changes are associated only with the impact of Mycoplasma, and these changes are reversible if bacterial impact is eliminated. If the mutation occurs, the elimination of bacteria cannot bring the cell to the previous state, and the transformation becomes irreversible.

Helicobacter pylori, apparently, can stimulate the increase of concentration of growth factor [13,14]. An example of proliferation uncontrolled by the organism can be leprosy (Hansen's disease), caused by Mycobacterium leprae [15].

Thus some bacteria, as well as some viruses, can be expected to become oncogenomes during the evolution, and, affecting cell CCR system, promote host cell division.

Further, there situation can progress as follows:

1. Viruses or bacteria, or both, stimulate the genes responsible for host cell division, suppress the function of controlling genes, and, if necessary, suppress apoptosis (viruses may need apoptosis suppression already in the beginning stages of infection process, since apoptosis is one of the ways organism resists viral infection). Those quasispecies which can first overcome the CCR system in one cell, get a chance to freely reproduce themselves and an evolutionary advantage over other viruses and bacteria. If those oncogenomes can prevent the cell entering G0 stage, but direct it to the following division (G1), then the reproduction speed of such oncogenomes will raise substantially. However, the result of it will be a cell not capable of fulfilling its functions as a highly specialized cell, i.e. it will not be a differentiated cell. These quasispecies will be able to spread to other cells of the organ, forcing them into continuous division escaping G0 phase, and, consequently, losing their differentiation. As viruses and bacteria spread to new cells and transfer them to a non-differentiated state, it gets harder for the organ containing these cells to carry out its function. A malignant tumor is formed. When the

process reaches the stage when the remaining cells of the organ cannot cope with the growing load, if the organ is critical for the organism's life, the organism dies. If these oncogenomes spread to other organs, metastasis occurs.

2. The action of viruses and bacteria is not sufficient to overcome CCR system. To prevent unnecessary for the organism cell division, CCR system increases the expression of genes, blocking the effect of oncogenome. This, in turn, leads to gene specific mutagenesis and decrease of CCR system resistance. After the resistance decreased and existing oncogenomes can stimulate cell division, unlimited proliferation will start. Nevertheless, in this case the tumor will be formed from a progeny of a single cell, and will not be able to spread to other cells, not containing such mutations. It will be a benign tumor.

3. The above options are relevant to the cells of highly specialized organs in G0 stage, and which, consequently, rarely divide. However, there are cells in human organism which divide practically continuously, e.g. epithelium cells. Such conditions are very favorable for reproduction of viruses (and of some bacteria), and there is no need to further stimulate the division of host cells. The problem is that such cells die quickly due to apoptosis. This situation is unlikely to be good enough for viruses, especially since it can be solved by prohibiting apoptosis. In this case proliferation of epithelium (e.g. adenoma) will be observed. Since the main task of all living things, including viruses and bacteria, apart from reproduction is invasion, as viruses and bacteria reproduce themselves in the favorable conditions of frequently dividing host cells, they will try to spread to adjacent cells in G0 phase. If there are oncogenomes among them, they may succeed, and then uncontrolled division will spread to both adjacent and distance cells (e.g. Carcinoma).

The common feature to all these processes is the uncontrolled by the organism cell proliferation.

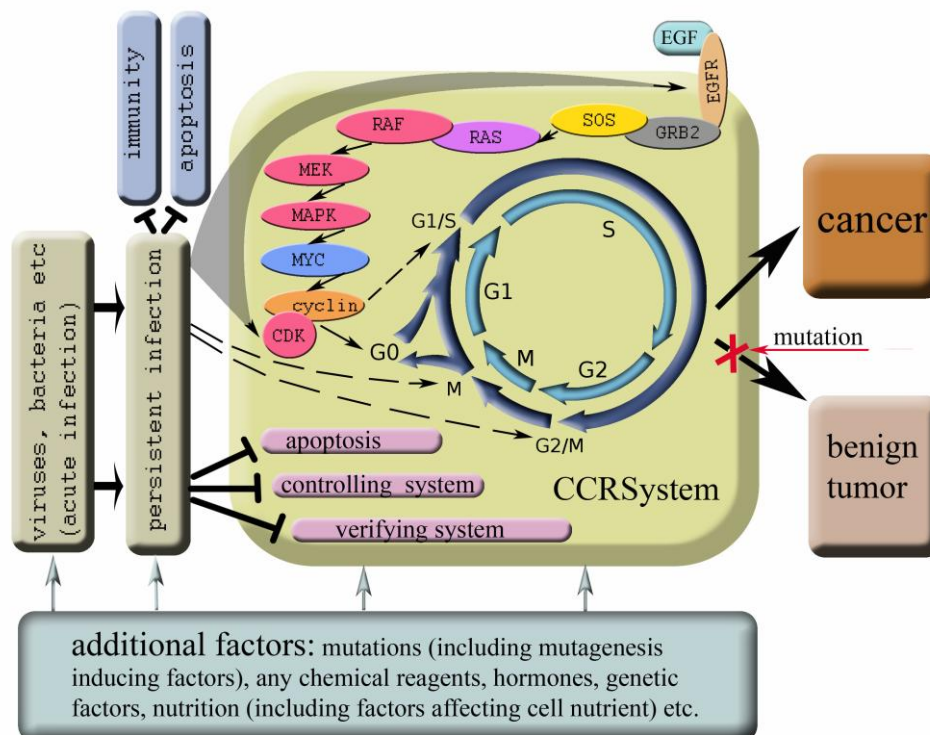Figure 1 shows the diagram of cancer development.

Figure 1 │ Oncogenome`s model of cancer development

As the uncontrolled proliferation requires the participation of a rather large number of genes, belonging to different systems (stimulation of division, inhibiting of controlling genes,

prohibition of apoptosis), a single type of virus or bacteria can hardly be expected to overcome the opposition of CCR system and stimulate cell division. More likely, action of several oncogenomes is necessary for stimulation of uncontrolled cell division. Several different viruses or bacteria, or both, having additive or cooperative action on the system of cell division regulation, are apparently able to force the cell to divide. It can be the reason why the presence of a virus or bacterium in the organism, including oncogenome, does not necessarily mean inevitable occurrence of cancer, since usually the presence several oncogenomes is necessary. But even if a number of oncogenomes capable of cancer induction are present, a delay period necessary for overcoming immune system and CCR system resistance exist, and the length of this period can vary significantly, since it depends on a number of factors (oncogenome type, speed of evolution in terms of adaptation to a given organism, immunity, genetic factors etc.). Different oncogenome combinations, capable of inducing uncontrolled cell division in a given organ seem to exist, the common feature of these combinations of viruses and bacteria would be the ability to exist in a given organ. All this can introduce certain difficulties in identification of oncogenomes provoking cancer, as well as in identification of correlation between cancer incidence and presence of some virus or bacterium in the organism.

Besides, the course of the uncontrolled division itself may vary, which will result in different forms of cancer. If the oncogenome can take the cell out of G0 phase and lead it to the S phase, but cannot overcome G2/M checkpoint, it will result in cell size growth. Sufficient stimulation and circumventing repeated S phase entrance restriction results in polyploidization. In case of strong division stimulation and shortage of time for recovery, cell size can decrease. Failure to terminate cell division during G2/M checkpoint can result in cell division before finishing DNA synthesis or chromosome disjunction, which can lead to different chromosomal aberrations during division. Besides, failure to terminate cell division for a system responsible for contact inhibition will lead to contact inhibition disruption. Which of the genes on the way of signal transduction from growth factors to cyclin/CDK is affected by oncogenome is also important. It determines to which extent uncontrolled proliferation will be different from normal cell division, including cell differentiation.

It is tenable to assume that additional external factors, which stimulate invasion of viruses and bacteria, decrease the resistance of the immune system of the organism and support the action of viruses and bacteria on Cell Cycle Regulation System will contribute to cancer incidence. Among such factors are the mutations (including mutagenesis inducing factors), any chemical reagents, hormones, genetic factors, nutrition (including factors affecting cell nutrient), urbanization, sex revolution etc. Situations when cancer is induced by external factors (except viruses and bacteria) only are difficult to imagine. First of all it is caused by the fact, that every human being is a carrier of a certain number of viruses and bacteria, possibly including oncogenomes (for example EBV found with 95% of population, and often found mycoplasmas). As the age increases, the number of viruses and bacteria increases as well, and they get more time for adaptation for a certain organism. So, the situation with the action of only additional factors is apparently impossible, but the action of the additional factors is summed to the action of viruses and bacteria and can contribute to cancer incidence, simplifying the beginning and uncontrolled cell division.

Thus, cancer is a two-stage process, the first stage of which is an infection process, with the main role of surviving of viruses and bacteria. The second stage is the stage of cancer development, responsible for giving the opportunity for viruses and bacteria to reproduce themselves and spread in the organism. The first stage is relatively independent, and the second stage (cancer) completely depends on the success of the first stage. However, infection process and cancer development stage are different processes, with different goals and different patterns of development. Nevertheless, since the cancer development stage depends on the first stage, some patterns of the infection process will remain during the process of cancer development.

Of course, the above mechanism of cancer incidence and development is greatly simplified. Actual processes can strongly differ from the above described, but the main principles must remain the same: viruses and bacteria (any organism benefitting from unlimited

proliferation of the host cells) are interested in stimulation of unlimited division of host cells, and are primarily responsible for cancer incidence and development.

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