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## Programming and Implementation of Age-Related Changes

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### 1. Introduction

From the songs of my childhood I can remember one such song: " The cranes are flying far and they will never come back, the rumour is spread ... . " The author of the song text assumes that the cranes can not come back , but he/she can't bear the thought of losing lovely birds and adds: " it's a rumour !" However ,I am saying once more he lets the thought that maybe the cranes won't be back any more .... I loved this song and while listening sorrow used to enter my soul quietly. Although I knew that birds return from warm countries ... And still there was something ominous in those " never come back." Then , after so long in Dinara Kasradze's monograph ("Quantum satis ", 2005) I read the following: "Each species has it's own quantity of wing waving , after which the bird dies ." ..yhat's where that subconscious sorrow came from ... mine or of that song text author, as we mentioned above... Yes, it's so, the organism tissues , cells "get worn" while acting and get restored too; The only bad thing is that with age , damage of cells exceeds their reparation i. e. the mentioned fact becomes expressed with aging! Every creature turned to have its own strictly defined potential, after which the life expires. Then where is immortality? Only in fairy tales ? "The truth used to be written in fairy tails , the truth , written in a creative and "fairy" way " ,-"In fairy tales , many secrets of nature are explained in "fairy" language ,many things that are unsolved and not clear at all! "... Then where's immortality? The water or spring of immortality ? Maybe it is nearby , here next to us...

### 2. Hayflick's limit

With the age, damage of molecules exceeds its reparation i. e. the mentioned fact gets more expressed with aging. The question is : What are molecular reasons for wearing cells out. Hayflick's experiments are important in this way: in 1961 Leonard Hayflick demonstrated ( at Wister Institute , Philadelphia ) that the cells of normal human fetus managed to divide 40-60 times. The scientist in vitro observed human, normal, diploid fibroblast cultures and he saw that these cells have absolutely defined life expectancy - they stop multiplication and get older after 50 times division (doubling). On the contrary, fibroblasts of the patients , ill

with Progeria or Verner syndrome (early aging), used to double 10-12 times - instead of 40-60. Adopted term, so acceptable nowadays, Hayflick's limit comes from the above. This limit i.e. border was fixed in the culture as for all differential (i.e. mature) cells, also for other multi cell organisms. Maximum number of divisions in one organism is different according to the type of the cell and difference is much more expressed in different organisms. For most of the cells Hayflick's Limit is 52 divisions. The history of Hayflick's experiments is also interesting. He worked together with Paul Moorhead. In one of the tests they mixed equal quantities of normal males' fibroblasts (that had been divided 40 times) and normal females' fibroblasts (that had been divided only 10 times) i.e. men's older cells were mixed with women's younger cells and they received mixed culture. "Not mixed" culture (males') was used for control. When division in the controlling culture of the males cells stopped, in that very moment mixed culture was studied and it turned out that only women's cells were left there. This meant: The older cells "remembered" that they were old, even when they were surrounded by young cells.

Hayflick differed the following phases of cell division in the culture: At the beginning of the experiment, he called the "firstly" culture "phase one"; then the period when cells were multiplying was the "phase two". Division (doubling) period after numerous months was called "the third phase phenomenon" - when cell growth was reduced and stopped. The reason for replication aging is uncertain. It is supposed that genes of aging are activated. (They are located in the first and fourth chromosomes), the growth regulating genes are changed or lost (which at last causes growth inhibition in aging cells too. The genes, speeding (accelerating) aging process are revealed. For example, reducing signal transmission by means of Factor 1, similar to insulin, causes *Drosophila*, also *Nematode c. Elegans* and increasing of life expectancy in mice. The reason for such difference in replication intensity is unknown. It can be caused by activating specific genes at an old age. For example, during reduction of replication Kinaza inhibitor genes (p21) are revealed. Replication aging is also induced by increased expression of p 16INK4a - the cell cycle inhibitor and DNA lesion.

### 3. The telomeres

The essence of genes' chromosome telomere shortening is interesting. The limited replication ability of the cell can be explained by the following: During each division, the chromosomal endings go through the unfinished replication (telomere shortening). After each division telomeres shorten, that ultimately causes stopping the cell division. Telomeres are important in stabilization of terminal parts of the chromosomes and also their fixing at the nucleus matrix. Telomeres gradually get shorter in later passages of the culture and also in older people's cell cultures. Telomeres are the longest in spermatozooids, they are longer in fetus than in an adult. As it seems, DNA loss in the terminal parts of chromosomes and telomere shortening causes deletion of important genes.

De novo synthesis of telomeres is regulated by means of enzym telomeraza. Correlation between the telomere length and telomeraza consistence is found. Hayflick's limit depends on telomere size reduction. Telomeres are DNA short repeated successions (TTAGGG) which are located at the end of chromosomes. If the cell doesn't have active telomeraza (as, for example, most of somatic cells), after each division the telomere size is reduced as DNA polymeraza can't replicate the ends of DNA molecule. In spite of this, taking this event into

consideration, telomeres must shorten very slowly-- by 3-6 nucleotides after one cell cycle; According to the Hayflick's limit, after certain number of divisions telomeres shorten by 150-300 nucleotides.

Nowadays, epigenetic theory of aging is delivered by B.A. Galitski (2009), according to which telomere erosion is explained first of all by activation of cell recombinases, which are activated in response to the DNA lesion, which is mainly caused by age depression of genome mobile elements. When after certain number of divisions telomeres absolutely disappear, the cell remains at certain stage of the cell cycle or it turns apoptosis mechanism on. It is interesting that A.M. Olivnikov (who was the first to suppose existence of telomeres (1973,1996)) said: "Telomeres action is proved. However, it shouldn't have had direct link with aging".

In spite of theories or certain plurality of opinions, it is clear today that cell aging is caused by a number of factors. Not only endogenous molecular way of cell aging is important, but also harmful exogenous affects during the whole life, which is followed by, so called, cell "wearing". In the course of time lethal changes are gathered in the cell lesions, which lead the cells to death, as ability to respond to lesions is gradually reduced.

Certainly human cells division is not infinite, except embryonic, sex and cancer cells. The cells which have short telomeres, are often "not valid" as their chromosomes are no longer stable. The chromosomes become less protected against various damaging factors, as in norm, their defending telomeres i.e. their endings can't protect them.

During the experiment researchers (group- "Geron Corporation") could change the route of the aging process: They installed genes in the DNA. The genes were responsible for telomerase synthesis. In these cells Hayflick's limit was doubled (100 divisions) and the life expectancy accordingly increased. According to these scientists' opinion, it is possible to change ordinary human cells that they will be able to divide infinitely. In January 1998 all the media sources informed the world that American scientists were able to force human normal cells to overcome Hayflick's limit: Instead of aging, the cells continued to multiply; and what is remarkable, they didn't transform into cancer cells. Brilliant! Bravo! If it was managed to overcome Hayflick's limit and increase life expectancy so, that cancer transformation didn't take place! And still we must point out that much care and attention is necessary in handling this process!

Telomerase was discovered in 1984 by Carol W. Greider. For opening of the protecting mechanisms of chromosomes (terminal replication by the help of telomerases) Elizabeth Blackburn, Carol Grider and Jack Szostak received Nobel Prizes. Human telomerase's structure was explained by Scott Cohen and his group (Australia, Children's medicine Research Institute, 2007). Telomerase consists of telomerase reverse transcriptase (TERT.), telomerase RNM (hTR or TERC) and diskernin (two molecules of each substance). TERT, as we pointed out, is the ferment reverse-transcriptase, which creates one-string DNA on the basis of template one-string RNA (i.e. telomerase represents a reverse-transcriptase and a special molecule of RNA is connected with it, which is used as a matrix for the reverse-transcriptase during lengthening of the telomeres.) Two subunits of the ferment are encoded by two different genes. TERT has a glove shape, which allows it to fix at the chromosome and add to one-string parts. It is considered that telomerase is the key to the cell immortality. Thanks to this ferment, cells multiply fast and don't get older.

Telomerase is the most intensively revealed in the embryonic cells, then in Germinational cells, very slightly in adult organism labile cells (cells, that must divide frequently, for example, intestinal epithelial cells), but their detection is difficult in the most of the somatic cells. (More correctly, it doesn't happen at all).

Telomerase is used in the cosmetic production (The product TA-65 was received from the plant *Astragal*, which activates telomerase). Michael Fossel supposed in one of the interviews (2006, int. by D, J Brown), that treatment by telomerase could be used not only for struggle against cancer, but also for fight against aging i.e. for increasing life expectancy.

When cells come closer to the Hayflick's limit, it is possible to stop aging if deactivation of those genes will happen, which are responsible for creation of the albumin (p53 and pR6), suppressing cancer. Sooner or later such, changed cells get to the condition, which is called "crisis" i.e. when big part of the cells (in the culture) die (However, sometimes the cell doesn't stop multiplication during the crisis period). As a rule, telomeres are absolutely destroyed at the time and condition of the chromosomes worsens after each division.

#### 4. Cancer

The naked endings of the chromosomes mean splitting of the both DNA strings. Neutralization of such type of lesion happens by connecting split endings. Also endings of different chromosomes can make confluence as they are no longer protected by telomeres. This story as if temporarily relieves telomere absence. However, in the anaphase of the cell division, linked chromosomes come apart quite accidentally, which is followed by a lot of mutations and chromosomal anomaly development and with the process development the cell genome is more and more injured. Ultimately the moment comes when apoptosis is turned on (The gene substance is so much injured) or the mutation is added to the injured genome which activates telomerase.

After activation of telomerase some types of cells obtain immortality. Their chromosomes don't become less stable for the number of divisions and the death process doesn't start. Many cancer cells are considered to be immortal as the telomerase gene is activated in them which allows these cells to divide infinitely and this is the reason for cancer growth.

Hela's cells are good example for cancer cells eternity, which were received in 1951 from Henrietta Lack's cervix cancer tissue. The name of the culture comes from the above. This culture is still used in studies today. Hela's cells are really immortal: They are produced daily in tons and they are descendants of the removed cancer cells from H. Lack's organism.

In spite of the fact, that cancer modeling in the cell culture is effective and it has already been used for years, it is still not exact. At first, it was unknown which was the influence, that causes cell multiplication in this model. Finding the answer became gradually possible: Different mutations were caused in the model cells (Which we meet in different cancer cells in human) which allowed the scientists to reveal several confluent mutations, that was sufficient for creating cancer cells from different types.

Mutations are confluent in different ways in different types of cells. However, in most of these confluences the following is fixed: 1. Activation of telomerase 2. Cycle damage of the albumin p 53. 3. Activation of Ras, Myc and other protooncogenes. 4. Violation of PP2A



phosphatase formation. These changes provide "turning off " the death mechanism by means of damaging chromosome destruction or apoptosis process. With this endless multiplication of the cell begins.

In cell cultures, this model of cancer clears up the telomerase's role in cancer development. In 90 percent of cancers telomerase's activation is observed.

In cancers without TERT activation in cells , they mainly used other mechanism of telomeres' protection , which is called ALT (alternative lengthening of telomeres). Details of this mechanism are unknown.

According to Elizabeth Blackburn's works (1985, 2001), telomerase is also involved in regulation of 70 genes which participate (or probably participate ) in cancer origin and development. Furthermore, telomerase activates glycolysis, which allows cancer cells to use sugar in order to maintain growth and division rate. This speed is equal to the same process rate in embryo.

Fight with the cancer is difficult. If it was possible to receive such a medication, which would cause telomerase's blockage in cancer cells, then telomere shortening would be renewed. Mutations would appear and cancer cells would die!

Working in this direction has started ( Koreans have just created the preparation "Telovak", which in the opinion of creators, activates immune system, that ultimately is directed to suppress telomerase. After trying it on volunteers, ill with cancer "Telovak" prolonged patients' life by merely one year. It also gifted three months of life to the patients who were on the last stage of cancer. The question is : Maybe not only in cancer cells is telomerase suppressed? Subsequently, will it ultimately make life shorter?

## 5. Senescence

Cancer cell is divided infinitely, telomerase's gene is expressed , " inserted " in it i.e. malignant cell looks like a sex or embryonic cell (Probably, these are the only cells and its product restores normal length of the telomere).

Hereby , we take the liberty of a small comment: Yes ! - Today, immortal cells of cancer are widely discussed , which is said to be the fault of telomerases . However, it shouldn't be absolutely right. Not all multiplied cancer cells are divided, i.e. among them there are some cells that divide ,so there is the limit too. As regards the culture, it is possible to initiate growth in all the ways . Besides , in vivo , cancer cells gradually cannot divide . Ultimately, they don't have "strength " of even it and die (These are famous facts , pathology -anatomists like to point it out. I remember the talk with Omar Khardzeishvili about this very question) i.e. part of cancer cells die by themselves in the lifetime of the ill organism. (It is an axiom today too); However, the person dies before all the cancer cells die !

In human fibroblasts, Kamoizin can increase Hayflicks's Limit by means of reduction of telomeres shortening quality. However, the scientists say , that vertebrates' cells have certain potential of replication. More importantly, A.Melk and his group (2003) saw that in vivo aging is possible without telomere shortening.

The surgeon, Nobeliant Alexis Carrel said : "All the cells , that grow in the culture , are immortal ; But if they reduced , the number of cell replications fell, it means that the way of cultivation, itself , is to be recovered and improved. " We take again the liberty of adding a comment of our own : "Growing cells in culture are immortal "- The multiplication process itself can be continuous. However, the cells probably change ; In this way a human is also immortal- by means of his/her generation or descendants ( since Adam till today ). Yes, exactly the same process! And don't let Carrel to deceive us. However, as regards the opinion, that "if the number of cell divisions reduced, then the way of cultivation must be improved. " This is right: It's necessary to improve conditions to increase birth-rate in people!).

Carrel's hypothesis (1921) was strengthened by the fact that the scientist had been growing the chicken's fibroblasts in the culture for 34 years. The part of scientists thought this was possible infinitely in vertebrates. However, there was a certain mistake during the experiment (i.e. in accuracy ) and most scientists didn't agree with the results. The mistake was in the fact that Carrel daily added chicken's embryonic, axial cells to the culture; This allowed the new cells to multiply and it wasn't multiplication of the initiate, original cells any more; but in this way cells' multiplication was possible unlimitedly. Some researchers are convinced that Carrel knew about this mistake (in the experimental procedure ), but he didn't admit it.

Briefly, Alexis Carrel's theory didn't succeed and his mistake was evident too. However, Alexei Olivnikov's theory is acceptable and corresponds to Hayflick's experiments: Telomerazas' inhibition is a good remedy in malignant cancer treatment.

Ultimately, in reduction of life expectancy the following is important : 1. Reduction of the cell replication i.e. what Hayflick's limit means ; 2. Telomeres' shortening ; 3. Accumulation of cells and reduction of axial cells number; 4. Changes , revealed in the cell with aging: accumulation of free radicals, influence of radiation, generation of oxygen free radical  $O_2^-$ , modification of albumins, lipids, nuclein acids , reduction of antioxidant mechanisms ( vitamin E, glutation peroxidaza) , accumulation of dot mutations; 5. Lowering of the reparation systems, lowering of the DNA helikaza activity i.e. defect (enzyme is involved in DNA replication, reparation and other functions, that are necessary for DNA perfection. Besides Verner syndrome, defect of this enzym is found in Ataxia-Telangiektazia); 6. Strengthened expression of antioxidant enzyme - SOD and katalaza (it has been seen in *Drosophila*) ; 7.It is thought that proteasome function can be lowered that is called proteolyses mechanisms. Its responsibility is elimination of abnormal and unnecessary intracellular albumen (Lesion of the organelles which is one of the reasons for cell aging).

Consequently, with aging, in all the organ systems, there are physiological and structural changes. The rate of aging process is associated with genetic factors, nutrition specialty, social condition , disease development , associated with age. For example, atherosclerosis, diabetes type 2, osteoarthritis.

The most effective way for increasing life expectancy is limitation of calories. It depends on sirtuins. They have hystondeacetylaza activity and probably they promote expression of different genes , products of which increase life expectancy. This products consist of proteins which increase metabolic activity, reduce apoptosis , stimulates albumens' third

structure formation ( fights with denaturation), inhibits free radicals of oxygen. Sirtuins also rise sensitivity on insulin and strengthen glucose metabolism. They can also be used in diabetes treatment. It's important that red wine activates sirtuins and this prolongs life.

So, probably nothing is impossible, among them defeating cancer disease and increasing life limit... However...

In spite of the fact that telomerase is the key to cell immortality i.e. "infinity" of cancer cell is caused by telomerase, we know and pointed out above that cancer cells ( where expression of this enzyme is high and where exactly telomerase is "accused " in persistent division of the cells), ultimately the condition is achieved when they don't divide any more ( more exactly -can't ), so their "infinity" is doubtful! Where is the immortality?

We set an example of studies above where there is indicated that aging is possible without telomere shortening or disappearing i.e. nor immortality or "not aging" reverse-process- the death (which follows the aging ) entirely depends on telomeres..... Consequently, it is doubtful again that telomerase is the key to the cell immortality! Then, where is the immortality!

In our opinion the key to immortality should be that "thing" which causes permanent renovation! Though, it's difficult to imagine it in our dimension , where everything has its beginning and the end , still I remember " immortality water" from fairy tales ! - Where is the immortality?

There are such albumen-stress albumens (which appear during different stresses in the cell and protect it from lesion spreading) - Chaperon , Chaperonins, sirtuin molecules are very important and we pointed out above their protecting and " rescuing " occupation ! Red wine turned to be sirtuins action stimulator! There is Resveratrol in the same red wine -plant estrogen, Melatonin's precursor ! Melatonin is a hormone which acts as an obstacle for lesion, "wearing out "; Melatonin has the most expressed regenerative capacity and consequently the ability to restore/maintain living structures!

In the preamble of my first monograph ( "melatonin" 2007) Dinara Kasradze wrote : "And in this system too, the most mysterious turned to be the Epiphysis... Epiphysis with its melatonin! However, it is the main thing where the life takes its origin (metaphor) -i.e. it is the "source " of light and darkness, mist and dawn . It causes sleep and waking up, tiredness and relaxing, wearing out and restoration, spring and autumn, summer and winter too .... It gives the world rhythm, biorhythm which gives us a birth, brings us up, breeds, ages or takes us into other..... It causes health and disease... and probably it is not surprising that in a creative way the "third eye" is called Epiphysis, maybe not entirely creatively. It can be so that overwhelming strength of the Lord is incarnated by means of Melatonin in our dimension.... Biological-cosmic key for immortality and constant transformations may probably lay ..... in the very magic molecule of Melatonin.... Who knows...."

## 6. Centriole, differentiation, senescence

Death is inevitable for any of living organisms, viruses, plants or animals. However, only multicellular animals, including human beings, die from ageing. A multicellular organism



(animal), containing a multitude of irreversibly differentiated cells, develops from only one cell the totipotent zygote. The potency to differentiate into a certain tissue or tissues (set by the factor which controls the possibility of repression and activation of genes) determines the individual histological state, or morphogenetic "status" of a cell. The final morphogenetic status means that such a cell is committed to programmed death (apoptosis). A 'zero' morphogenetic status means that the cell has not been committed to any irreversible pathway, i.e. it remains totipotent. Modification of morphogenetic status of a cell changes the whole spectrum of the tissues into which this cell can differentiate. In ontogenesis, this spectrum consequently narrows (totipotent / pluripotent/ multipotent/ unipotent/ non-potent) until the cell reaches the state of final differentiation (Malaitcev et al., 2002).

### 6.1 Need for a self-replicating controller

It has been established that morphogenetic status of a cell might be changed only through its division. We consider that cell division, differentiation and apoptosis may be controlled by a single intracellular structure. Naturally, this structure has to be self-replicating. Moreover, it has to have some way of counting or recording cell divisions. In a somatic cell potential candidates for this replicable structure are chromosomes, mitochondria (both contain DNA), and centrioles. To date the structures which might count cell divisions and, therefore, determine the morphogenetical status of a cell are generally thought to be telomeres (Bodnar et al., 1998; Greider, 1998; Shay and Wright, 2001). However, some data do not confirm the hypothesis that assigns the role of replication 'clock' to these parts of a chromosome.

Thus, the cells of mice bred by Blasco et al. (1997) did not have telomerase activity. Such mice were viable and could produce up to 6 generations, though the chromosomes of each subsequent generation had increasingly shortened telomeres. Only the sixth generation developed abnormalities caused by the extreme shortening of telomeres. The authors emphasised that 'ageing' of cells took place long before the marginal shortening of telomeres. Rudolph et al. (1999) showed that mice with inactivated genes of telomerase had shorter lifetime and increased frequency of oncological diseases, but physiological and biochemical tests did not reveal any signs of early ageing. Animal cloning disproves telomere hypothesis as well as other hypotheses, which suggest that a morphogenetic factor is located in nuclear DNA. In outline, the main point of cloning procedure is injection of the nucleus of a finally differentiated somatic cell into an oocyte with previously removed or destroyed nucleus. It was undoubtedly proved that the pattern of genes expression is changed to comply with the cytoplasm of a 'host' cell (Hardeman et al., 1986; Dominko et al., 1999). Injection of the nucleus of a frog carcinoma cells into an enucleated egg resulted in, not tumor cells, but normal tadpole development.

The key element of gene network controlling the processes of cell differentiation is an external factor for nuclear genome signal, which activates these groups of interactively expressing genes (Kolchanov et al., 2000). We suggest that the processes of cell ageing, differentiation and division are regulated by cytoplasmic factors. The structure, which regulates processes of irreversible differentiation, determination and modification of morphogenetic status, is most likely to be a centriole (centrosome).

Recent data indicate that centriole and nuclear cycles are not interdependent (Gorgidze and Vorobjev, 1994). It was shown that nucleus controls the synthesis of 'building material' (basically proteins) used by centrioles, thereby having control over the centriole cycle. When a cell has such 'building material' in excess (i.e. oocytes), cycles of centriole duplication may occur even if mitotic cycle has not been launched (Manandkhar et al., 1990). Phillips and Rattner (1976) also demonstrated that inhibition of RNA or RNA/protein synthesis suppresses the duplication of centrioles in cultured cells.

## 6.2 The rule of cell division

As a rule, somatic cells contain a diploid set of chromosomes and a pair of centrioles (diplosome). This ratio is maintained by the parallel reproduction of nuclear DNA and centrioles, which takes place while cells are being prepared for the next division. In the process of gametogenesis, the number of chromosomes is reduced and the cell becomes haploid. Studies of spermatogenesis performed in insects (*Sciara coprophila*, *Chrysopa carnea*, *Bombyx mori*) and mammals (*Heterohyrax syriacus* and *Memetes berdmorei*) discovered that at the first meiotic division spindle poles contain a pair of centrioles, while at the second division they contain only one centriole; in mammals spermatocytes get two centrioles after both first and second divisions (Kriouchkova and Onishchenko, 1999). On the contrary, oocytes of mammals (mouse, rat, and rabbit) and *Xenopus laevis* do not have visible centriolar structures during both the meiotic divisions (Kriouchkova and Onishchenko, 1999). During the process of fertilization, the chromosomal sets of a spermatozoon and an oocyte are mixed. The chromosomal sets/centrioles ratio, typical for somatic cells, may be restored either in a zygote or early blastomeres. Thus, in sea urchins, the spindle pole at first cell division contains a diplosome, while in mice they are centriole-free at both first and second divisions. Only at third division does a centrosome get a pair of centrioles. The literature reveals several hypotheses, which try to explain the formation of centrioles in embryonic cells. These structures may be obtained exclusively from the paternal cell, as in sea urchins. In most mammals zygotes, the centrosome is of maternal origin, but the centrioles are formed *de novo* only in the third cell cycle. It should be noted, however, that human centrioles, as well as centrioles of other mammalian species (sheep, cow, and marsupials), belong to the paternal sex cell (Breed et al., 1994; Nijs et al., 1996; Schatten et al., 1996).

Some studies demonstrate that centrioles act as the regulators that control the course of every phase of a cell cycle influencing the processes that take place at least two phases earlier (Neverova et al., 1996; Maniotis and Schliva, 1991).

## 6.3 Centrioles and cancer

Centrioles seem to play some role in inheritance of tumorigenic properties. Taking into account aforementioned facts, what molecular mechanism underlying the centriolar activity may control determination of morphogenetic status of a somatic cell? Centrioles may contain differently encoded RNA molecules stacked in a definite order. During mitosis these RNA molecules are probably released one by one into cytoplasm. This process presumably changes the status of repressed and potentially active genes and, subsequently, the morphogenetic status of a cell.

Centrioles may have such molecules controlling morphogenetic status contained in their internal chamber (the area of two electron-dense linear structures). It is also possible that they are packed in definite order. Some molecules may differ from the preceding ones and control different morphogenetic status. Other ones can be exact copies, thus determining the same morphogenetic status. In each mitotic division, one of these molecules is released and 'lost' in the cytoplasm, so the centrioles of daughter cells contain one molecule less than the centrioles of the maternal cell. The number of molecules contained in centrioles decreases after each mitotic division. The last molecule triggers the processes of programmed death (i.e. apoptosis). Thus, the number of hypothetical molecules must correspond to the number of possible mitotic divisions, counting down from the cell having the first morphogenetic status to the last offspring cell having the final morphogenetic status (the "Hayflick limit", Hayflick, 1997).

#### **6.4 Importance of small MW RNA (siRNA)**

The best candidate for the role of the carrier of information on morphogenetic status seems to be low molecular weight RNA. Indirect evidence for this hypothesis may be the discovery of new classes of small RNA e so-called interfering RNA (siRNA) and micro-RNA (miRNA) e having regulatory activity. The phenomenon of RNA interference occurs to inhibit selectively gene expression in animal cells (Fire et al., 1998; McManus and Sharp, 2002; Montgomery et al., 1998), including mammalian cells (Wianny and Zornicka-Goets, 2000). MicroRNA appeared to act as a regulator of cell differentiation and development in higher organisms. There direct data confirm the role of these molecules in the process of cell division (Lau et al., 2001; Lee and Ambros, 2001; Lagos-Quintana et al., 2001). In 2002, it was found that the influence of siRNA might not be limited to only temporary 'knockout' of genes on RNA level. Small RNA can modify the chromatin structure and make genes active or silent for quite a long period of time (Zilberman et al., 2003). In addition to post-transcriptional and transcriptional homology-dependent gene silencing links between DNA structure and RNA expose themselves in many other phenomena, like dose-dependent compensation in drosophila and mammalian X-chromosome inactivation (Stuckenholz et al., 1999).

The whole body of existing e though sometimes contradictory e data demonstrating that RNA may be located inside of centrosome or linked to this structure (Heath, 1980; Heidemann et al., 1977; Lambert and Nagy, 2000; Nadejdina et al., 1982; Peterson and Berns, 1980) makes it possible to suggest that small RNA (of 20e300 nucleotides) may be an ideal candidate for the role of the molecule if these are inside the centrioles.

#### **6.5 The centriole as the carrier of controlling siRNA**

Filling of centrioles with the molecules of RNA in various species apparently takes place in different cells: those, which develop at the first of second meiotic division of gametogenesis (spermatogenesis or oogenesis, depending on species), or in the first blastomeres at the time of centriole formation de novo. Those molecules are transcribed from nuclear DNA and stacked in a definite order within the centrioles. Following this process subsequent release of RNA molecules during mitosis determines the expression of nuclear DNA. Nuclear genome presumably 'chooses' and 'places' into centrioles the information about the

sequence of DNA loci activation in the offspring cells. Absence of centrioles in a stage of preleptotenic chromosome condensation in mice may be good illustration of 'zero' morphogenetic status of cells (Hartung and Stahl, 1977). Intracellular 'morphogenetic clocks' seems to be wound up at that moment returning to the initial 'zero' state.

### 6.6 Conclusions that can be drawn

Should centrioles indeed control the processes of cell differentiation and programmed death, the following may be concluded:

1. When a cell initially does not have centrioles (this situation denotes the absence of morphogenetical status), it will be totipotent;

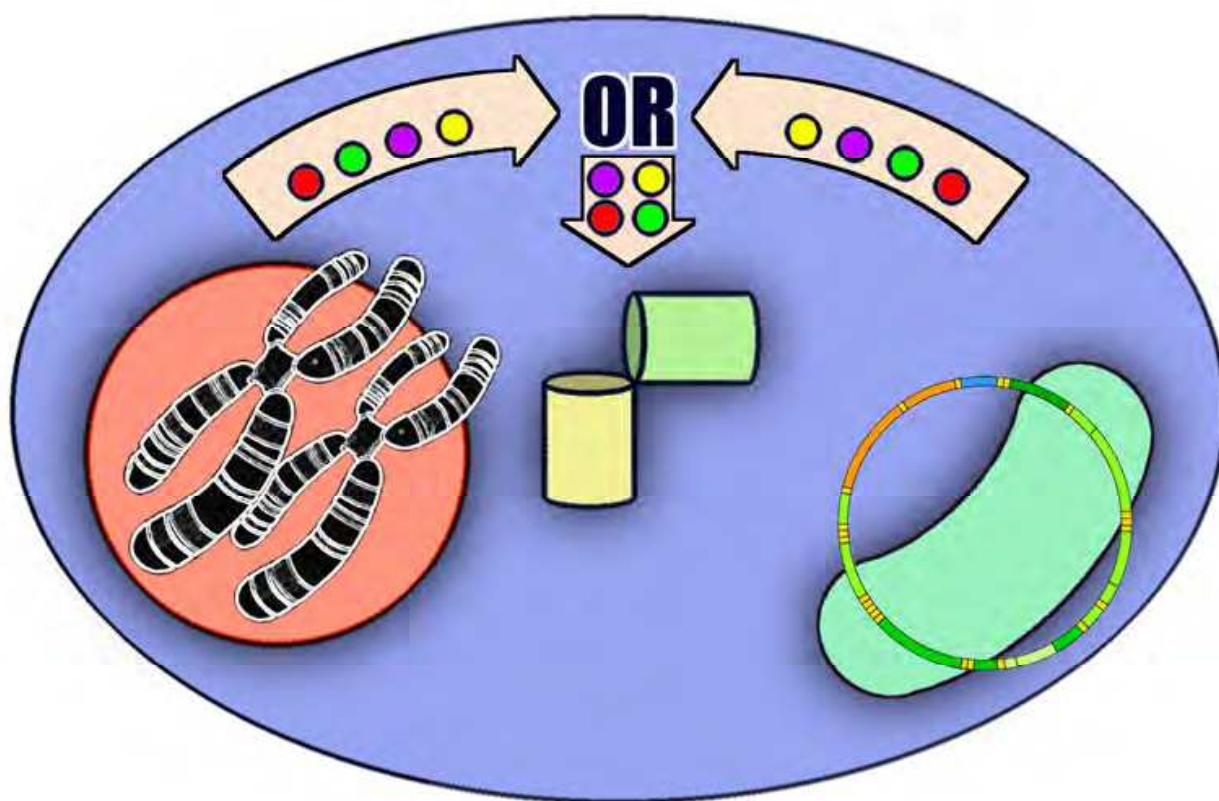


Fig. 1. Causing irrevocable differentiation – Protein or RNA-hypothetical molecular code must be encoded in DNA or mitochondrial or nuclear. It is expected that as many differentiation molecular codes should be encoded in DNA as the quantity of irrevocable differentiation stages, characteristic for each particular species. Molecular structure of the differentiation, complexing at centriol must have the features of matrix - while forming new centriols, it must repeat similar structure.

2. If a cell launches centriole synthesis de novo (the centrioles are considered to be formed de novo as long as the cell is not committed to irreversible differentiation), it will be totipotent and immortal, retaining its initial 'zero' morphogenetic status;



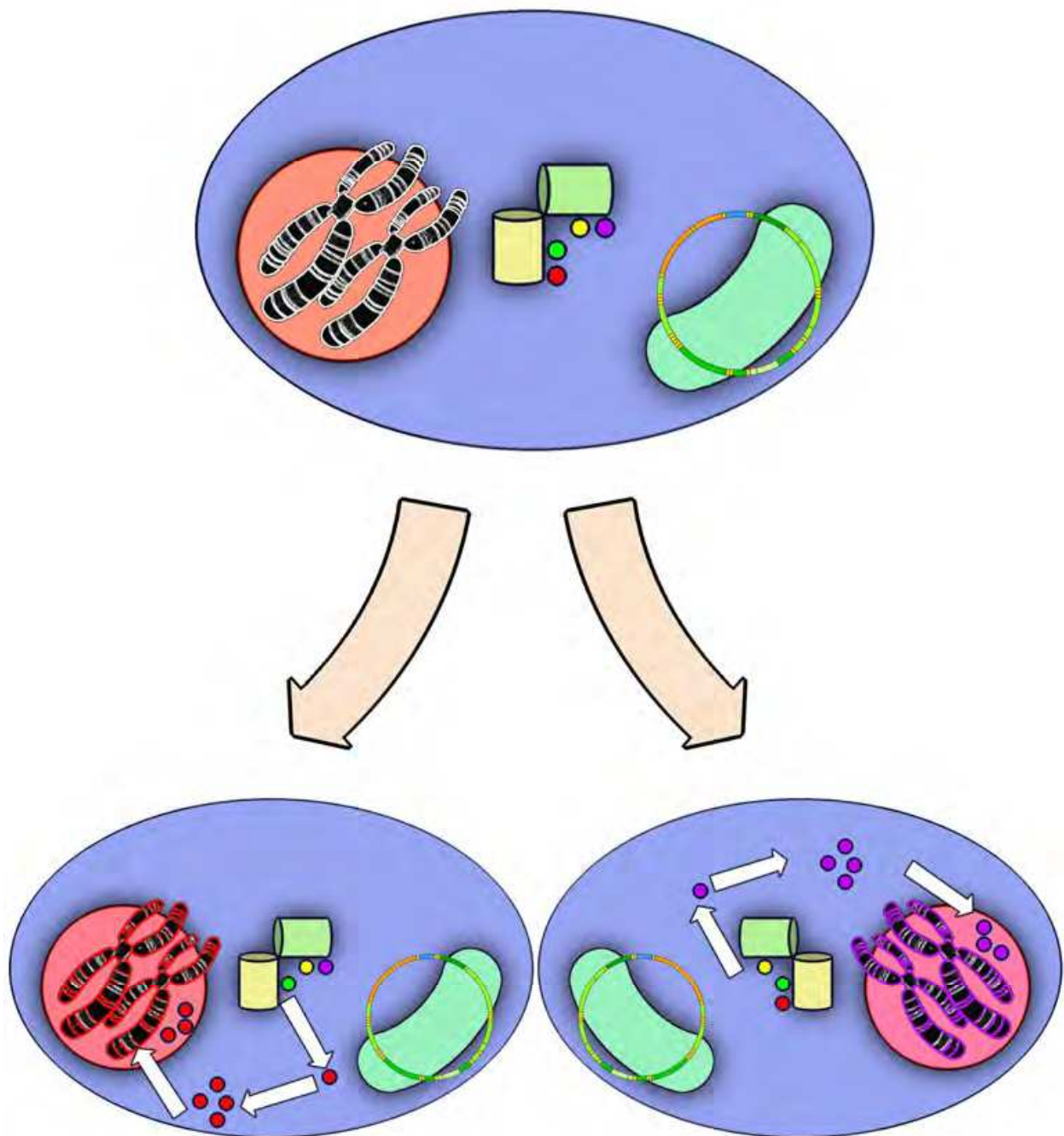


Fig. 2. Cell division, during which release of the molecule, causing differentiation happens, will finish with the irrevocable differentiation of the descendant cells. Probably, the molecule the albumen or RNA differentiation plays the role of the matrix. Ultimately, the small DNA molecule is formed, which enters the nuclear chromosomes, is inserted in them and so changes their structure and function, but not irrevocably.

3. Should a cell not to die due to programmed death when appropriate changes in centrioles do occur, it will be immortal, but not totipotent



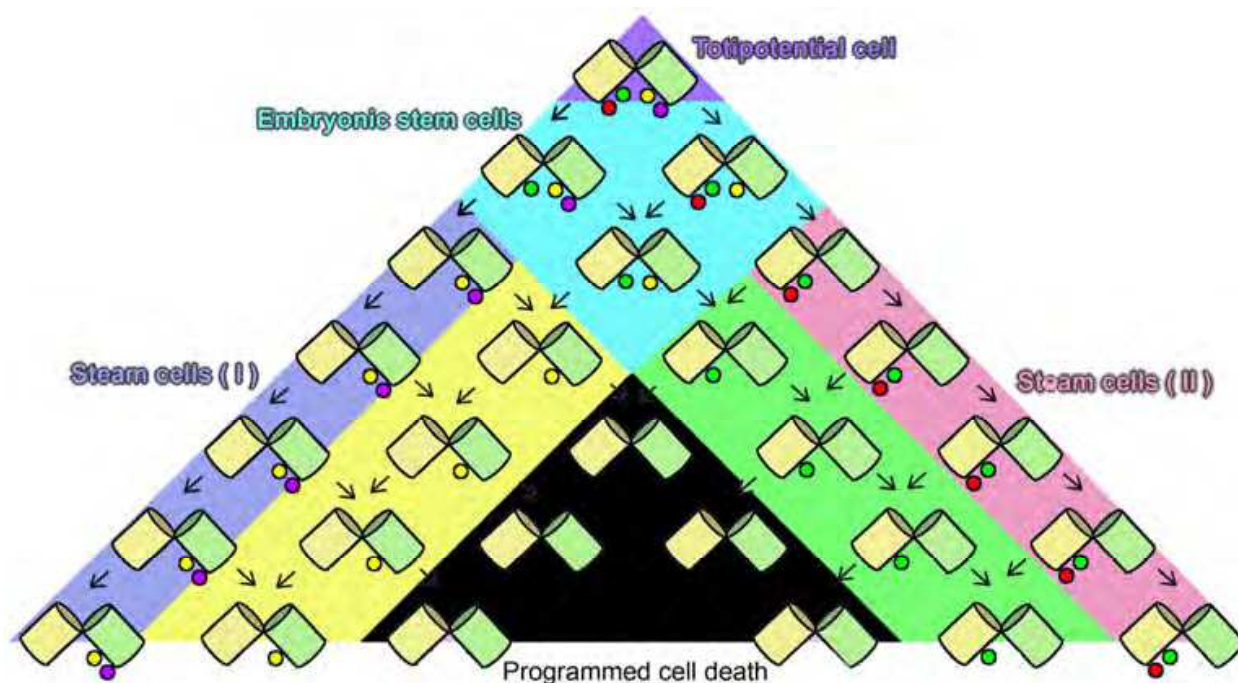


Fig. 3. Maintaining the quantity of the stem cells is explained by the reason, that irrevocable differentiation divisions have asymmetric nature (asymmetric division). Existence of asymmetric division and differentiation structure can also explain the fact that different types of cells give not only different (various), but also similar descendant cells.

Many existing data may be explained on the basis of the proposed hypothesis:

1. Centrioles are initially absent in the cells of higher plants (Sluiman, 1985), zygote and the first blastomeres of some animals (Abumuslimov et al., 1994 Calarco-Gillam et al., 1983). According to our conception they are fully potential and immortal;
2. Centrioles formed de novo in a zygote and the first blastomeres (Maro et al., 1991) belong to the fully potential and immortal cells;
3. Tumor and transformed cells are immortal, but not totipotent. This state may be due to the presence of a certain 'non-zero' morphogenetic status at the moment of transformation.

It is possible that centriolar and nuclear cycles of tumor and transformed cells are irreversibly disengaged. The nucleus loses its ability to perceive some intracellular and extracellular signals, including those which control the morphogenetic status of a cell. The cell becomes immortal, though it has 'non-zero' morphogenetic status.

Based upon the proposed hypothesis, we suggest that centrioles realize their function of 'counting' mitotic divisions. The number of divisions (generations) of a cell is limited; this means that the number of cells of various types is fixed too. Consequently, the possibility of cellular regeneration will be also limited. Sooner or later, regenerating tissues experience a lack of cells: then the organism will not be able to further provide its 'homeostatic' support for long-living cells (for instance, neurons). Thus, death from ageing seems to be a phenomenon affecting the whole organism.

Our proposed hypothesis is verifiable, but needs also be tested to destruction. It may be easily checked if the chemical composition of the internal chamber of centrioles is studied more closely. According to the hypothesis, there must be some difference in chemical composition, as well as in ultrastructure (morphology), of the inner chamber of centrioles in different types of somatic cells. Attention should be also paid to monocellular organisms having centrioles.

It should be emphasised that until now the changes of ultrastructure of the centrosome during the processes of maturation of sex cells and their fusion during insemination, as well as in the course of the first embryonic cell cycles, have not yet been studied in any detail. This kind of investigation should throw light upon the problem of centrioles (diplosome) 'inheritance' in embryonic blastomeres. It would be interesting to know how and to what extent the hetero- and homo-gametic states are related to the 'inheritance' of centrioles. It is also important to find out what kind of divisions produce changes in morphogenetic status and how great is the number of such divisions.

### 6.7 Final remarks

The final resolution of the centriole question, however, can be through their transplantation from differentiated cells of one type into the cells of another type. Today such transplantations are quite possible. To preserve the functional activity of centrioles, they should be extracted immediately after their maturation is finished, i.e. in the middle of metaphase, and injected at the moment the chromosomes are formed. Of course, the centrioles of the recipient cell have to be removed earlier from the spindle poles. Then one could observe whether such 'hybridization' provokes changes in the expression of nuclear genes. In our opinion, the expression of nuclear genes should be changed to resemble that of the donor cell. It would confirm the hypothesis, which states that centrioles (diplosome) are actually the structure controlling the morphogenetical status of a cell.

According to this hypothesis, there must a constant number of stem cells, which is sufficient for regeneration of tissues and organs. However, this doesn't conform with reality. With aging, number of stem cells is reduced. It has to be searched: What is the reason for it? - Influence of the outer factors (e.g.: Gathering mutation in generations, which makes the cell lose the viability) or inner factors, the programmed process (e.g.: Telomeres' shortening in generations, that ends up with transformation in cancer cell or cell death).

### 7. Centrosomal RNA

In 2006 a group of researchers discovered a specific centrosome-associated RNA, which is called cnRNA. New developments and findings in this direction will clarify the issue whether the differentiation molecules have a protein or RNA nature. It is desirable as well to identify which section of the ovule genome carries the information about these molecules.

### 8. Conclusion

In spite of the fact, that Telomerase is the key to the cell immortality or that cancer cell "eternity" is caused by Telomerase, we know and have pointed out above that cancer cells (where enzyme expression is high and where every Telomerase is "to be blamed" for constant division of cells), ultimately achieve the condition when they don't divide any more (can't divide is more correct) - i.e. their "eternity" is suspicious! - Where is the immortality?

In our point of view, the “key” to immortality must be “something” which caused constant renovation of the “worn”. It’s impossible to stop aging, only, it’s possible to turn the biological clock back (even for several times). However, it’s difficult to imagine in our dimension, where everything has its beginning and end... and still I can remember “water of immortality” from my childhood - Where is the immortality?

The fact that it was possible to induce totipotential qualities in the stem cell, gives us some hope. If we can discover the damaged DNA and replace it with healthy code, it’s already possible to return totipotential features to this cell.

If we return this cell to the organism, theoretically, it is expected that the “aged” stem cells “are replaced” by the “rejuvenated” stem cells.

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