Review Article **IJOAR (2021) 4:81**

International Journal of Aging Research (ISSN:2637-3742)

Epithelial tissue response to pathological effects in various age groups. Participation of morphofunctional zones and Src-kinase in this process

Tatiana Yavisheva[1*], PhD, ScD and Sergey Shcherbakov[2], PhD, ScD

[1,2]JSC "R-Pharm", scientific laboratory of mechanisms of stem cells regulation, Moscow, Russian Federation

ABSTRACT

The response of human organism tissues to various pathological effects depends to a large extent on the presence of the total amount of key protein in the organism - Src-kinase and the ratio of its active part to inactive. With a sharp preponderance of an inactive portion of this protein over the active, the proliferative activity of cells is suppressed, and with a significant preponderance of the active part, proliferation is inadequately increased. The amount of this protein is embedded in embryogenesis and individually in each person. In the age aspect, a decrease in the Src-kinase content in the human organism is observed. The epithelial tissue of two age groups: 20-40 and 75 years and older responds most acutely to pathological effects, including the entering of viruses, since in 20-40 years the number of Src-kinase is the greatest in relation to other age groups, and in 75 years and older - the least, which causes a decrease in the reactivity of organism tissues or, conversely, hyperactivity.

Keywords: Epithelial response; Labile groups 20-40 and 75 years and older; Pathological effects; Src-kinase

***Correspondence to Author:**
Tatiana Yavisheva
PhD, ScD, JSC "R-Pharm", 31, Valovaya str., apt. 50, 115054, Moscow, Russian Federation. Tel. 7-905-735-45-90 (mobile)

How to cite this article:
Tatiana Yavisheva and Sergey Shcherbakov. Epithelial tissue response to pathological effects in various age groups. Participation of morphofunctional zones and Src-kinase in this process . International Journal of Aging Research, 2021; 4:81

eSciPub LLC, Houston, TX USA.
Website: https://escipub.com/

Introduction

At each age, there are features of the response of organism tissues to the effect of certain pathological factors. This is largely due to the different proliferative activity of the cells in the age aspect, which in turn determines the immune status of the organism inherent to concrete age.

Proliferation of epithelial cells is determined by the activity of cambial cells that function in morphofunctional zones. With age under normal conditions, proliferation of cambial epithelial cells decreases. Adverse environmental conditions or the action of toxic agents alter the proliferative activity of all epithelial cells, and at different ages in different ways. Therefore, such a change in epithelial tissue in pathological conditions occurring against the background of a certain hormonal status of a person indicates that the central nervous system is included in the regulation of the proliferative activity of cambial cells and the organism's response to adverse environmental conditions. In turn, the central mechanisms regulate these processes mainly with the help of a key protein – Src-kinase, which obviously determines the proliferative activity of cambial cells and the reactivity of organism's tissues.

1. Functioning of peripheral morphofunctional zones with aging in norm

Cambial cells function in the epithelial layer in specific structures - morphofunctional zones consisting of two subunits, in each of which 12 cambial cells are located. At first, cambial cells of the first subunit proliferate, as a result of which 12 pairs of mother and daughter cells are formed, which generate an electric field due to a potential difference between these cells. Indeed, cambial cells have a vertical axis of division, which causes the mother cell to be in close proximity to the basal membrane, and the daughter cell to be above it. The action of growth factors, such as transforming growth factor β, located in the basal membrane and having spastic properties, prevents the spreading of the mother cell, which increases the negative charge of the chromatin of the mother cell relative to the daughter. Hence, the redistribution of superficial charges between the two cells and the emergence of an electric field occur [1, 2]. The daughter cells are stretched by the forces of the electric field, generated by the division of the 12 cambial cells, and certain chromosome loci are untwisted, allowing transcription of these sites, i.e. the cells are prepared for differentiation. After functioning of the first subunit, the second subunit begins to work in a similar way. It should be noted that if the number of cambial cells in one of the subunits drops to 6 cells, then the electric field excited by these cells becomes insufficient to stretch the daughter cells, i.e., there is no differentiation [3].

Daughter cells, undergoing differentiation and further division, form oval cells, which then replenish the reserve cell depot necessary for the regeneration of the epithelial layer. Previously, on a large experimental and clinical material, we showed that reserve cells make up the largest share in the population - 30%. The cells of this depot, when proliferative processes increase, are transformed into transitional and then elongated cells, 5% of which directly enter into mitosis. As a result, round cells are obtained, gradually maturing to the final cells to be eliminated [4, 5].

Thus, in the epithelial layer there are two flows of proliferating cells, the 1st stream - these are cambial cells and their earliest descendants (daughter, oval cells, the latter of which ultimately form reserve cells); The 2nd stream is the reserve cells and their derivatives: transitional and elongated, maturing in consequence into round and final cells. Cambial cells, compared to other cells, have a very short mitotic cycle, so their number in the population is judged by the content of daughter cells obtained during their division [6, 7].

With aging, in norm a decrease in the proliferative activity of epithelial cells is observed. However, in each age group: 20-40 years old, 41-59, 60-74 and 75 years and older, there are their own features.

Thus, in persons aged 20 to 40 years and 41-59 years, high mitotic activity in epithelial tissue is observed, as evidenced by changes in the activity of cells of the 1st and 2nd streams [8]. There is an active transition of cells of the 2nd stream:

reserve into elongated. At the same time, the number of reserve cells decreases from 30 to 11.6-11.9%, and the proportion of elongated cells that directly enter into mitosis increases from 16 to 22.6%. The number of daughter cells of the 1st stream decreases from 10 to 7.7% due to their conversion into oval. The number of the latter increases from 10 to 15.7%. This indicates that two subunits of the morphofunctional zone work in these age groups according to the norm, in turn.

In people aged 60 to 74 years, the proportion of reserve cells of the 2nd stream decreases more than in the first two age groups (up to 10.3%). At the same time, the number of elongated cells into which reserve cells pass is slightly reduced compared to the previous two groups and amounts to 21.7%. Therefore, there is no faster conversion of reserve cells into elongated ones, but a decrease in the proliferative activity of these cells, as well as their precursors - cambial ones. Indeed, the number of daughter cells that are a criterion for cambial cell abundance in this age group is reduced to 7%, while in 20-40 and 41-59 years it is 7.7%. Then the daughter cells are gradually transformed into oval cells, the proportion of which, as in the other two groups, is 15.6%. This indicates that at the age of 60-74 years, compensator mechanisms are still able to ensure the normal alternating function of two subunits of the morphofunctional zone and thereby carry out physiological regeneration of the layer at a sufficiently high level.

A completely different pattern is observed in persons of 75 years and older. The number of reserve cells of the 2nd stream remains quite high (11.5%), and the number of elongated cells is reduced compared to the previous three groups and is 20.7%. Thus, there is a significant slowdown in the entry of cells into mitosis, which can cause cell deficiency in the epithelial layer and its disruption. In order to compensate the insufficient number of cells in the morphofunctional zone, another subunit is included in the work along with the first. This is evidenced by an increase in the level of oval cells of the 1st stream to 17.4% (in other age groups - about 15%). Due to the inclusion of the second subunit, the total number of daughter cells also begins to increase to 8.2%. In fact, the number of daughter and cambial cells in one subunit of the morphofunctional zone decreases dramatically in this age group.

If in the group of persons 20-40 and 41-59 years old the number of cambial cells is 12 in one subunit, then in people aged 60-74 years their number decreases by 1.1 times, which is about 11 cells. In people 75 years and older, the number of cambial cells increases 1.2 times compared to the previous group due to the inclusion of another subunit and amounts to about 14 cells per two subunits of the morphofunctional zone or 7 cells per subunit.

Thus, in the population of epithelial tissue, the number of cambial cells remains stable up to 59 years - 12 cells in one subunit. At 60, the first decrease in the number of cambial cells in the morphofunctional zone occurs and up to 74 years remains unchanged - 11 cells. At 75 years and older, there is an avalanche-like drop in the number of cambial cells to 7 in one subunit of the morphofunctional zone, which approaches the threshold value of 6 cells when there is no differentiation.

Physiological regeneration of epithelium due to cambial cells in the age groups 20-40 and 41-59 years remains high; in persons aged 60-74, it begins to decline, but remains sufficient to ensure the alternating function of the two subunits of the zone; in persons 75 years and older, the proliferative activity of epithelial cells slows down significantly, so the two subunits of the zone work simultaneously to ensure the regeneration of the epithelial layer

2. Peripheral epithelial morphofunctional zones in chronic alcohol intoxication in age aspect

It is known that in the conditions of pathology, the mechanisms of regulation of vital processes in the norm, compensatory and adaptive reactions are more fully disclosed, since both these processes (pathology and norm) develop on the same material basis.

2.1. Functioning of epithelium with high pro-

liferative potentials in intoxication. Epithelium in 20-40 and 75 years and older is the most labile to intoxication

A study of morphofunctional zones of the basal layer of the epidermis in conditions of chronic alcohol intoxication showed that two age groups: 20-40 and 75 years and older most strongly respond to the effects of pathological agents compared to other groups.

So, in people 20-40 years with toxic exposure, there is an intensive transition of epithelial cells of 2nd stream: reserve into elongated and preparation for mitosis, while the number of reserve cells decreases to 8.9% (in control 11.6%), and the number of elongated cells increases compared to normal skin to 26.3% (normally 22.5%). At the same time, the number of daughter cells of the 1st stream obtained by division of cambial cells decreases to 6.9% (in control 7.7%). Therefore, in this age group, under conditions of pathology, regeneration processes are intensified against the background of cell death of the epithelial growth layer [9].

In patients 75 years and older with chronic intoxication, as well as in young people, there is an increase in the cells proliferative activity. This is evidenced by a decrease in the number of reserve cells to 10.4% compared to healthy skin (11.5%), and in parallel with this, an increase in the proportion of elongated cells to 24.9% (in control 20.7%). Interestingly, the number of daughter cells of the 1st stream decreases to 7.2% (in normal skin - 8.2%), and the number of oval cells decreases from 17.4% to 13.9%. This indicates that the two subunits of the morphofunctional zone in this age group work in turn in the conditions of intensification of proliferation, ensuring the regeneration of the epithelium. At the same time, the number of daughter cells remains lower than at the ages of 41-59 and 60-74 years old, i.e., a drop in the cells number of the growth layer is observed.

In two other age groups: 40-59 and 60-74 years old, the cells of the growth layer are not exposed to such effects as at 20-40 and 75 years old and older. The number of daughter cells approaches the norm - 7.8-7.9%. At the age of 40-59 years, there is a fairly high mitotic activity of cells under conditions of intoxication. This is evidenced by a decrease in the number of reserve cells to 8.2% (normally 11.9%) due to their more intensive transition into elongated ones - 24.9% (normally 22.6%).

In the group of patients from 60 to 74 years old, the number of reserve cells with toxic exposure decreases to 7.1% compared to the control (10.3%), as they actively move into elongated cells, the proportion of which increases to 25.4% (in the control 21.7%), which practically corresponds to that at 41-59 years. The number of oval cells is high 15.3% (in control 15.7%), therefore, the two subunits of the zone function in turn, and the compensatory mechanisms are able to maintain the desired number of cells of the epithelial layer.

Thus, by comparing the change in the quantitative values of the cell populations of the epithelium in the age aspect in norm and with prolonged toxic effects, the following conclusion can be drawn. In epithelial tissue with high proliferative capabilities in all age groups, during chronic alcohol intoxication, regenerative processes are enhanced and compensatory mechanisms continue to operate to regulate the number of cells sufficient for the functioning of the epithelial layer. However, in only two age groups 20-40 and 75 years and older, the death of growth layer cells occurs, in the other two groups 41-59 years and 60-74 years, the number of these cells remains at the same level.

2.2. Endothelial cells with low reparative capabilities in pathology conditions. Corneal endothelium of 20-40 and 75 years and older is most vulnerable to toxic exposure

Interestingly, a similar response to prolonged intoxication was found by us in tissue with low repair capabilities - the endothelium of eye cornea [10]. The corneal endothelium of two age groups (20-40 and 75 years and older), like the epidermis, reacts most vigorously to pathological effects, and at 41-59 years and 60-75 years - more calmly.

In chronic alcohol intoxication, patients of 20-40 years old experience the largest reduction in

endothelial cell density compared to control and other age groups due to their mass death. If at 41-75 years the endothelial cell density during chronic intoxication decreases by 6.4-8%, then at 20-40 years - by 10%, which leads to an increase in the area of average cell, because there is no mitotic activity in the adult endothelium. Therefore, the compensatory mechanisms of the organism under conditions of intoxication and cell death try to maintain the functional activity of the endothelium by connecting large cells to a number of average cells. The latter perform the main functions in the corneal endothelium and are the most active.

Studies have shown that two age groups (20-40 and 75 years and older) have the largest increase in a number of average cells due to large cells both compared to control and other age groups [11]. In 20-40 years, this parameter increases to 10 classes (in control 7), in 75 years and older to 16 classes (in control 8). As a result, the number of average cells under conditions of pathology increases to 64.76% in 20-40 years (61% in control), and to 71.18% in 75 years and older (49% in control). At the same time, in the age group 41-59 years, a number of average cells increases by only 1 class, and in 60-75 years there is no increase.

Large diploid cells are functionally less resistant than average cells. At the first stage, they can perform a compensatory function, but ultimately die faster, which leads to destabilization of the endothelial layer under conditions of pathology [12]. An increase in the number of average cells due to the large in corneal endothelium of persons 20-40 and 75 years and older by 3 and 8 classes, respectively, indicates more significant destructive processes in the endothelium of old people compared to young.

Thus, comparing the two varieties of epithelium (epidermis - dynamic population and human corneal endothelium - stationary population), it should be said that they are equally included in the response to chronic alcohol intoxication. At the same time, the corneal endothelium, like the skin epidermis of patients aged 20-40 and 75 years and older, most acutely respond to the effects of adverse factors. However, in old age, compared to young people, there is an acceleration of destructive processes.

3. Function of peripheral zones is controlled by the central zone using Src-kinase

The features of proliferative activity of morphofunctional zone cells during aging and the different reactivity of epithelial tissue in age groups under pathology conditions can be explained from the perspective of the key protein of morphofunctional zones – Src-kinase.

Importantly, our control studies do not show a gradual decrease in the number of cambial cells and their proliferative activity, but a sharp decrease in these parameters after 75 years during advanced hypoestrogenemia. Therefore, human hormonal status has the greatest effect on cambial cell proliferative activity.

Among the main structures responsible for hormonal regulation, the hypothalamus with its hypophysiotropic region can be distinguished, which is a central morphofunctional zone that controls peripheral morphofunctional zones using the key Src-kinase protein [13].

Consequently, Src-kinase plays a crucial role in the functioning of cells of both central and peripheral morphofunctional zones.

3.1. Value of active and inactive Src-kinase in morphofunctional zones operation

On the periphery, Src-kinase expression occurs during the stretching of the daughter cell by the electric field excited by 12 pairs of mother and daughter cells. Previously, the cortex of the epithelial daughter cell should be relaxed due to stromal growth factors, such as fibroblasts growth factor, which abundantly activate Src kinase [14].

In central structures, the individual amount of Src-kinase is embedded in embryogenesis [15].

In its inactive form, this protein promotes microtubule formation by connecting tubulin dimers through its SH2 domain [16]. In addition, Src kinase potentiates the formation of intermediate microfilaments, which together with microtubules stretch the cell nucleus, promoting cell differentiation.

The direction of cell differentiation and prolifera-

tion depends on the ratio of active to inactive form of Src-kinase [9]. So, with the predominance of inactive Src-kinase over the active, an epitheliocyte is formed, since the stretching of the daughter cell in the electric field and the unwinding of chromosomes occurs closer to the telomeres. If the active form of Src-kinase increases moderately, then this will lead to an increase in the mitotic activity of cells, because active Src-kinase stimulates the most important transduction pathways and transcription factors leading to an increase in the proliferative activity of cells [17]. The remaining sufficient amount of inactive Src-kinase is involved in the formation of microtubules and division spindle. This provides high mitotic activity of epithelial cells.

On the contrary, if the active form of this protein prevails over the inactive one, then the chromosome loci stretch closer to the centromere, causing the formation of a fibroblast-like cell.

Thus, the participation of Src-kinase in the performance of the most important functions of cells requires a high content of this protein in morphofunctional zones.

4. Src-kinase in nerve signaling and hormone synthesis. High Src kinase content in 20-40 years

Expression of inactive Src-kinase in the hypothalamus in childhood and young adulthood is high, as follows from brain development from the ectoderm, which has an initially high content of this protein [13]. Under the influence of the chorda in the neural plate, only a transient increase in the active Src kinase occurs, which leads to the predominance of inactive Src-kinase over its active form in neuroepithelium. Therefore, the unwinding and transcription of chromosomes here will occur, as in epithelial tissue, closer to telomeres. As a result, neurotransmitters produced by nerve cells also increase the percentage of inactive Src kinase in their surrounding tissues.

It should be noted that the non-receptor Src-kinase is activated not only by the corresponding ligands, but also by various kinds of oxidants, i.e., it is a redox-sensitive molecule [18, 19, 20]. In this regard, it is involved in the transmission of a nerve impulse in the brain [21]. Thus, under the influence of light, photoreceptors and retinal melanopsin cells are excited, which leads to a decrease in their proportion of inactive Src-kinase and an increase in active. It in turn causes increase in an exocytosis in a synapse due to reduction of rigidity of a cellular membrane as the active Src-kinase phosphorylates protein of p190 RhoGAP which in turn inactivates RhoA participating in construction the actin of microfilaments and a cell cortex. In addition, the synthesis of neurotransmitters by these cells is reduced due to the displacement of the nucleus stretch closer to the centromere. As a result, the proportion of inactive Src-kinase will decrease in the regulatory chain, making it possible to transmit a signal to the regulatory centers of the hypothalamus and pituitary, in which the synthesis of the corresponding releasing factors and hormones, which then affect the target organs, begins. In the latter, hormones begin to be produced, the action of which is aimed at increasing the proportion of inactive Src-kinase in the surrounding tissues, as well as in the hypothalamus and pituitary. This leads to increased neurotransmitter synthesis and difficulty in exocytosis in these structures, which blocks further hormone production. Such blocking signals are essentially inhibitory signals. These include glucocorticoids produced by the adrenal glands under the action of adrenocorticotropic hormone (ACTH) [22].

Estrogens produced by the sexual glands, unlike glucocorticoids, have an excitatory effect on tissues and central mechanisms. Indeed, estrogens activate Src-kinase by reducing its inactive proportion by G proteins that bind to its catalytic domain. The amount of active Src-kinase increases as estrogens accumulate, which improve exocytosis and, therefore, the amplitude and frequency of gonadotropin release in the sex center of the hypothalamus. As a result, follicle-stimulating hormone (FSH) synthesis is activated by the pituitary, which in turn affects the sexual glands, contributing to the aromatization of androgens. Subsequently, with increased exposure, target cells cease to respond to this stimulus, i.e., a refractory period occurs. This leads to a drop in androgen aromatization, a

decrease in the portion of estrogens and a decrease in their effect on the sex center of the hypothalamus. As a result, gonadotropin pulsation is reduced, which leads to the production of luteinizing hormone (LH) by the pituitary gland [22].

Thus, starting from the puberty, the effects of estrogens, unlike glucocorticoids, are aimed at constantly reducing the portion of inactive Src-kinase in tissues of various organs, including the brain. However, in healthy people aged 20-40 years, these changes are still insignificant.

4.1. Decreased portion of inactive Src in the brain leads to hyperestrogenemia in people 41-59

Due to the fact that over time the percentage of inactive Src-kinase in the brain decreases and the active part increases, there is a shift in the stretching of the nuclear material of the nerve cell closer to the centromere, which causes a decrease in the synthesis of neurotransmitters and an increase in the excitatory signal in the brain [21, 22]. Due to this, the incoming signal very quickly increases the portion of active Src-kinase in monoaminergic neurons, which increases exocytosis in these cells and the release of the mediator. Further, the enhanced signal is transmitted to the peptidergic neurons of the hypothalamus and then to the pituitary, where the part of active Src-kinase increases sharply, which leads to an increase in FSH synthesis. Ovaries begin to synthesize estrogens very actively, so the intensity of the follicular phase increases with age, which shortens its duration. As a result, the proportion of inactive Src-kinase in the brain falls and especially in the hypothalamus, in which there are many receptors to estrogens. All these processes lead to the development of a period of hyperestrogenemia with increased FSH synthesis. At first, the amount of FSH prevails over LH, but as a result, the level of LH also increases due to the fact that exocytosis is increased in cells during signal transmission, then tissue insensitivity to this stimulus appears, which ultimately leads to reduced impulse and increased LH synthesis.

In peripheral morphofunctional zones, as well as in central zone, due to hyperestrogenemia, an increase in the active portion of Src-kinase in relation to inactive ones occurs. This increases the influence of the stroma on epithelial tissue, since the expression of active Src-kinase is especially enhanced in fibroblasts having many receptors to Src. As a result of the increased influence of the stroma, epithelial cells without obstacles are stretched by the forces of the electric field and differentiated. The proliferative activity of epithelial cells under normal conditions at the age of 41-59 years is quite high, so the number of cambial cells remains stable - 12 cells in one subunit of the morphofunctional zone.

With the progression of hyperestrogenemia and the increase in the portion of active Src- kinase in the brain and peripheral epithelium, cells begin to stretch closer to the centromere, which causes the formation of fibroblast-like cells. Therefore, during the period of developed hyperestrogenemia, the epithelial tissue of parenchymal organs, including brain neurons, begins to be gradually replaced by connective tissue.

4.2. A further decrease of inactive Src in the brain leads to the development of moderate hypoestrogenemia in people 60-74 years and deep hypoestrogenemia in 75 years and older

The continued decrease in the portion of inactive Src-kinase and neurotransmitters to a critical level in the brain and especially the central morphofunctional zone leads to the fact that the resulting high excitability of the cells of the sexual center of the hypothalamus and pituitary gland leads to a constant and massive release of FSH and LH into the blood. Target cells of the sexual glands with such exposure become insensitive to this stimulus, so they stop producing estrogens in response to FSH. As a result, the period of hyperestrogenemia is replaced by hypoestrogenemia.

Thus, during the period of moderate hypoestrogenemia in people aged 60 to 74 years, due to a further decrease in the reserve of inactive Src kinase in the brain, there is a decrease in the number of estrogens in the blood. This leads, in contrast to hyperestrogenemia, to a decrease in active Src kinase in peripheral organ cells and,

therefore, to a decrease in cell proliferative activity. In addition, epithelial cell spasm is increased due to the activation of protein RhoA, which complicates the mitotic activity of these cells. It is at the age of 60, when the hormonal activity of the organizm decreases, the first drop in the number of cambial cells occurs to 11 in one subunit of the morphofunctional zone.

As hypoestrogenemia progresses in persons of 75 years and older, not only the proliferative activity of epithelial cells deteriorates, but also their differentiation due to the weak influence of the stroma, which does not provide relaxation of the cortex of epithelial cells and their stretching in the electric field. As studies have shown, the number of cambial cells in one subunit of the morphofunctional zone in this age group immediately drops to 7, which is close to the limit when cell differentiation does not occur. Therefore, this age group is most vulnerable to the occurrence of malignant tumors [23].

Thus, normally in people of 20 to 59 years old, rather high proliferative activity of epithelial cells is maintained in morphofunctional zones. From 60 to 74 years old during moderate hypoestrogenemia, cell proliferation decreases slightly. From the age of 75, with deep hypoestrogenemia, the mitotic activity of epithelial cells drops sharply, the number of cambial cells approaches to critical level, in which cell differentiation is absent, which promotes the development of a malignant tumor. This is due to the depletion of inactive Src kinase resources in the brain, embedded in embryogenesis.

5. Increased epithelium proliferation during intoxication in different age groups is associated with the total content of Src and its enhanced active part. Features in 20-40 and 75 years and older

In order to explain the reactivity of organism tissues in a particular age group under the influence of chronic alcohol intoxication, it is necessary to take into account, as in the norm, the hormonal background on which adverse factors occur. In fact, with prolonged alcohol intoxication, hypoestrogenemia develops to one degree or another in all age groups.

One of the main actions of alcohol, which it has on the central and peripheral morphofunctional zones, is the strengthening of peroxidation processes, which leads to the development of oxidative stress [24]. This leads to an increase in the part of active Src-kinase in patients of all ages and a greater than normal depletion of inactive Src-kinase stores in the brain and peripheral tissues. However, the amount of inactive Src-kinase, as well as the norm, will remain the largest in 20-40 and the smallest in 75 years and older.

As shown above, in control, a large amount of inactive Src-kinase suppresses not only hormone production, but also proliferative processes, because the portion of active Src-kinase involved in the activation of various transcription factors decreases, and epithelial cell spasm is also increased due to the development of a strong actin layer under the plasma membrane of the cell.

In 20-40 years, with chronic alcohol intoxication, compared with the norm, the resource of inactive Src-kinase in the organism and its deterrent effect on proliferative processes are reduced, so proliferation will occur more actively than in norm. Increased proliferation of cells leads to destabilization of the epithelial layer, accelerated cell exfoliation, reduced content of cambial elements.

At 75 years and older, the content of inactive Src-kinase is the lowest of all age groups, as a result of which its restraining effect on proliferation will be very weak. Therefore, increasing the proportion of active Src-kinase in chronic intoxication conditions significantly increases the proliferative activity of cells at this age. However, escalated proliferation will occur against the background of destructive processes, because sufficient quantity of inactive Src-kinase involved in the construction of the cell cytoskeleton is necessary to perform the mitosis.

Age groups 41-59 and 60-74 years old occupy an intermediate position between the above two groups according the proliferative activity.

Thus, the response of human epithelial tissues to chronic alcohol intoxication is manifested in the enhancement of proliferative processes in all

age groups, but especially intensively in the two extreme groups - 20-40 and 75 years and older. This is primarily due to the degree of decrease in the total amount of Src-kinase in the organism (at 20-40 years - the smallest decrease of all age groups, at 75 years and older - the largest) and an increase in the active share of Src-kinase in relation to inactive.

6. The decrease in epithelium proliferation in adverse conditions - winter season, is due to the increase of inactive Src. Features in 20-40 and 75 years and older

It is interesting to trace the reactivity of human epithelial tissue in other adverse circumstances. So, the winter season, when acute respiratory diseases erupt, is also a kind of stressful situation for the functioning of the human organism. In winter, Src-kinase activity decreases. Indeed, Src-kinase is a redox-sensitive molecule that actively responds to light, including short wavelength rays: UV, blue light [20]. Therefore, at different times of the year and day, the expression of the active part of this protein in the human organism will vary. So, in summer, the proportion of the active form of Src- kinase in all age groups increases sharply due to the high solstice and the large angle of incidence of rays, which enhances the illumination of the earth. In winter, the activity of this protein decreases due to lower illumination, because the sun at this time of year is low above the horizon.

In people 20-40 and 75 years and older, compared to other age groups, there is the greatest instability of the organism in winter.

So, at the age of 20-40 years old at this time of year, the proportion of inactive Src-kinase increases even more, which inhibits the proliferative activity of all cells in the organism. At the same time, the immune status of the organism decreases, as the proliferation of cambial cells of bone marrow tissue, built according to the type of morphofunctional zones, is slowed down [25]. People 75 years and older have deep hypoestrogenemia, which is characterized by a general low content of inactive Src-kinase and at the same time very low expression of its active portion, which causes low proliferative activity of cells. A further increase in the proportion of inactive Src-kinase relative to its active portion in winter even more impairs tissue proliferative activity and organism resistance in this category of persons.

Age groups 41-59 and 60-75 are intermediate, although the latter group is less stable than the previous one. So, at 41-59 years old, there is a partial weakening of hyperestrogenemia, which improves the proliferative activity of cells and immune status. At 60-74 years of age with moderate hypoestrogenemia and the beginning of a decrease in the total level of Src-kinase, some increase in the content of inactive Src-kinase will lead to a moderate decrease in the proliferative activity of cells.

Thus, two age groups 20-40 and 75 years and older are most responsive to environmental conditions in the winter season. This response is determined primarily by the initial amount of inactive Src-kinase in the organism and its increase in relation to the active part, which enhances its deterrent effect on cell proliferation and the immune status of the organism.

In order to moderately increase the active Src-kinase in the human organism of all age groups and, therefore, improve immunity, it is very important to lead an active lifestyle in winter and, if possible, be outdoors more.

7. Src-kinase is a key protein targeted by viruses in winter

As shown above, one of the factors changing the ratio of active to inactive Src-kinase in the human organism is the different illumination associated with the rotation of the earth around its axis and the sun. Therefore, the content of this protein in the human organism is closely related to the function of the solar system and determines in many ways the strategy of the organism in certain living conditions, being one of the key proteins.

So, in winter, with reduced illumination, favorable conditions are created for the introduction of respiratory viruses, as the proliferative activity and immune status of a person decreases. Along with this, compensatory mechanisms in the cell increase the thickness of the actin layer

under the cell membrane, which is a barrier to the penetration of pathological agents. This is due to the fact that the prevalence of the inactive Src-kinase portion in the cell promotes the nucleation of actin from a new fixed point and the formation of a network of actin filaments, rather than long strands of stress fibers [26]. In this regard, the main actions of the virus are aimed at transforming the most part of the Src-kinase into the active form.

Initially, virus adsorption occurs on the cell membrane by interaction of a viral protein with cell receptors, which triggers receptor-induced expression of a cascade of proteins, including Cdc42, RhoA, Rac – small G proteins and Src-kinase. As a result, the actin layer under the plasma membrane rearranges, with the formation of membrane folds, filopodia, which contribute to the capture of the viral particle, while forming strands of stress fibers, which together with microtubules and motor proteins cause the movement of formed endosomes deep into the cell [27, 28]. Further, as the endosome moves towards the lysosomes, the pH of the endosome content decreases due to proton pump proteins located in their membranes and injecting hydrogen ions. [29, 30, 31]. In addition, the viral matrix protein forming the ion channels further reduces the pH of the internal content of the virion [29, 30, 31, 32]. The acidic environment plays a huge role in separating the virus from cellular receptors and promotes the fusion of the virus with the endosome. At the same time, due to the acidic content, Src-kinase located on the membranes of endosomes is activated, which leads to thinning of their actin layer, therefore, the fusion of late endosomes with lysosomes is facilitated. Further, the virus is stripped from its remaining viral envelopes due to hydrolytic enzymes of lysosomes activated in an acidic medium. In this case, the virus enters into the cytoplasm of the cell.

Thus, entering into the human organism by increasing the proportion of active Src-kinase, the virus causes profound changes in the host cell in order to stop the normal function of the cells and carry out its vital activity. First of all, the actions of the virus are aimed at destroying the cytoskeleton of the host cell, because the cytoskeleton plays a major role in maintaining the correct architectonics of the cell and the nucleus, which contributes to the normal functioning of the cell, including differentiation. Indeed, as a rule, intermediate microfilaments are connected to microtubules and together stretch the nucleus of the cell and chromosomes attached to the nuclear membrane, which leads to the unwinding of certain chromosome loci and their transcription [17, 33]. In this case, the cell produces the normal cellular proteins necessary for its life.

The virus entry increases the portion of active Src-kinase in the cell, which has a low affinity for tubulin, which leads to disruption of the assembly of microtubules, which normally promote the formation of intermediate microfilaments [34, 35]. Due to low polymerization of microtubules, the collapse of the intermediate microfilaments occurs; they are detached from the nuclear membrane and collected in the form of dense bunch near the nucleus. Interestingly, other researchers observed a similar pattern when the SARS-Cov-2 virus entered into the cell [36].

Therefore, in viral intoxication, intermediate microfilaments cease to perform function, which leads to a decrease in the unwinding of chromosomes and a stop of transcription factors due to a mechanical obstacle [17]. As a result, the transcription processes of normal cell proteins cease.

At this time, viral proteins can ensure the reproduction of the virus: transcription of genetic material and the most important viral proteins. Then, in the mitochondria of the cell there is a translation of the viral proteins, and not the host, because viral RNA have the identical to cellular 5’-end. Therefore, the ribosomes of the cell are not able to distinguish viral RNA from cellular. Further, the virus takes not only mitochondria, but also other important cell structures: the endoplasmic reticulum and the Golgi complex, which provide the assembly of virions and their transportation to the plasma membrane.

It has been shown above that epithelial tissue of two age groups 20-40 and 75 years and older is most affected by environmental conditions

during the winter season. Therefore, in the case of viruses, the epithelial response of these two groups also has features compared to other groups.

Thus, persons aged 20-40 have the highest portion of inactive Src-kinase compared to other age groups. Under conditions of virus infection, the active part of Src and, therefore, cell proliferation are increased, but to a lesser extent than at 41-59 years old, which causes a rather low immune response.

The people of 75 years and older compared to the patients of other ages respond most vigorously to the virus entry, because this group has the lowest content of inactive Src-kinase, which cannot restrain the increase in the proliferative activity of human cells in conditions of a significant rise in the portion of active Src-kinase. This can cause hyperreactivity of the organism due to inadequate intensification of proliferative processes, lead to an increase in the fibrous tissue formation, because stretching of epithelial cells will occur closer to centromeres, etc.

Various factors, including comorbidities (obesity, diabetes, cancer, etc.), in which a portion of active Src-kinase in the human organism is increased, also promote a more aggressive course of viral infection.

Conclusion

From all the above, it follows that the response of tissues to certain pathological effects depends primarily on the presence of the total amount of Src-kinase in the human organism, as well as on the ratio of its active part to inactive, which determines many processes in the organism, including the proliferative activity of tissues, the immunological status. With a sharp predominance of the inactive portion of Src-kinase, cell proliferation is suppressed and, conversely, with a significant increase in its active part, the proliferative process is enhanced. Each individual has its own stock of Src-kinase, laid down in embryogenesis, but in general, with age there is a decrease in the amount of this protein. The most labile groups in response to pathological agents are people aged 20-40 and 75 years and older, and the most stable are 41-59 and 60-74 years old. In this regard, it is not advisable to combine two age groups 60-74 years and 75 years and older into a single, so-called 65 + group, because these age groups (60-74 and 75 years and older) have a completely different response to the effects of pathological agents and adverse meteorological conditions. Due to the fact that the key protein Src-kinase to a greater extent determines the strategy of the organism in any given situation, the action of pathological agents, in particular viruses (including SARS-Cov-2), is primarily aimed at this protein. Putting most of this protein into an active state, the virus destroys the cell's cytoskeleton, thereby stopping normal cellular processes while triggering its own.

References

[1] Yavisheva T.M., Shcherbakov S.D., Golubeva I.S., Sharafutdinov G.Z., Savluchinskaya L.A. To the question of the structural organization of the basal layer and morphofunctional features of cambial cells of the mouse epidermis. Byulleten Eksperimentalnoi Biologii I Meditsiny, 2004; 137(3): 584-588.

[2] Yavisheva T.M., Shcherbakov S.D., Dubinkin I.V. Proliferative features of cambial cells of mouse skin epidermis. Kketochnye tehnologii v biologii I meditsine, 2005; 3: 136-139.

[3] Yavisheva T.M., Shcherbakov S.D., Golubeva I.S., Savluchinskaya L.A. Comparative analysis of morphofunctional zones in normal epithelium, fibroadenoma and breast cancer. Byulleten Eksperimentalnoi Biologii I Meditsiny, 2005; 140(8): 201-205.

[4] Yavisheva T.M., Yagubov A.S. Quantitative morphology of cells of the basal layer of the multilayered mouse cornea epithelium and human lung cancer Ontogenez, 1996; .27(2):.95-99.

[5] Yavisheva T.M., Shcherbakov S.D., Sharafutdinov G.Z. On epithelial cell differentiation in the system of tissue units. Doklady. Biol. Nauk, 2005; 401(6): 833-836.

[6] Astemirova L.T., Pavlova T.V., Yavisheva T.M. Quantitative method of analysis of morphofunctional state of skin epidermis. Aspirant I soiskatel, 2005; 4: 142-144.

[7] Yavisheva T.M., Shcherbakov S.D., Golubeva I.S.Savluchinskaya L.A., Rizhova N.I.The relationship between the epidermal melanocytes, Langerhans cells and epidermal cambial cells. Byulleten Eksperimentalnoi Biologii I Meditsiny, 2012; 153(3): 346-349.

[8] Yavisheva T.M., Shcherbakov S.D. Morphofunctional changes of cambial cells and their derivatives in human skin in age aspect. Byulleten Eksperimentalnoi Biologii I Meditsiny, 2009; 148(9): 326-329.

[9] Yavisheva T.M., Shcherbakov S.D. Epithelial-stromal morphofunctional zones: structure and functions (in Russian). Moscow: RAMN, 2013; 57-62, 99-108.

[10] Fedorov S.N., Ronkina T.I., Yavisheva T.M. Human cornea endothelium. Moscow.: MNTK "Microsurgery of the eye"; 1993; 126.

[11] Yavisheva T.M., Yagubov A.S., Noginov A.A. Some patterns of the organization of the endothelial layer of the human cornea in norm and pathology. Arhiv Patologii, 1994: 3: 72-76.

[12] Uglova M.V. Cytological features of age-related adaptation of human heart neurons in persons of advanced and senile age. .Voprosy serdechno-sosudistoy patologii, 1976: 101-104.

[13] Yavisheva T.M., Shcherbakov S.D. Participation of morphofunctional zones in the process of aging. Uspekhi Gerontologii, 2012; 25(4): 604-611.

[14] Yavisheva T.M., Shcherbakov S.D., Golubeva I.S., Sharafutdinov G.Z. Interaction of cambial dermal cells (fibroblasts) and epidermis in morphofunctional zone of mouse skin. //Byulleten Eksperimentalnoi Biologii I Meditsiny, 2007; 144(11): 594-599.

[15] Yavisheva T.M., Shcherbakov S.D. On the general mechanisms of proliferation of cambial somatic and sexual cells and the concept of cambial cells. Byulleten Eksperimentalnoi Biologii I Meditsiny, 2012; 153(1): 94-97.

[16] Yavisheva T., Shcherbakov S. Participation of an inactive and active Src-kinase in formation of a cytoskeleton and melanogenesis in Hep2 cells. International journal of current microbiology and applied sciences, 2016; 5(12): 583-593.

[17] Yavisheva T.M., Shcherbakov S.D. Characteristic features of proliferation and differentiation of cambial and daughter cells in morphofunctional zones in normal epithelium and cancer in age aspect. Uspekhi Gerontologii, 2009; 22(4): 605-613.

[18] Aikawa, R., Komuro, I., Yamazaki, T., Zou, Y., Kudoh, S., Tanaka, M., Shiojima, I., Hiroi Y. and Yazaki, Y. Oxidative stress activates extracellular signal-regulated kinases through Src and Ras in cultured cardiac myocytes of neonatal rats. Journal of Clinical Investigation, 1997; 100(7):1813-1821.

[19] Burova, EB., Gonchar, IV. and Nikolsky, NN. Stat1 and stat3 activation by oxidative stress in A431 cells involves src-dependent EGF receptor tranactivation. Tsitologiya, 2003; 45(5): 466-477.

[20] Devary Y, Gottlieb R., Smeal T., Karin M. The mammalian ultraviolet response is triggered by activation of Scr tyrosine kinases. Cell,1992; 71(7): 1081-91.

[21] Yavisheva T., Shcherbakov S. Participation of Src-kinase in age changes of a brain central zone. Journal of psychiatry and psychiatric disorders,2018; 2(6): 179-182.

[22] Yavisheva T., Shcherbakov S. To a question of structial and functional organization of the morphofunctional zones in age aspect, participation of Scr-kinase in the work of morphofunctional zones. International journal of current medical and pharmaceutical research, 2018; 4(6A): 3336-3344.

[23] Yavisheva T., Shcherbakov S. Participation of morphofunctional zones in aging processes. Advances in aging research, 2014; 3: 72-78.

[24] Ammendola A., Gemini D., Iannaccone S. et al. Gender and peripheral neuropathy in chronic alcoholism: a clinical-electroneurographic study. Alcohol, 2000; 35(4): 368-371.

[25] Monichev A.Y.. Hematopoietic dynamics. Moscow: Meditsina, 1984; 176.

[26] Yavisheva T.M., Shcherbakov S.D. Features of proliferation and differentiation of cambial and daughter cells of epidermal-dermal morphofunctional zone in normal epithelium and in cancer. Kketochnye tehnologii v biologii I meditsine, 2010; 2: 88-94.

[27] Porat-Shliom N., Milberg O., Masedunskas A. and Weigert R. Multiple roles for the actin cytoskeleton during regulated exocytosis. Cell Mol Life Sci, 2013; 70(12): 2099–2121.

[28] Wang J. and Richards D. Spatial Regulation of Exocytic Site and Vesicle Mobilization by the Actin Cytoskeleton PLoS One. 2011; 6(12): e29162.

[29] Chentsov Y.S.Introduction in the cellular biology (in Russian). Moscow: «Akademkniga», 2005; 239-250.

[30] Chizmadzhev Yu.A. How the virus penetrates the cell. Priroda, 2003; 4: 69-75.

[31] Zhou, T., Tsybovsky, Y., Gorman, J., Rapp, M., Cerutti, G., Chuang, G.-Y., Katsamba, P.S., Sampson, J.M., Schön, A., Bimela, J., Boyington, J.C., Nazzari, A., Olia, A.S., Shi,W., Sastry, M., Stephens, T., Stuckey, J., Teng, I.-T., Wang, P., Wang, S., Zhang, B., Friesner, R.A.,Ho, D.D., Mascola, J.R., Shapiro, L., Kwong, P.D., Cryo-EM Structures of SARS-CoV-2 Spike without and with ACE2 Reveal a pH-Dependent Switch to Mediate Endosomal Positioning of Receptor-Binding Domains. Cell Host and Microbe, 2020; doi: https://doi.org/10.1016/j.chom.2020.11.004.

[32] Shiryaev V.A., Klimochkin Y. Heterocyclic viroporin inhibitors in the design of antiviral compounds. Himiya geterotsiklicheskih soedineniy, 2020; 56 (6): 626-635.
[33] Alberts B., Bray D., Lewis J., Roberts K., Watson J. Molecular biology of the cell. Moscow.: Mir, 1994; 118-143.
[34] Chang L., Shav-Tal Y., Trcek T. Assembling an intermediate filament network by dynamic cotranslation. Journal of cell biology, 2006; 172(5): 747-758.
[35] Godsel L., Hobbs R., Green K. Intermediate filament assembly dynamics to disease. Trends in cell boil, 2008; 18: 28-37.
[36] Cortese, M., Lee, J.-Y., Cerikan, B., Neufeldt, C.J., Oorschot, V.M.J., Köhrer, S., Hennies, J., Schieber, N.L., Ronchi, P., Mizzon, G., Brey, I.R., Santarella-Mellwig, R.,Schorb, M., Boermel, M., Mocaer, K., Beckwith, M.S., Templin, R.M., Gross, V., Pape, C., Tischer, C.,Frankish, J., Horvat, N.K., Laketa, V., Stanifer, M., Boulant, S., Ruggieri, A., Chatel-Chaix, L., Schwab,Y., Bartenschlager, R., Integrative imaging reveals SARS-CoV-2 induced reshaping of subcellular morphologies. Cell Host and Microbe, 2020; doi: https://doi.org/10.1016/j.chom.2020.11.003