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Point of View

On The General Mechanisms of both, Somatic Cambial Cells and Germ Cells Proliferation, and the Concept of Cambial Cells

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Abstract

Having applied the previously mentioned cambial epithelium cells functioning scheme to the process of early embryogenesis, it has been shown that cambial, or stem cells, originate from a presumptive ectoderm, and protein RhoA that is strongly expressed and Src kinase, is weakly expressed in them. This gives them their stem cell qualities and an absence of certain differentiation. Primordial germ cells represent the stem cells that became separated and entered an environment, which expresses Src kinase to a certain degree in them, and causes their polarization and specialization. For certain cambial cells differentiation, it is necessary to enhance the Src kinase expression to an optimum degree for each tissue. IJBM 2011; 1(4):242-244.
Key words: *cambial cells, embryogenesis, RhoA protein, Src kinase.*

In our previous research conducted using our own experimental material and literary data, the characteristics of epithelial cambial cells in normal, as well as those under certain kinds of pathological conditions, had been elaborated upon [6]. Some functional parameters of cambial cells responsible for their stem-like features have been thus defined. However, there were some obscure questions concerning fundamental characteristics of these cells emanating from their embryogenesis. Their fertilization represents an extremely unique phenomenon, however, the same mechanisms of cellular signals' transduction which control intracellular processes in somatic cells also participate in the process [1]. Having applied the aforementioned functioning scheme of cambial cells to the process of early embryogenesis, together with some mechanisms and pathways of their occurrence, certain differentiations have been revealed.

We previously reported that somatic cell polarization is conditioned by the activization of Src kinase, one of the basic regulators of proliferation, differentiation, and migration of cells [6]. When these cells are attached to a substrate, the cell develops in a membrane by means of its locus, in which is present the Golgi complex that affects a large number of membranes on which Src is localized. Because the Src kinase participates in the assembling of microtubules and actin microfilaments assembly, the leading edge of the cell, at the expense of the growth of the outer areas of the cells takes place. Hence, Src kinase provides the cell and nucleus with the ability of distention, and unwinds the loops of certain chromosomes' sites, which are necessary for transcription. However, when these cells undergo a spasm, the less they undergo stretching. It is well known that cell constriction occurs due to the contraction of the cortical actin-myosin complex. The critical importance, thus, is the RhoA protein, which is one of the small G-proteins. Hence, two key proteins define cell differentiation: Src kinase and RhoA [6]. When there is a normal level of Src expression, which sharply reduces RhoA, it activates additional formins, which generate nonbranching filaments necessary for the formation of stress fibers. Thus, the cell is spread in parallel with the basal membrane, and chromosomes' loops unwinding closer to the telomeres, defining an epidermal differentiation of cells as the process take place. When the Src kinase expression is high, the RhoA activity decreases

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because of the Src phosphorylate p190 RhoGAP protein, which inactivates RhoA. In this connection, there is a decreasing of the formation of active formins and the activity of RhoA kinase that leads to cortex relaxation, and to a depression of stress fibers. In this situation, the cell cannot be spread in parallel with the basal membrane, but is sharply extended in a vertical direction. Thus, the unwinding chromosomes' loops are closer to the centromeres, defining mesodermal cells differentiation. With Src depression, formins react in a classic capping protein mode, or nucleate actin, from a new fixed point, resulting in a decrease in the formation of stress fibers. However, the cell constriction increases due to the intensification of RhoA and Rho kinase that enhances interaction of the actin-myosin complex. The cell expression, in this case, takes place in a slightly vertical direction. Hence, the degree of Src expression in relation to RhoA defines a concrete cell differentiation.

Src kinase is weakly expressed in cambial cells, this leads to intensifying the RhoA expression, absence of distention, and differentiation of the cell [3]. From the literature [6], it is known that pluripotent cambial cells and primordial germ cells (PGC) in their early stages of development have many general features, and derive from proximal epiblast, a presumptive ectoderm, i.e. before the transformation into epidermis and a neural tubule. Hence, in PGCs, as well as in cambial cells, there is high RhoA expression and weak Src kinase. Further, PGCs migrate in the yolk sac, in ovary germ epithelium, and the gonads germ, mesenchyme, excreting growth factors as fibroblasts growth factor (FGF) type. We had previously reported that such factors in somatic cells cause appreciable Src kinase activization in the leading edge of the cell [6]. Hence, Src kinase also must be activated in oogone, not over the cell, but in its leading edge, i.e. in the direction of the Golgi complex localization. It will lead to Src accumulation and RhoA inactivation in this location. Hence, at the stage during which the oogons are in the epithelium and stroma of the gonads, their initial polarity with the vegetative pole in the given part is formed, where the Src kinase expression is raised and RhoA is decreased. The animal pole is formed at the opposite side where the RhoA expression is a raised or lowered Src. Until the general RhoA expression in the cell considerably exceeds Src kinase, mitotic division of oogons will proceed, because, for the removal of proliferation inhibitors and formation of an actomyosin ring, maintaining an increased RhoA [6] is necessary. During the oogons functioning in the ovary stroma, the Src kinase expression will increase and RhoA decrease in them, which will lead to a decrease in formation of formins, and a reduction proliferation of inhibitors, that will cause the termination of mitoses. Therefore, to renew mitotic activity in oocytes, it is necessary to raise the RhoA expression in them. In fact, in puberty, one of the main hormones that exercise influence over follicles is luteinizing hormone (LH) [4]. During the early stages of follicle development, LH receptors (LHR) are present in theca cells. Under the influence of LH, these cells develop testosterone, which enters granulosa cells and undergoes transformation into estrogen there, which in turn stimulates formation of LHRs by granulosa cells. LHRs are members of a large superfamily of G-protein-coupled receptors (GPCRs). During linkage of these receptors with LH, there is a transactivation of epidermal growth factor receptors (EGFR) [5]. These receptors possess low affinity to Src in comparison with FGF receptors [6]. Hence, moderate expression of Src and p190RhoGAP inactivating RhoA, will provide an appreciable opportunity for RhoA activization in granulosa cells. Hence, during ovulation (maximum LH rising),RhoA expression in an oocyte animal pole will strengthen with the influence of granulosa cells. Therefore, the biological meaning of LH action consists in intensifying RhoA, i.e. for oocyte and somatic cells; the same principles of proliferation are a characteristic. In ovulation, when LH levels rise sharply, stimulating RhoA, the contractile ability of the oocyte animal pole cortical layer increases in comparison with the vegetative. Therefore, the meiotic spindle becomes irregularly tightened with one shoulder attached to the animal pole. Because the material the microtubule-organizing center (MTOC) contains much Src -kinase, and the RhoA expression is sharply raised in the animal pole, the point of contact of the spindle shoulder with the egg cytoplasm cortical layer will be formed there at the dense layer of actin filaments. This takes place at the expense of formins activization. Because RhoA stimulates Rho kinase which phosphorylates the myosin light chain, the formins' contractile ability increases sharply which leads to the formation of cleavage furrow and the first polar body. Therefore, a part of the cytoplasm and MTOC material splits off, and this will decrease the Src kinase level in this area. Therefore, a division spindle will be developed in parallel with the plasma membrane. Hence, the following increase in Src-kinase level is necessary for the splitting of the second polar body in the given egg locus to facilitate the division spindle settling at an angle to a plasma membrane and formins activization. It is provided with an acrosome sperm reaction and contains cortical granules. In fact, the sperm acrosome vesiculate is homologous to egg cortical granules, and is formed by the Golgi complex, and contains membrane-like structures on which it is Src kinase-localized [5]. Therefore, in a place of coalescence of the sperm head with the oocyte, Src kinase and formins are activated, which leads to dense hillock formation. Besides, since Src kinase participates in polymerization of microtubules,therefore their will be more in a sperm penetration place, than in the other fields. Considering the large contractile ability of such a field, and the dense network of microtubules in it, the division spindle will be developed at an angle to the egg plasma membrane. The same processes, as at the splitting of the first polar body, will continue. Because at the splitting of the second polar body there was a particulate elimination of MTOC pericentriolar material, and the Src kinase level in this locus was reduced, the actin-myosin complex and microtubules will be largely expressed in a sperm penetration place. At the expense of the pull of microtubules force and contractile formins force, the nucleus will be tightened in a sperm-penetration orientation with a simultaneous turn of cytoplasm cortical layers. The nucleus' long axis, reflecting anatelophase orientation along which there will be further divisions of blastomeres, accompanied by certain chromosomes' loops unwinding, is as a result, established. Thus, the vegetative cytoplasm in which Src is activated will be slightly displaced in the animal pole. However, together with the

action of nucleus and cytoplasm, there will be the same action in the Golgi complex, which is bound to the nucleus' membranes. Hence, at the boundary between the animal and vegetative regions, which is inverse to sperm penetration, there will be conditions for maximum Src expression, which will gradually decrease towards the animal and vegetative egg poles. Src kinase depression, to a larger degree, will be expressed more in the animal pole direction than the vegetative, since its activity is initially high. Maximum Src activity in such a region will cause appreciable depression of RhoA expression. It will lead to a thinning and softening of this egg cortex region, and create ideal conditions for gastrulation, and will cause blastopore dorsal labium (BDL) occurrence to further increase here. It is important to observe that at the blastocyst stage, proliferation will be more active near the animal, not vegetative egg pole, because of high RhoA expression on the animal pole, and this will cause the inner cell mass (ICM) formation here. Vegetative pole cells essentially differ from animal pole cells because they have a raised Src kinase expression and a lowered proliferation and, apparently, are the source of trophoblast formation. Probably, that the hypoblast will be formed at the expense of the trophoblast inductive influence on ICM inferior departments and the Src expression in these cells. The cells of the epiblast formed after that, are not homogenous on Src kinase expression in them, and the greatest activity of Src will be in cells in the BDL field, i.e. in the epiblast-proximal segments. Therefore, in this region, cells at the expense of RhoA depression will drop active formins, stress fibers, and focal contacts in quantities that will drive cells' distention in parallel with the basal membrane, and will enlarge their motility. Microtubules at high Src kinase expression will be very well developed, which enlarges cells and provides their mesodermal differentiation. At the expense of high motility and elongation, these cells are the first to penetrate the blastocoele through a proximal area to form the chorda. Because epiblast cells have different Src-kinase activity, invaginating cells will differ in their cell and nucleus distention degree, i.e. a differentiation, and also motility and sequence of occurrence in the blastocoele. Next, the chorda induces the ectoderm to develop in a neural tubule. In fact, in the chorda material, Src kinase is very strongly expressed, while in the ectoderm lying over it, the RhoA is strong. Therefore, Src expression will prevail over RhoA in this ectoderm region, and this will lead to RhoA depression, decreasing of formins formation, and stress fibers. Ectoderm cells will be stretched in a vertical direction (but to a lesser degree) than in the chorda, resulting in the formation of the neural plate. Inductive influence of the chorda on peripheral segments of the neural plate is weaker than in the central, i.e. Src kinase expression will weaken from the plate center to its periphery, and RhoA, accordingly, will be increased. It will lead to a sharp increase of RhoA expression in the peripheral segments of the neural plate (neural folds), therefore, there will be activization of the actin–myosin complex and contractile ability of these cells. It generates a wave of contractions in all cells which are firmly bound by their apical extremities, that causes neural plate bending and its formation in a neural tubule. Thus, neural folds move towards each other and then merge, giving rise to cells of the neural crest. All components of the peripheral neural system, and also cell of adrenals, as well as pigment cells, are formed practically at the neural crest and in the field of a head – cartilage, bone, and other types of connective tissue [1]. Hence, cells of the neural crest are pluripotent stem cells which have arisen from a presumptive ectoderm at the border of strongly expressed RhoA, and weak Src kinase. Therefore, for all practical purposes, there is no nucleus distention and definite differentiation of these cells concerning their stem qualities. The same RhoA expression and Src kinase are available in somatic cambial epithelium cells and PGC in their early developmental stages. Hence, stem cells are the cells that have originated from the ectoderm, i.e. with a strong protein RhoA expression and weak Src kinase. To effect a differentiation of these cells it is necessary to express Src in them by means of biologically active factors, which express Src in conformity with those tissues, which develop them. Appreciable Src prevalence over RhoA will cause rearrangement of cell cytoskeleton, cell-stretching upright to a basal membrane, and loop unwinding of certain chromosomes' sites relative to their anatelophase orientation that will cause the formation of mesodermal cells. Moderate Src augmentation and strong RhoA expression will cause a differentiation in the epithelial type since well-developed stress fibers and microtubules will stretch the cell parallel to the basal membrane and untwisting in other sites. Germ cells also represent cambial cells, but in which there was certain Src kinase activization that has led to the conforming and specialization of these cells.

References

1. Alberts B, Bray D. Lewis J, Raff M, Roberts K, Watson J. Molecular biology of the cell. Moscow, Mir; 1994.
2. Conti M, Hsieh M, Park J, Su Y. Role of the epidermal growth factor network in ovarian follicles. Molecular Endocrinology 2006; 20:715-723.
3. De-Miguel M, Arnalish-Montiel F, Lorez-Iglesias P. et al. Epiblast-derived stem cells in embryonic and adult tissues Int. J. Dev. Biol. 2009; 53:1529-1540.
4. Diban A. Early development of mammals. Leningrad, Nauka; 1988.
5. Gilbert S. Developmental biology. Moscow, Mir; 1993.
6. Yavisheva T, Shcherbakov S. 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; 22:605-613.