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Commentary

Ubiquitous expression of FSH/LH/hCG receptors, OCT-4, and CD133 in adult organs and cancers reflects novel VSELs biology

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ABSTRACT

Very small embryonic-like stem cells (VSELs) were first reported in bone marrow and cord blood. We detected them by immunolocalization studies using polyclonal OCT-4 antibody on human testicular and ovarian cell smears. Cells with nuclear OCT-4A were the VSELs and cytoplasmic OCT-4 was expressed in the immediate descendants, i.e. spermatogonial stem cells and ovary germ stem cells. VSELs are postulated to be primordial germ cells, and during their migration to the gonadal ridge during embryonic development, they also migrate to various somatic organs, serve as a backup pool for tissue-specific adult stem cells to maintain life-long tissue homeostasis, and are also postulated to be the 'embryonic remnants' whose uncontrolled proliferation possibly results in cancer. VSELs express receptors for gonadotropin and sex hormones and express OCT-4, CD133, and hCG and thus their presence, differentiation, and uncontrolled proliferation during cancer could explain ubiquitous expression of OCT-4, CD133, hCG and receptors for sex and gonadotropin hormones in various normal and cancerous somatic and gonadal tissues.

1. Commentary

I read the editorial by Rao and Ticconi in the first issue of JRHM[1] with great interest. They are intrigued by the presence of hCG receptors on a wide variety of nongonadal tissues in females (nonpregnant human uterus, endometrium, human placenta, fetal membranes, and deciduas) similar to that in males (sperm, secondary sex organs, prostate, epididymis, seminal vesicles, and penis). hCG/LH receptors are also reported in several somatic tissues (blood cells like macrophages and monocytes, brain, adrenal cortex, spinal cord, neural retina, skin, bone, mammary glands, urinary bladder, endothelial cells, and umbilical cord) and also in various gynecological cancers (ovary, breast, and prostate). A careful survey of literature suggests that hCG/LH receptors have been reported in extragonadal tumors[2] including pancreatic[3] and lung[4] cancer.

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A very similar editorial was recently published by Kumar[5] entitled 'Extragonadal FSH receptor: is it real?' FSH receptors that were till now understood to be expressed on Sertoli cells in testis and granulosa cells in the ovary and indirectly drive FSH-mediated differentiation of germ cells have also been reported on extragonadal tissues (placenta, uterine tissue during pregnancy, nonpregnant endometrium in both proliferative and secretory phases, cervical glandular epithelium, muscle fibers, nonpregnant myometrium, cervix, endothelial cells, arterial smooth muscle cells, etc.)[6,7] and also in blood vessels in various nongonadal cancers.[8] Pancreatic neuroendocrine tumors aberrantly express FSHR in neoplastic cells (rather than in the blood vessels).[9,10] Mariani et al.[11] reported FSHR in normal (9/13 cases), benign hyperplasia (8/15 cases), and prostate cancer (21/30 cases) in the glandular epithelium and stromal cells. Ghinea[12] also reviewed extragonadal FSH action and the group[13] has reported FSHR in >1300 human tumors (colon, prostate, breast, lung, ovary, testis, kidney, pancreas, urinary bladder, kidney, liver, stomach, and ovary). Pawlikowski et al.[14] reported FSHR in pituitary adenomas cell cytoplasm and blood vessels and adrenal tumors (adrenocortical, pheochromocytomas, and malignant adrenal tumors). Hong et al.[15] have developed an immunoPET tracer to image FSHR in cancer tissues and propose that FSHR could be a potential target for cancer therapy.

CD133 (prominin-1) is a cell surface glycoprotein initially identified as a marker for primitive hematopoietic stem cells.[16] It has also been reported in several solid tumors as well as leukemias and is considered as a marker for cancer initiating cells as well as for circulating tumor cells with properties like low proliferative rates, high self-renewing capacity, propensity to differentiate into actively proliferating tumor cells, resistance to chemotherapy or radiation, and also tumor formation on xenografting; however, it is still associated with controversies.[17] Similarly, Lengner et al.[17] summarized various somatic tissues expressing OCT-4 based on published literature (Table 1[18] in supplementary section). They were confused that if OCT-4 is a critical regulator of pluripotency then what role it has in the somatic tissues[18] and we recently reviewed that OCT-4 is also widely reported in various cancers.[19]

We postulate that this ubiquitous pattern of expression of receptors for hCG/LH/FSH along with CD133 and OCT-4 in adult body tissues and cancerous tissues is suggestive of the presence of very small embryonic-like stem cells (VSELs) in various body organs, which are also the possible 'embryonic remnants' whose uncontrolled proliferation results in various cancers. VSELs were first reported in adult mouse organs in 2006 by Ratajczak's group[20] and now more than 100 papers are published by various groups describing various aspects of these stem cells. VSELs are proposed to be the primordial germ cells (PGCs) that en route to the gonadal ridge during early embryonic development – migrate and settle in various adult body organs.[21] They are the most primitive, pluripotent stem cells that serve as a backup pool to give rise to adult tissue specific stem cells throughout life by undergoing asymmetric cell divisions. The adult stem cells then undergo rapid proliferation, clonal expansion, and further differentiation into specific cell types and thus lifelong homeostasis is maintained. VSELs are quiescent in nature and it has been postulated that they are the possible 'embryonic remnants' that undergo uncontrolled proliferation resulting in increased incidence of cancer in adult life.[22–25] It is also intriguing to point out that these stem cells express a functional SDF-1-CXCR4 axis and are easily mobilized under conditions of stress and disease[26] and it is this potential of VSELs to mobilize under normal conditions of stress/disease that is possibly manifested as metastasis during cancer as suggested earlier also.[26]

As VSELs are postulated to be pluripotent PGCs, they express pluripotent embryonic as well as PGC-specific markers.[27] The very presence of VSELs became controversial when one leading stem cell biologist group could not isolate them from mouse bone marrow[28] but it was more of a technical problem, as explained by Ratajczak's group.[29] VSELs do exist and we have recently detected and characterized them in human cord blood.[30] Also another independent group confirmed their presence and characterized them in mouse bone marrow.[31] These cells have better potential compared to hES and iPS cells.[19] Interestingly, the VSELs located in adult ovary surface epithelium express functional FSHR[32] and the ovarian VSELs respond to FSH treatment by undergoing asymmetric cell division, proliferation, and clonal expansion to form germ cell nests followed by meiosis and resulting in postnatal oogenesis and primordial follicle assembly.[33,34]

Recently, Mierzejewska et al.[21] extensively characterized mouse bone marrow hematopoietic LIN−/CD45+ stem progenitor cells (HSPCs) and LIN−/CD45− VSELs for pituitary and gonadal sex hormone receptors. They observed that LIN−/CD45− VSELs express FSHR and also LHR and expand *in vivo* to hormonal treatment as evidenced by BrdU uptake. Just like reproductive biologists, the hematologists are also intrigued by observing similar chromosomal aberrations between leukemias or lymphomas and germline tumors, suggesting their shared clonal origin.[35–38] There exists a developmental link between germline and hematopoiesis. A functional erythropoietin receptor (EpoR) is shared between germline-derived cells and also with hematopoietic stem cells.[39] Similarly, we recently observed hCG expression on cord blood VSELs (using antibody kindly provided by Prof. G.P. Talwar, Talwar Research Foundation, New Delhi). hCG expression has been reported on several cancers by various investigators.[40–42] Expression of PGCs specific and pluripotent markers in testicular cancer has confused reproductive biologists and they have postulated that testicular cancers in young adolescents indeed initiates during fetal development from gonocytes.[43] We need to accept the fact that few PGCs survive in adult testis as VSELs in both mice[44] and humans.[45]

Thus, VSELs express these functional receptors/pluripotent markers and when they differentiate, the progenitor cells also express them as we have shown FSHR and OCT-4 expression in differentiated oocytes obtained from the VSELs in the OSE[31] or as Ratajczak's group has shown in the HPSCs[21] and gradually the expression of these VSELs specific markers is lost as cells become further committed/differentiated. Uncontrolled proliferation of VSELs leading to cancer explains expression of these markers in wide variety of cancers.[19]

It is a very exciting time for stem cells biology as the presence of VSELs and their potential will challenge several existing dogmas and provide explanation to several perplexing observations that have accumulated in published literature. We need to work with an open mind and accept newer