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Editorial

Stemness Markers and Biomarkers of Pituitary Cytogenesis: Current Armamentarium of Molecular Targets

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Editorial

This editorial emphasizes recent advances in neonatal and adult stem cells, stem cells of Anterior Pituitary (AP) and stemness markers and biomarkers of pituitary cytogenesis.

Therefore concise information for each specific stem cell biomarker is presented in the light of recent cellular and molecular research.

Stemness markers have diverse effects either in pituitary embryogenesis and tumor development. This puzzling group consists of several elements, i.e. nestin, Sca1, Sox2+/E- cadherin, S100 proteins, Prop-1, Oct-4, Bmi-1, CD133, beta-catenin, SOX2, Pax6, Notch2, Notch3, Pit1, p57. Each specific marker has an eloquent effect on intimate molecular pathways which take part in pituitary cytogenesis. Therefore their formal roles will be briefly mentioned herein [1,2].

Nestin is expressed in various stem (Sox2+) cells in situ (marginal zone) and in culture (pituispheres) [3-5]. It is not only expressed by pituitary stem cells but also pituitary's non-hormonal cell population as well as in some pericytes [6-8].

Sca1– (Stem Cell Antigen 1) is more or less expressed in Stem Cell-enriching Side Population (SC-SP) fraction [5]. Additionally it is expressed in pituispheres [3] and in some colony-forming cells [9]. The exact function of Sca1 expressivity in the pituitary needs further elucidation.

Sox2+/E-cadherin+ Stem Cells. Tumor suppressor gene E-cadherin is a classical member of the cadherin super family [10,11]. As a family cadherins regulate signaling pathways that organize cell proliferation and motility controlled by process of Epithelial–Mesenchymal Transition (EMT) [12]. Rathke's cleft overlying marginal cells and S100+ cells within AP lobe robustly express E-cadherin (Cdh1) [3].

S100 proteins are engaged in regulation of Ca++ homeostasis, protein phosphorylation, the dynamics of cytoskeleton constituents, cell growth and differentiation, transcription factors, inflammatory response and enzyme activities. Randomly distributed folliculostellate cells of pituitary present distinct nuclear and cytoplasmic S100 reactivity hence these cells are believed to be the analogs of brain glial cell lineage [6,7,13,14].

Prop1 is a protein that in humans is encoded by PROP1 gene and also a homeobox protein prophet of PIT-1 [15]. Major two functions of PROP1 are its transcriptional activation ability and DNA binding. So its expressivity guides ontogenesis of pituitary gonadotropes, somatotropes, lactotropes, and thyrotropes. PROP1 inactivation results in deficits Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Growth Hormone (GH), Prolactin (PRL), and Thyroid-Stimulating Hormone (TSH) [15]. Its inactivation terminates in failure of embryonic progenitors to leave dorsal Proliferative Region of RP (Rathke's pouch) for supplementary differentiation and colonization of development of AP [16].

Oct-4 (Octamer-binding transcription factor 4) is a homeodomain transcription factor of the POU family [17] that has a role in protracting self-renewal capacity of adult somatic stem cells (i.e. stem cells from epithelium, bone marrow, liver, pituitary, etc.) [18].

Bmi-1 is an oncogene activated in lymphoma [19], exclusively adjust Hematopoietic Stem Cells (HSC) [20] and Neural Stem Cells (NSC) [21]. In half of human pituitary adenomas Bmi-1 over expressivity is present which is interpreted as this stem cell marker might have profound role in pituitary tumorigenesis [22].

CD133 is also referred Prominent 1 (PROM1) which is a member of pentaspan transmembrane glycoproteins (5-transmembrane, 5-TM), which specifically localize to cellular protrusions [23]. In addition to its expressivity in hematopoietic stem cells [24], endothelial progenitor cells [25], glioblastoma, neuronal and glial stem cells [26], various pediatric brain tumors [27], adult kidney, mammary glands, trachea, salivary glands, placenta, digestive tract, testes, its presence was documented in isolated stem/progenitor- like cells from pituitary adenoma. Therefore expression of neuronal progenitor markers including CD133 supported CD133+ cells continuation in pituitary adenomas [28].

Beta-catenin (or β-catenin) is a protein responsible for regulating the coordination of cell - cell adhesion and gene transcription. Its extensive location in AP is also associated within somatotropes and cells in marginal zone [29].

Sox2 is SRY (sex determining region Y)-box 2, also known as Sox2, is a transcription factor in maintaining self renewal of undifferentiated embryonic stem cells. Co-expression of nest in and Sox2+ in some stem cells (marginal zone) and in culture (pituispheres) was documented [3-5]. Sox2 expressivity in pituisphere cultures is a

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marker for higher proliferation rate and rapid differentiation capacity [30].

Pax6 is a member of transcriptional regulators and signaling factors those of which has some critical roles in early embryogenesis of pituitary, (viz. Hesx1, Lhx4, Prop1, Pax6, Otx2, and specific Notch pathway components). Its expressivity culminates in non- Sca1high SP [31-36].

Notch 2 as a member of the notch signaling pathway family, it has been identified in embryonic periluminal progenitor zone [34,36]. In adult pituitary a wide spectrum of molecules SC-SP (in particular Jag1, Notch2, Notch3, Hes1 and Hey1) are present [5,37,38]. So these cells present important transcriptional, signaling and growth-regulatory factors previously thought to be restricted to the pituitary embryonic phase (such as Hesx1, Lhx4, Pax6, Prop1, Otx2, Notch2, Notch3 [5,37]. Notch1 and Notch2, and legends Jag1 and Jag2 are not co localized with hormones but with S100 (except for Jag2) in about half of the (S100+) marginal cells [39].

Notch 3 is Transgenically activated gene encodes notch pilots to amplify Sox2 immunoreactivity in embryonic pituitary [40]. Intensified Prop1 and Sox2 are mediated by Notch signaling system in adult pituitary stem cells. So Notch 3 is responsible for protracting self-renewal/proliferation of stem cells as in other adult tissues [41,42].

Pit-1 is a member of the POU family of transcription factors that regulate mammalian development. This pituitary-specific transcription factor is responsible for pituitary histogenesis and hormone expression in mammals. Pit1 is also important for regulation of the genes encoding prolactin and Thyroid-Stimulating Hormone beta subunit (TSH-beta) by Thyrotropin-Releasing Hormone (TRH) and cyclic AMP [43,44]. In embryonic rat pituitary Pit-1 and Prop1 are co-localized in pituitary in as small percentage of cells (1-10%) but in postnatal life Pit-1+ cells progressively diminish whereas no Prop1 cells subsist in adult pituitary [45]. Prop1 is probably down regulated before stem cell differentiation enhances [12]. By chemical composition Pit1 is consisted of 2 major protein domains, POU-specific and POU-homeo, both are necessary for high affinity DNA binding on genes encoding Growth Hormone (GH) and prolactin (PRL).

P57 a cyclin-dependent kinase inhibitor 1C (p57, Kip2, CDKN1C) which is encoded by the CDKN1C imprinted gene in humans. This cyclin-dependent kinase inhibitor 1C is a tight- binding inhibitor of several G1 cyclin/Cdk complexes and a negative regulator of cell proliferation. High levels of p57 (CDKN1C) mRNA in adult SC-SP may point to a similar role for p57 in stem cell compartment of adult pituitary gland [37].

Future Aspects

A wide spectrum of stem/progenitor cell biomarkers has recently been characterized in the last decade. Extrapolated information indisputably expands our awareness of pituitary physiology and pathology. Comprehension of ceaseless alterations of stem cells both in pituitary neoplastic, vascular, non-neoplastic and senescent conditions will enlighten pathogenetic mechanisms of pituitary. Stemness markers unhesitatingly shed light about mechanistic changes of underlying circumstances. Biomarker armamentarium will be an incentive in medicine for stratification and extraction of putative stem cells that will most likely lead allow clinicians in management of new treatment modalities of diverse pituitary pathologies.

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