

ABSTRACT Identification of regional stem cells and progenitor cells remains one of the key challenges of the developmental biology, the solution of which will promote progress of regenerative medicine. Recently, a receptor of stem cells factor - CD117 (C-kit) - has been treated as one of the most successful and widely used marker of stem and progenitor cells. Objective of this study was to analyze the possible affinity of C-kitpositive cells of the pancreas to the pool of regional stem cells. The study was conducted using whole embryos and human fetal organs derived during the period of week 4 to 28 of gestation, and pancreas autopsy of 2 months children and adults up to 50 years old. Paraffin histological sections were immunohistochemically stained with antibodies to stem cell factor receptor C-kit, insulin, and glucagon. To identify the proinsulin mRNA, the hybridization reaction was conducted in situ. During human prenatal development, the earliest (starting from week 4 of gestation) and pronounced expression of C-kit was observed in the originating nervous system (spinal cord, dorsal root ganglia, and Schwann cells). Since week 5 of gestation these cells appeared in the mesenchyme of the dorsal mesentery, and then in the derivatives of splanchnic mesoderm of the digestive tube where they spread over the smooth muscle cells of the muscle membrane. Expression of Ckit in the endodermal epithelium of the stomach occurs from week 13.5, and week 8.5 of gestation in some cells of the pancreatic ducts. C-kit-positive cells formed islets in the pancreas and started synthesizing hormones, such as glucagon and insulin from 8.5 and 11.5 week of gestation, respectively. C-kit-positive islet cells, expressing both insulin and glucagon, were found both in prenatal and postnatal pancreas. The resulted findings and the analysis of C-kit expression during human prenatal development allow referring the receptor of stem cells factor to the markers of committed precursor cells, the expression of which coincides with the functional differentiation of precursor cells. In the human pancreas there is a common C-kit-positive progenitor cell of α - and β -cells of the islets of Langerhans, which remains in the organ after birth. Keywords: prenatal development, pancreas, progenitor cell, C-kit, islet cells, nervous system, intestinal tube.

REFERENCES

- [1] Volkova O.V. Embryology and developmental histology of human internal organs / O.V. Volkova, M.I. Pekarskii. - M.: Medicine, 1976. - p. 416
- [2] Knorre A.G. Fetal histogenesis / A.G. Knorre. - L.: Medicine, 1971. - p. 432
- [3] Anderson DM, Lyman SD, Baird A et al. Molecular cloning of mast cell growth factor, a hematopoietin that is active in both membrane bound and soluble forms. *J. Cell.* 1990; 63:235-243.
- [4] Blume-Jensen P, Claesson-Welsh L, Siegbahn A. et al. Activation of the human c-kit product by ligandinduced dimerization mediates circular actin reorganization and chemotaxis. *EMBO J.* 1991; 10:4121– 4128.
- [5] Chabot B, Stephenson DA, Chapman VM, Besmer P, Bernstein A. The protooncogene c-kit encoding a transmembrane tyrosine kinase receptor maps to the mouse W locus. *Nature.* 1988;335:88-89.
- [6] Der-Silaphet T, Malysz J, Hagel S et al. Interstitial cells of Cajal direct normal propulsive contractile activity in the mouse small intestine. *J. Gastroenterol.* 1998; 114:724–736. ISSN: 0975-8585 July– August 2015 RJPBCS 6(4) Page No. 2183
- [7] Dolci S, Williams DE, Ernst MK. et al. Requirement for mast cell growth factor for primordial germ cell survival in culture. *Nature.* 1991; 352:809-811.
- [8] Funasaka Y, Boulton T, Cobb M et al. C-kit kinase stimulates a cascade of protein tyrosine phosphorylation in normal human melanocytes in response to mast cell growth factor and activates MAP kinase, but is down-regulated in melanomas. *J. Mol. Biol. Cell.* 1992; 3:197-209.
- [9] Godin I, Deed R, Cooke J et al. Effects of the steel gene product on mouse primordial germ cell survival in culture. *Nature.* 1991; 352:807-809.

- [10] Hemesath T., Price E. R., Takemoto C. et al. MAP kinase links the transcription factor Microphthalmia to c-Kit signaling in melanocytes. *Nature*. 1998; 391:298–301.
- [11] Herrera PL, Huarte J, Zufferey R et al. Ablation of islet endocrine cells by targeted expression of hormone-promoter-driven toxigenes. *Proc. Natl. Acad. Sci. USA*. 1994;91:12999–13003.
- [12] Jensen J, Heller RS, Funder-Nielsen T et al. Independent development of pancreatic α - and β -cells from neurogenin3-expressing precursors a role for the notch pathway in repression of premature differentiation. *J. Diabetes*. 2000;49:163-176.
- [13] Jin K, Mao XO, Sun Y, Xie L, Greenberg DA. Stem cell factor stimulates neurogenesis in vitro and in vivo. *J. Clin. Invest*. 2002; 110:311–319.
- [14] Leonard J., Peers B., Johnson T. et al. Characterization of somatostatin transactivating factor-1, a novel homeobox factor that stimulates somatostatin expression in pancreatic islet cells. *Mol. Endocrinol*. 1993; 7:1275-1283.
- [15] Li J, Goodyer CG, Fellows F, Wang R. Stem cell factor/c-Kit interactions regulate human islet-epithelial cluster proliferation and differentiation. *Int. J. Bioch. Cell Biol*. 2006; 38:961–972.
- [16] Linnekin D. Early signaling pathways activated by c-Kit in hematopoietic cells. *Int. J. Biochem. Cell Biol*. 1999; 31:1053–1074.
- [17] Lue d'Auriol, Marie-Geneviève Mattei, Catherine Andre, Francis Galibert. Localization of the human ckit protooncogene on the q11–q12 region of chromosome 4. *J. Human Genetics*. 1987; 78:374-376.
- [18] Maeda H, Yamagata A, Nishikawa S et al. Requirement of ckit for development of intestinal pacemaker system. *J. Dev*. 1992; 116; 369–375.
- [19] Matsui Y, Toksoz D, Nishikawa S et al. Effect of Steel factor and leukaemia inhibitory factor on murine primordial germ cells in culture. *Nature*. 1991; 353:750-752.
- [20] Ohlsson H, Edlund T. Sequence-specific interactions of nuclear factors with the insulin gene chancer. *Cell*. 1986; 45:35-44.
- [21] Papayanopoulou T, Bice M, Broudy VC, Zsebo KM. Isolation of c-kit receptor expressing cells from bone marrow, peripheral blood, and fetal liver: functional properties and composite antigenic profile. *J. Blood*. 1991; 78:1403-1412.
- [22] Plushkina AS, Kaligin MS, Andreeva DI et al. C-kit-positive pancreas islets cell of rat's pancreas as an endocrine cells progenitor during alloxan diabetes. *J. Genes&cells*. 2013; 3:113-115.
- [23] Popescu LM, Hinescu ME, Ionescu N et al. Interstitial cells of Cajal in pancreas. *J. Cell Mol. Med*. 2005; 9:169–190.
- [24] Sohal GS, Ali MM, Farooqui FA. A second source of precursor cells for the developing enteric nervous system and interstitial cells of Cajal. *Int. J. Dev. Neurosci*. 2002; 20:619–626.
- [25] Thomsen L, Robinson TL, Lee JC et al. Interstitial cells of Cajal generate a rhythmic pacemaker current. *Nature Med*. 1998; 4:848–851.
- [26] Torihashi S, Ward SM., Sanders KM. Development of c-Kit-positive cells and the onset of electrical rhythmicity in murine small intestine. *J. Gastroenterol*. 1997; 112:144–155.
- [27] Wallace AS, Burns AJ. Development of the enteric nervous system, smooth muscle and interstitial cells of Cajal in the human gastrointestinal tract. *J. Cell Tiss*. 2005;319:367-382.
- [28] Van Dijk T, van den Akker E, Parren-van Amelsvoort M et al. Stem cell factor induces Phosphatidylinositol 3-kinase-dependent Lyn/Tec/Dok-1 complex formation in hematopoietic cells. *J. Blood*. 2000; 96:3406–3413.
- [29] Xiaomin S, Baoping Y, Long X et al. Interstitial cells of Cajal in the murine gallbladder. *J. Gastroenterology*. 2006; 41:1218-1226.
- [30] Yee NS, Paek I, Besmer P. Role of kit-ligand in proliferation and suppression of apoptosis in mast cells: basis for radiosensitivity of white spotting and steel mutant mice. *J. Exp. Med*. 1994; 179:1777-1787.

[31] Young HM. Embryological origin of interstitial cells of Cajal. *J. Microsc. Res. Tech.* 1999; 47:303–308. [32] Zsebo KM, Wypych J, McNiece IK et al. Identification, purification, and biological characterization of hematopoietic stem cell factor from buffalo rat liver-conditioned medium. *J. Cell.* 1990; 63:195-201.