Acta Haematologica Polonica 2023
Number 2, Volume 54, pages 72–76
DOI: 10.5603/AHP.a2023.0014
ISSN 0001–5814
e-ISSN 2300–7117

REVIEW ARTICLE

VIA MEDICA

Association between tumor markers and anemia: a short review

Narjes Soltani[1], Bahareh Moghimian-Boroujeni[2], Mehrnaz Abdolalian[3], Mohammad Reza Javan[3*]

[1]Cancer Molecular Pathology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

[2]Thalassemia & Hemoglobinopathy Research Center, Health Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

[3]Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Iranian Blood Transfusion Organization, Tehran, Iran

Abstract

Tumor markers are a group of molecules used to diagnose certain diseases, including cancer. These molecules can alter cellular pathways, including those associated with some anemias, by expressing or influencing certain cellular mediators. The present study is based on data obtained from the PubMed database (1970–2019) using the key words 'tumor markers', 'anemia' and 'iron'. We found that some tumor markers can affect hepcidin expression and iron uptake by altering cell pathways. Several other tumor markers also increase in some anemias, so that they can sometimes be used to diagnose and confirm the type of anemia. The role of some tumor markers remains unclear despite the increase in some anemias. In general, some tumor markers are involved in the pathophysiology of a number of anemias or help diagnose anemia. However, studies of the role of tumor markers in the diagnosis, development or progression of anemias have been very limited.

Key words: tumor markers, anemia, iron, hepcidin

Acta Haematologica Polonica 2023; 54, 2: 72–76

Introduction

Tumor markers refer to a group of molecules that help to detect cancer and predict how cancers behave in the body [1, 2]. These molecules have impacts not only in terms of disease diagnosis in asymptomatic patients, but also in differential diagnosis in patients with symptoms [2, 3]. In fact, genetic changes in tumor cells affect the gene expression pattern of cells and surrounding tissues and lead to the formation of some tumor markers. However, only a small number of tumor markers are used for disease diagnosis [4, 5]. Furthermore, these genetic alterations affect parts of cellular pathways via expressing certain proteins or cellular mediators [6]. Given that the pathophysiology of anemia is cell-dependent, it is possible that a group of tumor markers could cause and promote anemia. In this study, we aimed to investigate the role of tumor markers in the formation and progression of anemia.

Cancer antigen 15-3

Pernicious anemia is an autoimmune disorder characterized by gastric atrophy, decreased gastric acid and pepsinogen secretion, increased serum gastrin concentration, and malabsorption of vitamin B12. The detection of tumor markers in serum represents a useful tool in the diagnosis and follow-up

*Address for correspondence: Mohammad Reza Javan, Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Iranian Blood Transfusion Organization (IBTO), Tehran, Iran, phone +98 915 523 9 724, e-mail: javaneee@gmail.com

Received: 30.07.2022 Accepted: 10.11.2022 Early publication date: 23.03.2023

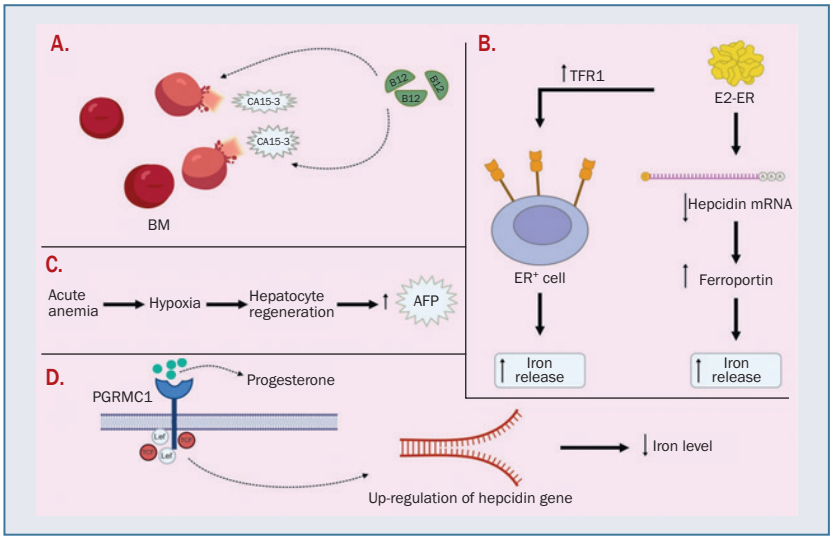

Figure 1. Role of tumor markers in some anemias: **A.** Decrease of B12 vitamin causes increase of cancer antigen (Ca) 15-3; **B.** 17β-estradiol-estrogen receptor (E2-ER) complex increases iron release to circulation by an increase of transferrin receptor-1 (TFR1) expression in ER+ cells, also E2-ER complex increases ferroportin activity and iron release by suppression of estrogen responsive element region (ERE) in promoter of hepcidin gene; **C.** Acute anemia with creation of hypoxia affects hepatocyte regeneration and leads to increase of alpha-fetoprotein (AFP); **D.** Progesterone-progesterone receptor membrane component 1 (PGRMC1) complex can reduce iron levels through SFK (Src family kinases) pathway and with help of T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) by increasing hepcidin gene expression

of malignant gastrointestinal disorders [7, 8]. Cancer antigen 15-3 (CA 15-3) tumor marker has long been used as a proven test for the diagnosis, as well as the staging, of adenocarcinomas, especially breast cancers. Studies have shown that there is an increase in CA 15-3 levels in the serum of most pernicious patients and this is not related to the *Helicobacter pylori* infection. Screening of megaloblastic anemia patients' serum has shown an unexpected increase in CA 15-3 that is not associated with the presence or progression of breast cancer [9, 10]. Elevated CA 15-3 levels in both gastrectomy patients with a limited portion of normal gastric mucosa, and in non-gastrectomy patients with atrophic mucosa, suggest that this finding is associated with cobalamin deficiency, but not gastric disease. The association between levels of CA 15-3 and serum hemoglobin, lactate dehydrogenase (LDH) and B12 vitamin suggests that accelerated production of CA 15-3 may be consistent with the severity of megaloblastic anemia.

The increase in CA 15-3 levels in bone marrow supernatants suggests megaloblastic bone marrow as the site of increased CA 15-3 production. Thus, the increase in serum CA 15-3 levels in patients with megaloblastic anemia is probably due to B12 deficiency, which is secreted by apoptotic megaloblastic erythroblasts (Figure 1A, Table I). This increase does not appear to be related to breast cancer or other cancers [11].

Alpha-fetoprotein

Alpha-fetoprotein (AFP) is a tumor-related embryonic protein that is classified as an 'oncofetal' protein due to its dual role in tumor and embryonic activity. Physiologically, different AFP isoforms can act as a tumor regulator (growth enhancer or inhibitor) [12].

Much of the growth regulation is mediated by receptor-mediated endocytosis, in which an AFP-cell surface receptor complex is located inside the tumor [13, 14].

Adult liver oval cells appear to be the only source of AFP synthesis/secretion, and there is almost no AFP storage in liver parenchymal cells [15]. Studies have shown that patients with the bilateral mutation *FANCD1/BRCA2* had higher serum AFP levels than patients with other Fanconi anemia (FA) genotypes. In this study, patients had a steady increase in AFP levels for one year after hematopoietic cell transplantation (HSC), with the exception of one patient who returned to normal after one year. A percentage of patients with normal levels of normal AFP showed an increase in the level of this factor after one year of HSC. However, the absence of high AFP does not rule out FA, and all patients still need diagnostic chromosomal fragility testing [16].

Hypoxic status due to acute anemia may affect liver cell regeneration and lead to increased AFP synthesis because shortly after acute bleeding, a moderate increase in serum AFP is observed in these patients (Figure 1C, Table I). Therefore, an increase in serum AFP is important in patients with severe anemia without liver cell damage [17].

Calcitonin

The physiological role of gastrin has been suggested as a hormonal mediator of calcitonin secretion in the intestine

Table I. Role of tumor markers in anemia

Tumor marker	Role	Ref.
Cancer antigen (CA) 15-3	B12 deficiency increases serum levels of CA-15.3 in patients with megaloblastic anemia secreted by megaloblastic apoptotic erythroblasts	[11]
Alpha-fetoprotein (AFP)	Hypoxic status due to acute anemia may affect liver cell regeneration and lead to increased AFP synthesis; some studies have shown that patients with bilateral mutation *FANCD1/ /BRCA2* had higher serum AFP levels than patients with other Fanconi anemia genotypes	[16, 17]
Calcitonin	An increase in calcitonin has been reported in some people with pernicious anemia, but exact information on cause is not yet available	[22, 23]
Estrogen receptor	Estrogen-estrogen receptor (E2-ER) complex participates in iron metabolism by acting on hepcidin and ferroportin	[33]
Progesterone receptor membrane component 1 (PGRMC1)	Progesterone-PGRMC1 complex can reduce iron levels by increasing hepcidin expression	[36, 37]

[18]. Intravenous or intramuscular injection of pentagastrin (synthetic human gastrin-17) increases serum calcitonin concentrations in animals. No precise information is available on the ability of pentagastrin to stimulate calcitonin secretion in humans. *In vivo* injection of pentagastrin increases both serum and urine calcitonin by two to three times. Patients with pernicious anemia (PA) have high levels of endogenous gastrin, possibly due to achloridria (the absence of hydrochloric acid in gastric secretions) [19, 20]. In contrast, in another study, an increase in serum calcitonin was observed in 25% of patients with PA and no association with serum gastrin levels was shown. However, such an association may be complex because calcitonin reduces gastric acid and serum gastrin. Even so, no explanation is apparent for the increase in calcitonin concentration, and the main regulator of calcitonin secretion is still unknown [21]. Some studies have shown that in long-term hypergastrinemic conditions, such as PA for duodenal ulcers, there is no change in the normal fasting level of serum calcitonin, while in some other studies, calcitonin levels have increased in some patients with PA. A study examining the relationship between serum gastrin concentration and serum calcitonin in patients with PA (Table 1) and healthy individuals showed that patients with PA have normal serum calcitonin concentrations despite very high serum gastrin levels [22, 23].

Increases in serum calcitonin concentrations after food stimulation have been reported in animals and patients with duodenal ulcers, possibly due to increased serum gastrin concentrations. In normal people, no increase in calcitonin has been observed after eating. In one study, there was a transient increase in serum calcitonin in five PA patients 5–10 minutes after a meal, whereas in healthy subjects, no increase was observed. The reason for the initial increase in serum calcitonin in some PA patients is unknown, but it is probably not due to gastrin, because the increase in serum calcitonin started before any increase in serum gastrin [24].

Estrogen receptor

Estrogen receptor (ER) is one of the markers that is used as a measure in breast cancer. ER is known as a tumor marker and is used to determine prognosis and treatment goals for breast cancer [25]. Estrogen as a sex hormone plays an important role in reproductive development and female characteristics. Evidence suggests that estrogen also has an important role in the development and growth of breast cancer [26]. 17β-estradiol (E2), the most active form of estrogen, is expressed highly in young women, while iron level (Fe) is low ain this group, but the opposite is the case in older postmenopausal women, since they usually have low E2 and high iron levels, which could indicate the possible role played by E2 in iron level alteration [27, 28]. Hepcidin as an iron-regulating peptide hormone inhibits iron entry into the plasma by the degradation of the iron exporter ferroportin [29]. Studies have shown that hepcidin mRNA in human liver HuH7 and HepG2 cells is suppressed by E2 treatment through binding E2 to ER. Suppression of hepcidin by E2-ER complex acts directly on the estrogen-responsive element region (ERE) in the promoter of the hepcidin gene [27, 30, 31]. With decreased hepcidin levels, ferroportin activity increases, and subsequently iron release escalates (Figure 1B). Also tissue iron decreases due to its over excretion. E2-ER complex also increases the expression of transferrin receptor-1 (TfR1) in ER+ MCF-7 cells that were treated with E2, which leads to rises in the amounts of iron released (Figure 1B) [30, 32]. Studies have shown that the G-coupled protein 30 (GPR30)–bone morphologic protein 6 (BMP6) pathway, which is separate from the ER-mediated signaling pathway, is involved in E2-induced hepcidin expression in mice. As an estrogen membrane receptor, GPR30 regulates iron metabolism through affecting hepatic hepcidin expression. As a result of this regulation, ferroportin is upregulated in the duodenum and hepcidin mRNA expression is decreased in HepG2 cells, and subsequently iron release

increases [33]. Accordingly, estrogen participates in iron metabolism by acting on hepcidin and ferroprotein (Table I).

The interaction of the E2-ER complex with iron metabolism at the systemic level is still not fully understood. Although various factors can play a role in iron level alteration in women, the role of estrogen and its receptor is a possible factor. According to animal studies, it seems that ER as a tumor marker plays a role in iron metabolism by affecting the expression of hepcidin and subsequently ferroportin. Confirming the role of ER in iron metabolism will require more extensive studies in the future.

Progesterone receptor membrane component 1

Progesterone receptor membrane component 1 (PGRMC1) has been linked to multiple cancers, such as breast cancer [34]. PGRMC1 is a small hemoprotein that can play a role in the differentiation of the erythroid lineage. PGRMC1 has a single transmembrane domain and a heme-binding site. Increased progesterone by binding to PGRMC1 can reduce iron levels through the Src family kinases (SFK) pathway also, with the help of T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) transcription factors, via more expression of hepcidin gene (Figure 1D) [35]. Hepcidin can deliver heme to ferrochelatase (FECH) and apo-hemoprotein. In addition, hepcidin with PGRMC1 can be introduced as a chaperone and regulator for FECH.

PGRMC1 can also act as a sensor to regulate heme production. This hemoprotein directly coordinates FECH activity with stabilizing or destabilizing mitochondrial heme contents. Therefore, progesterone can reduce iron levels by increasing hepcidin expression during binding to PGRMC1 [36, 37].

Conclusions

Tumor markers are a group of molecules that are used to diagnose certain diseases. Some tumor markers can affect iron uptake and metabolism or play a role in the identification, development, and progression of some anemias. Elevated CA 15-3 levels are probably associated with vitamin B12 deficiency and megaloblastic anemia. Checking AFP levels can help diagnose Fanconi anemia. An increase in calcitonin has been reported in some people with PA but exact information on the cause is not yet available. E2-ER can increase iron exportation to blood circulation by affecting and suppressing hepcidin, whereas progesterone — PGRMC1 decreases iron levels by increasing hepcidin expression. So far, limited studies have been conducted on the relationship between tumor marker levels and types of anemia, which limits our knowledge in this area. Therefore, further studies on this topic are needed.

Acknowledgments

The authors wish to thank all our colleagues in Karolinska Institute & High Institute for Research and Education in Transfusion Medicine.

Authors' contributions

MJ conceived manuscript and revised it. NS, BM and MA wrote manuscript and prepared figure.

Conflict of interest

The authors declare no conflict of interest.

Financial support

This review article received no funds.

Data availability

All data has been included in manuscript and will be made available upon publication.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

References

1. Duffy MJ. Clinical uses of tumor markers: a critical review. Crit Rev Clin Lab Sci. 2008; 38(3): 225–262, doi: 10.1080/20014091084218.
2. Duffy MJ. Tumor markers in clinical practice: a review focusing on common solid cancers. Med Princ Pract. 2013; 22(1): 4–11, doi: 10.1159/000338393, indexed in Pubmed: 22584792.
3. Bevilacqua V, Chan MK, Chen Y, et al. Pediatric population reference value distributions for cancer biomarkers and covariate-stratified reference intervals in the CALIPER cohort. Clin Chem. 2014; 60(12): 1532–1542, doi: 10.1373/clinchem.2014.229799, indexed in Pubmed: 25261558.
4. Diamandis EP, Fritche HA, Lilja H, et al (ed). Tumor markers: physiology, pathobiology, technology, and clinical applications. AACC Press, Washington, DC 2002.
5. Sharma S. Tumor markers in clinical practice: general principles and guidelines. Indian J Med Paediatr Oncol. 2009; 30(1): 1–8, doi: 10.4103/0971-5851.56328, indexed in Pubmed: 20668599.
6. Yao F, Zhang C, Du W, et al. Identification of gene-expression signatures and protein markers for breast cancer grading and staging. PLoS One. 2015; 10(9): e0138213, doi: 10.1371/journal.pone.0138213, indexed in Pubmed: 26375396.
7. Bidart JM, Thuillier F, Augereau C, et al. Kinetics of serum tumor marker concentrations and usefulness in clinical monitoring. Clin Chem. 1999; 45(10): 1695–1707, indexed in Pubmed: 10508114.
8. Karlson BM, Ekbom A, Wacholder S, et al. Cancer of the upper gastrointestinal tract among patients with pernicious anemia: a case-cohort study. Scand J Gastroenterol. 2000; 35(8): 847–851, doi: 10.1080/003655200750023228, indexed in Pubmed: 10994624.

9. Cheung KL, Graves CR, Robertson JF. Tumour marker measurements in the diagnosis and monitoring of breast cancer. Cancer Treat Rev. 2000; 26(2): 91–102, doi: 10.1053/ctrv.1999.0151, indexed in Pubmed: 10772967.
10. Zimmerman RL, Fogt F, Goonewardene S. Diagnostic value of a second generation CA 15-3 antibody to detect adenocarcinoma in body cavity effusions. Cancer. 2000; 90(4): 230–234, doi: 10.1002/1097-0142(20000825)90:4<230::aid-cncr5>3.0.co;2-6, indexed in Pubmed: 10966563.
11. Symeonidis A, Kouraklis-Symeonidis A, Apostolopoulos D, et al. Increased serum CA-15.3 levels in patients with megaloblastic anemia due to vitamin B12 deficiency. Oncology. 2005; 67(5-6): 359–367, doi: 10.1159/000082919.
12. Mizejewski GJ. alpha-fetoprotein as a biologic response modifier: relevance to domain and subdomain structure. Proc Soc Exp Biol Med. 1997; 215(4): 333–362, doi: 10.3181/00379727-215-44143, indexed in Pubmed: 9270717.
13. Mizejewski GJ. Review of the adenocarcinoma cell surface receptor for human alpha-fetoprotein; proposed identification of a widespread mucin as the tumor cell receptor. Tumour Biol. 2013; 34(3): 1317–1336, doi: 10.1007/s13277-013-0704-4, indexed in Pubmed: 23446764.
14. Mizejewski GJ. The alpha-fetoprotein third domain receptor binding fragment: in search of scavenger and associated receptor targets. J Drug Target. 2015; 23(6): 538–551, doi: 10.3109/1061186X.2015.1015538, indexed in Pubmed: 25766080.
15. Sell S. Heterogeneity of alpha-fetoprotein (AFP) and albumin containing cells in normal and pathological permissive states for AFP production: AFP containing cells induced in adult rats recapitulate the appearance of AFP containing hepatocytes in fetal rats. Oncodev Biol Med. 1980; 1(2): 93–105, indexed in Pubmed: 6169057.
16. Salem B, Mitchell R, DeFor TE, et al. Elevations in serum alpha fetoprotein levels in patients with Fanconi anaemia. Br J Haematol. 2019; 184(6): 1032–1035, doi: 10.1111/bjh.15223, indexed in Pubmed: 29676781.
17. Masahiro F, Haruto U. Elevation of serum alpha-fetoprotein in anemic patients. Clin Chim Acta. 1981; 113(1): 7–11, doi: 10.1016/0009-8981(81)90434-4.
18. Becker KL, Silva OL, Cyrus J, et al. Hypercalcitonemia in pernicious anemia. Experientia. 1980; 36(11): 1330–1331, doi: 10.1007/BF01969618, indexed in Pubmed: 7449924.
19. McGuigan JE, Trudeau WL. Serum gastrin concentrations in pernicious anemia. N Engl J Med. 1970; 282(7): 358–361, doi: 10.1056/NEJM197002122820703, indexed in Pubmed: 5411129.
20. Thrall JH. Parathormone and calcitonin radioimmunoassay in various medical and osteoarticular disorders. P. Franchimont and G. Heynen. Philadelphia, Lippincott, 1976, 134 pp, $15.00. JNM. 1976; 17(12): 1118.
21. Franchimont P, Heynen G. Parathormone and calcitonin radioimmunoassay in various medical and osteoarticular disorders. Lippincott Williams & Wilkins, Philadelphia 1976.
22. Brandsborg M, Nielsen HE, Brandsborg O, et al. The role of serum gastrin in the secretion of calcitonin: studies in patients with pernicious anaemia and in healthy subjects. Scand J Gastroenterol. 1980; 15(1): 23–28, doi: 10.3109/00365528009181426, indexed in Pubmed: 7367817.
23. Deftos LJ, Roos BA, Bronzert D, et al. Immunochemical heterogeneity of calcitonin in plasma. J Clin Endocrinol Metab. 1975; 40(3): 409–412, doi: 10.1210/jcem-40-3-409, indexed in Pubmed: 163843.
24. Nozaki K, Noda S, Obi S, et al. Secretion of gastrin and calcitonin after ingestion of meat extract in patients with peptic ulcer. Endocrinol Jpn. 1976; 23(1): 83–86, doi: 10.1507/endocrj1954.23.83, indexed in Pubmed: 945157.
25. Lindström LS, Karlsson E, Wilking UM, et al. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. J Clin Oncol. 2012; 30(21): 2601–2608, doi: 10.1200/JCO.2011.37.2482, indexed in Pubmed: 22711854.
26. Bhardwaj P, Au CC, Benito-Martin A, et al. Estrogens and breast cancer: mechanisms involved in obesity-related development, growth and progression. J Steroid Biochem Mol Biol. 2019; 189: 161–170, doi: 10.1016/j.jsbmb.2019.03.002, indexed in Pubmed: 30851382.
27. Jian J, Pelle E, Huang X. Iron and menoause: does increased iron affect the health of ostmenoausal women? Mary Ann Liebert, Inc., New Rochelle, NY 2009.
28. Miller EM. Hormone replacement therapy affects iron status more than endometrial bleeding in older US women: A role for estrogen in iron homeostasis? Maturitas. 2016; 88: 46–51, doi: 10.1016/j.maturitas.2016.03.014, indexed in Pubmed: 27105697.
29. Ganz T, Nemeth E. Hepcidin and iron homeostasis. Biochim Biophys Acta. 2012; 1823(9): 1434–1443, doi: 10.1016/j.bbamcr.2012.01.014, indexed in Pubmed: 22306005.
30. Yang Q, Jian J, Katz S, et al. 17β-estradiol inhibits iron hormone hepcidin through an estrogen responsive element half-site. Endocrinology. 2012; 153(7): 3170–3178, doi: 10.1210/en.2011-2045, indexed in Pubmed: 22535765.
31. Hilton HN, Clarke CL, Graham JD. Estrogen and progesterone signalling in the normal breast and its implications for cancer development. Mol Cell Endocrinol. 2018; 466: 2–14, doi: 10.1016/j.mce.2017.08.011, indexed in Pubmed: 28851667.
32. Dai J, Jian J, Bosland M, et al. Roles of hormone replacement therapy and iron in proliferation of breast epithelial cells with different estrogen and progesterone receptor status. Breast. 2008; 17(2): 172–179, doi: 10.1016/j.breast.2007.08.009, indexed in Pubmed: 17928227.
33. Ikeda Y, Tajima S, Izawa-Ishizawa Y, et al. Estrogen regulates hepcidin expression via GPR30-BMP6-dependent signaling in hepatocytes. PLoS One. 2012; 7(7): e40465, doi: 10.1371/journal.pone.0040465, indexed in Pubmed: 22792339.
34. Pedroza DA, Rajamanickam V, Subramani R, et al. Progesterone receptor membrane component 1 promotes the growth of breast cancers by altering the phosphoproteome and augmenting EGFR/PI3K/AKT signalling. Br J Cancer. 2020; 123(8): 1326–1335, doi: 10.1038/s41416-020-0992-6, indexed in Pubmed: 32704174.
35. Piel RB, Shiferaw MT, Vashisht AA, et al. A novel role for progesterone receptor membrane component 1 (PGRMC1): a partner and regulator of ferrochelatase. Biochemistry. 2016; 55(37): 5204–5217, doi: 10.1021/acs.biochem.6b00756, indexed in Pubmed: 27599036.
36. Li X, Rhee DK, Malhotra R, et al. Progesterone receptor membrane component-1 regulates hepcidin biosynthesis. J Clin Invest. 2016; 126(1): 389–401, doi: 10.1172/JCI83831, indexed in Pubmed: 26657863.
37. Zhao N, Zhang AS, Enns CA. Iron regulation by hepcidin. J Clin Invest. 2013; 123(6): 2337–2343, doi: 10.1172/JCI67225, indexed in Pubmed: 23722909.