Association between tumor markers and anemia: a short review

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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

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 mal-absorption of vitamin B12. The detection of tumor markers in serum represents a useful tool in the diagnosis and follow-up of pernicious anemia.
Narjes Soltani et al., Tumor markers and anemia

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/secrection, 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
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].

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 secretion, 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].

Table 1. Role of tumor markers in anemia

<table>
<thead>
<tr>
<th>Tumor marker</th>
<th>Role</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>Cancer antigen (CA) 15-3</td>
<td>B12 deficiency increases serum levels of CA-15.3 in patients with megaloblastic anemia secreted by megaloblastic apoptotic erythroblasts</td>
<td>[11]</td>
</tr>
<tr>
<td>Alpha-fetoprotein (AFP)</td>
<td>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</td>
<td>[16, 17]</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>An increase in calcitonin has been reported in some people with pernicious anemia, but exact information on cause is not yet available</td>
<td>[22, 23]</td>
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<tr>
<td>Estrogen receptor</td>
<td>Estrogen-estrogen receptor (E2-ER) complex participates in iron metabolism by acting on hepcidin and ferroportin</td>
<td>[33]</td>
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<tr>
<td>Progesterone receptor</td>
<td>Progesterone-PGRMC1 complex can reduce iron levels by increasing hepcidin expression</td>
<td>[36, 37]</td>
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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. 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]. The most active form of estrogen, is expressed highly in young women, while iron level (Fe) is low in 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]. Heparin 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 heparin mRNA in human liver HuH7 and HepG2 cells is suppressed by E2 treatment through binding E2 to ER. Suppression of heparin by E2-ER complex acts directly on the estrogen-responsive element region (ERE) in the promoter of the heparin gene [27, 30, 31]. With decreased heparin 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 of the erythroid lineage. PGRMC1 expression of hepcidin and subsequently ferroportin.

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Authors’ contributions

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

Conflict of interest

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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**


