Medical Hypotheses 82 (2014) 282–285

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

A novel mechanism of abnormal hematological indices in liver cirrhosis: Bone marrow endothelial cell dysfunction caused by humoral inhibitor affects the hematopoietic function of bone marrow ☆

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ARTICLE INFO

Article history:
Received 8 March 2013
Accepted 15 December 2013

ABSTRACT

Abnormal hematological indices (HIs), a complication of liver cirrhosis (LC), present difficulties in the treatment of LC and pose a serious threat to the survival of patients. LC is a dynamic wound-healing process that occurs in response to repeated liver injury and is a chronic disorder associated with changes in various organs and tissues. It has been reported that humoral inhibitor in the formation of LC could affect the hematogenic functions of bone marrow (BM) by acting on erythroid differentiation. This indicates that the BM microenvironment is affected by humoral inhibitor in LC. Bone marrow endothelial cells (BMECs) are very important components of the BM microenvironment that function as the cytoskeleton to support the adhesion of hematopoietic stem cells (HSCs). In addition, they can secrete cytokines, which have important functions in regulating positioning, homing, proliferation, differentiation and other functions of HSCs on the BM microenvironment. These functions of BMECs may be affected due to direct contact with blood and long-term exposure to an environment with humoral inhibitor in the presence of LC. Multiple studies have shown that during the formation of LC, hepatic sinusoid endothelial cells were damaged and secreted cytokines and matrix proteins. Moreover, these cytokines and matrix proteins were involved in the formation and development of LC. Similar in function to mature-stage BM, liver at the embryonic stage also functions as a type of hematogenic organ. With similar anatomical position and functions to that of hepatic sinusoid endothelial cells, BMECs may undergo similar changes and impair hematogenic function of BM. More importantly, we found even more convincing evidence in that the humoral inhibitor in LC could lead to the ultrastructural damage of BMECs that were positively related to the degree of severity of LC. Therefore, we hypothesise the existence of a novel mechanism for abnormal HIs in LC: the continuous humoral inhibitor may lead to abnormal cytokine secretion of BMECs and attenuate their supporting functions, and such alterations of BMECs may lead to BM microenvironment disorder and dysfunction of HSCs, finally causing abnormal HIs.

Introduction

Liver cirrhosis (LC) is a serious digestive system disease that has been threatening the survival and health of human beings for a long time, always having a poor prognosis after surgical treatments and internal medical treatments. Abnormal haematological indices (HIs) are frequently observed in chronic liver diseases, particularly in patients with LC. In a recent analysis of homogenous patients with compensated Child-Pugh class A/B cirrhosis, 84% were found to have abnormal HIs. These abnormalities were primarily simple thrombocytopenia or combined thrombocytopenia and granulopenia, and the prognosis of these patients was poor [1]. Additionally, these abnormal HIs may lead to severe clinical complications and may be the limiting factors in corresponding invasive operations such as liver puncture, liver biopsy, endoscopy or surgical treatments. Leucopenia may increase the risk of infection after operation. Thrombocytopenia may increase the risk of haemorrhage, both of oesophageal varices and otherwise, during and after operations, while anaemia may lead to even more serious consequences after haemorrhagic events [2]. Some studies have reported results in reference to the pathogenesis of abnormal HIs in cases of LC. Hypersplenism or decreased thrombopoietin in LC may lead to aleucia [3]. Portal hypertension may cause alimentary tract haemorrhage, hemolysis and loss of hematopoietic substances, such as ferrum, folic acid and others, which may further lead to anaemia [4]. Bone marrow (BM) depression induced by viral hepatitis, drug

☆ This work was supported by National Natural Science Foundation of China (811170397).

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http://dx.doi.org/10.1016/j.mehy.2013.12.010

or alcohol abuse may also affect hematopoiesis [5–6]. Furthermore, previous studies have indicated that LC is a type of dynamic repairing process for wounds in response to liver damage and that it is related to multiple organs and systems [7–8]. Bauer et al. found that humoral inhibitor in the formation of LC could affect the hematogenic functions of BM by acting on erythroid differentiation [9]. This indicated that the BM microenvironment is affected by humoral inhibitor in cases of LC.

The major hematogenic cells during BM hematopoiesis are hematopoietic stem cells (HSCs), and the place for their survival and function is referred to as the BM microenvironment. Bone marrow endothelial cells (BMECs) are very important components of the BM microenvironment, constituting the barrier between the BM microenvironment and peripheral blood circulation [10]. BMECs directly contact with blood and are thus continuously exposed to the systemic environment, which will result in exposure to etiological factors of LC for a long duration. Conversely, BMECs function as the cytoskeleton to support the adhesion of HSCs. More importantly, they can secrete cytokines, such as interleukin 6 (IL6), interleukin 11 (IL11) and transforming growth factor-beta (TGF-beta), among others, into the BM microenvironment by paracrine secretion [11,12]. Several reports have confirmed that these cytokines have important functions in the regulation of positioning, homing, proliferation and differentiation, among other functions, of HSCs [13–15]. If BMECs are damaged, resulting in dysfunction, the hematopoietic function of BM may therefore also be damaged.

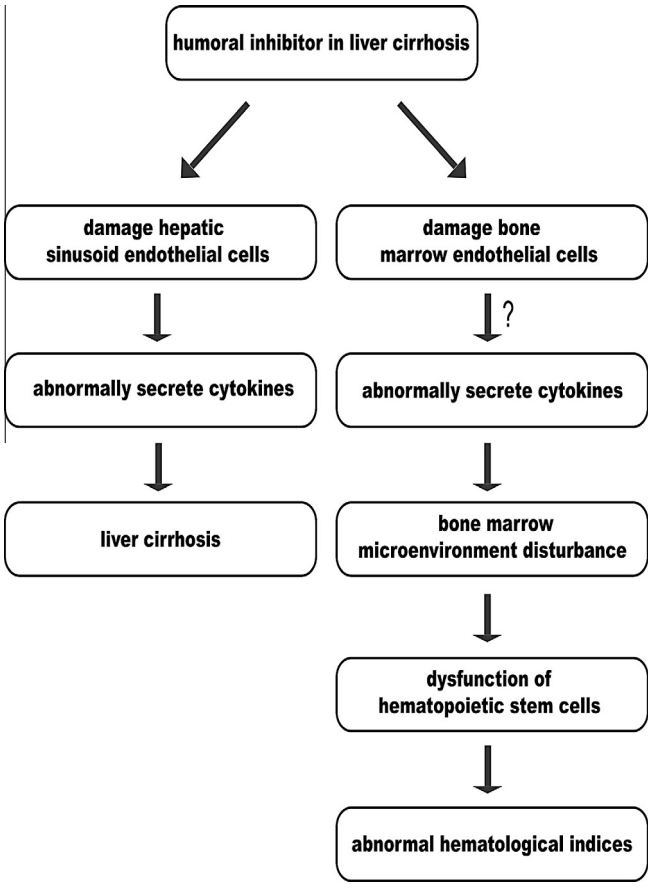

Fig. 1. The brief roadmap of our hypothesis. The biological process depicted on the left has been confirmed: the liver sinusoidal vascular endothelial cells are damaged and abnormally secrete cytokines in cases of LC. The cytokines promote the formation and development of LC. The biological process on the right represents our current hypothesis and needs to be confirmed. Similar to the function and anatomical location of liver sinusoidal vascular endothelial cells, BMECs may be damaged and abnormally secrete cytokines in LC.

Moreover, numerous studies have shown that hepatic sinusoid endothelial cells were damaged during the formation of LC and subsequently secreted cytokines and matrix proteins such as TGF-beta, perlecan and fibronectin, among others. These cytokines and matrix proteins are involved in the formation and development of LC [16–19]. It is well known that similar to the functions of BM at mature stages, liver at the embryonic stage also functions as a hematogenic organ. However, it is not known if BMECs with similar anatomical positions and functions as those of hepatic sinusoid endothelial cells undergo similar changes and impair hematogenic functions of BM.

Therefore, we hypothesise that the continuous humoral inhibitor during the formation of LC could lead to damage and abnormal cytokine secretion of BMECs, attenuating their supporting functions. Disturbance of the BM microenvironment and dysfunction of HSCs may be a result of such damage to BMECs. Investigation to address this hypothesis may potentially provide a novel mechanism to explain abnormal HIs in LC.

Hypothesis

It has been confirmed by previous studies that humoral inhibitor in LC may lead to poor differentiation of initial cells in BM, indicating that the BM microenvironment can be affected in LC [1]. As important components of the BM microenvironment, BMECs express adhesion molecules and secrete cytokines to regulate the functions of HSCs, and they are exposed to humoral inhibitor in LC for relatively long periods of time [10–12]. Additionally, BMECs, which are similar in function and in anatomical location of liver sinusoidal vascular endothelial cells, may be damaged and abnormally secrete cytokines in cases of LC [16]. Thus, it is reasonable to hypothesise that the continuous humoral inhibitor that is a feature of LC may lead to damage and abnormal cytokine secretion of BMECs, ultimately attenuating their supporting functions. The results may lead to BM microenvironment disturbance and dysfunction of HSCs and finally cause abnormal HIs. Our hypothesis will provide a new angle for the investigations of the mechanisms for abnormal HIs in cases of LC, as well as potential new treatments for LC in the future.

Evaluation of the hypothesis

As a severe digestive system disease, the therapeutic efficacy using currently available therapeutic methods for LC is not satisfactory. Moreover, HI abnormality further increases the difficulties in treatments for LC and brings more serious threats for the survival of patients. Therefore, the investigation of abnormal HIs in LC have great importance in reducing the risk for the current LC treatments and improving the prognosis of patients. Multiple studies have shown that hepatic sinusoid endothelial cells were damaged, secreting cytokines and matrix proteins during the formation of LC, such as TGF-beta, perlecan and fibronectin, among others [16–19]. TGF-beta is the strongest accelerator in the formation of LC [20]. Hepatic stellate cells can be activated by fibronectin, which is a key step in the formation of LC [19]. In addition, as with the functions of mature-stage BM, liver at the embryonic stage also functions as a hematogenic organ. Therefore, we hypothesise that BMECs, which have a similar anatomical position and functions as that of hepatic sinusoid endothelial cells, also undergo similar changes, affect the BM microenvironment and impair hematogenic functions of BM. This may be one of the reasons for the impairment observed in the hematogenic functions of BM.

As mentioned above, the major functional cells in BM are HSCs. The location for the positioning, proliferation, differentiation and maturation of HSCs is termed the BM microenvironment. BMECs