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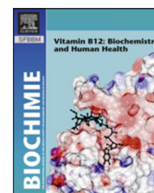

Review

Cellular uptake of cobalamin: Transcobalamin and the TCblR/*CD320* receptor

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ABSTRACT

Cellular uptake of cobalamin is facilitated by a receptor-mediated endocytosis process involving transcobalamin, a plasma protein that binds cobalamin and a cell surface receptor that specifically binds transcobalamin saturated with cobalamin. Intracellular Cbl concentration is maintained by modulating the expression of the receptor, which is cell cycle associated with highest expression in actively proliferating cells and an efflux system that shunts the excess cobalamin out of the cells for mobilization to other tissues where it is most needed. This review describes the process, proteins involved and genes encoding these proteins.

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1. Introduction

The essential role of vitamin B_{12} (cobalamin, Cbl) in recycling of folate for single carbon exchange reactions, purine and pyrimidine synthesis and methylation of homocysteine for the production of *S*-adenosylmethionine is exerted by the participation of this vitamin as methylCbl in the methionine synthase reaction [1]. As adenosyl Cbl, it is a cofactor for methylmalonyl mutase enzyme in a rearrangement reaction that converts methylmalonyl CoA to succinyl CoA [2]. Cbl deficiency produces interruption of folate pathways, resulting in homocysteinemia due to inhibition of the methionine synthase pathway and methylmalonic acidemia due to inhibition of the mutase pathway [3]. The anemia and hematologic changes in the form of megaloblastic bone marrow are due to abnormal DNA synthesis attributed to folate deficiency as a consequence of Cbl deficiency [4]. However, the demyelination of the spinal cord and peripheral nerves seen in Cbl deficiency has not been linked to any specific pathways involving Cbl. Among the multiple causes of Cbl deficiency are dietary deficiency and genetic defects involving Cbl dependent pathways [5]. The absorption, blood transport and cellular uptake of Cbl are complex processes involving multiple proteins and receptors. The gastric phase of Cbl assimilation and ileal absorption is described by Alpers in this issue [6]. This review will address the role of two proteins, transcobalamin (TC) and the receptor for TC saturated with Cbl, in the absorption of Cbl in the gut and cellular uptake.

Early observations that there is no free Cbl in serum and that all of the Cbl is bound to proteins initiated the quest to identify these proteins and their function [7,8]. These proteins were subsequently characterized and identified as transcobalamin 1 (current nomenclature, haptocorrin, HC) and transcobalamin II (current nomenclature, transcobalamin, TC) [9,10].

2. Transcobalamin

a. TC in Blood, Apo and holo TC

While total Cbl in serum has been used as an indicator of Cbl status, its utility as a sensitive marker of Cbl deficiency has been questioned primarily because most of the circulating Cbl is bound to HC and this fraction is not available for cellular uptake in tissues other than the liver [11,12]. About 70–80% of the Cbl in serum is bound to HC and only 20–30% is bound to TC; however it is this latter fraction that is available for uptake into cells and constitutes newly absorbed Cbl [13–15]. Orally administered Cbl appears to peak around 8–10 h post-ingestion [16]. This represents transit time from the stomach to the distal ileum followed by absorption and release of Cbl into the circulation. Traditionally Cbl malabsorption has been diagnosed using the Shilling test, which involves the administration of radioactive B_{12} and collecting 24 h urine sample [17]. This test is no longer available. Some success has been achieved by monitoring the appearance of Cbl in blood following a dose of $^{57}CoB_{12}$ [18,19]. However, radioactive Cbl for this use is no longer available. What is feasible with current technology is an accurate estimate of holo TC in serum [20–22]. In theory, Cbl

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malabsorption could be monitored by measuring the amount of holo TC before and after an oral dose of Cbl. The available assay appears to be sufficiently sensitive to discern a change in holo TC status at peak time following a 5–10 μg oral dose. Cbl on TC in the blood appears to reach peak level in about 8 h and is rapidly distributed to tissues [15,18,19]. Plasma clearance of radiolabeled TC protein in the rabbit has shown rapid clearance of the protein with a half-life of ~90 min Ref. [23]. Therefore, following oral ingestion of dietary Cbl, the holo TC would reach a steady state and overnight fasting serum holo TC is likely to provide an accurate measure of Cbl status and decrease in holo TC may indicate chronic and sustained Cbl depletion. It is this characteristic of holo TC that may provide a more sensitive and precise indication of physiologic Cbl status. Herzlick and Herbert [24] were the first to identify the utility of measuring holo TC but the method lacked the precision and sensitivity demanded of the assay to quantify the changes in the smaller TC-bound fraction of the total serum Cbl. Methodological improvements have provided a simple assay in kit form for the routine measurement of holo TC in a diagnostic laboratory setting [21,22]. Recent studies comparing serum total Cbl versus holo TC have shown that holo TC correlates better with elevated HCY and MMA as a measure of low Cbl status [25,26]. While it is generally accepted that TC-bound Cbl is taken up by all cell types, Cbl does not appear to accumulate in most tissues, rather is recycled by an active transport mechanism [27]. The ATP dependent ABCC1 transporter involved in the translocation of Cbl absorbed in the intestine (*vide infra*) appears to have a role in the export of Cbl from tissue cells [28] (Fig. 1). This process is at opposite poles to what happens in the liver and kidney where Cbl accumulates disproportionately. The Cbl accumulation in the kidney may be attributed to binding of TC–Cbl to the highly expressed megalin involved in the reabsorption of a number of proteins including TC–Cbl [29,30]. Megalin expression is very low in the liver and therefore, could not account for the TC–Cbl sequestration. In the human liver, HC-bound Cbl uptake by the asialoglycoprotein receptor has been purported to be the likely mechanism for Cbl accumulation [11]. This could not account for the Cbl accumulation in the mouse liver since mouse has no HC like protein in the blood and all of the Cbl is carried on TC [31]. The Cbl binding proteins such as HC and TC cannot retain Cbl in tissues such as the liver and kidney since they are destroyed and the Cbl released during uptake into cells. The only known proteins likely to retain Cbl in cells are the two enzymes MS and MMU [27,32]. The saturation state of these enzymes and total enzyme activity in liver and kidney can account for only a fraction of the Cbl in liver and kidney. Therefore, a second look at Cbl accumulation in these tissues is warranted.

b. Source of TC in blood

Having identified the function of TC in the cellular uptake of Cbl, the search was on to locate the source of this protein. Early studies suggested the liver as the source because liver perfusate contained TC and this was affected by liver damage [33,34]. This notion was soon dismissed when studies showed that total hepatectomy did not affect TC level in blood [35]. TC synthesis *in vitro* by primary and established cell lines in culture suggested that most cell types could

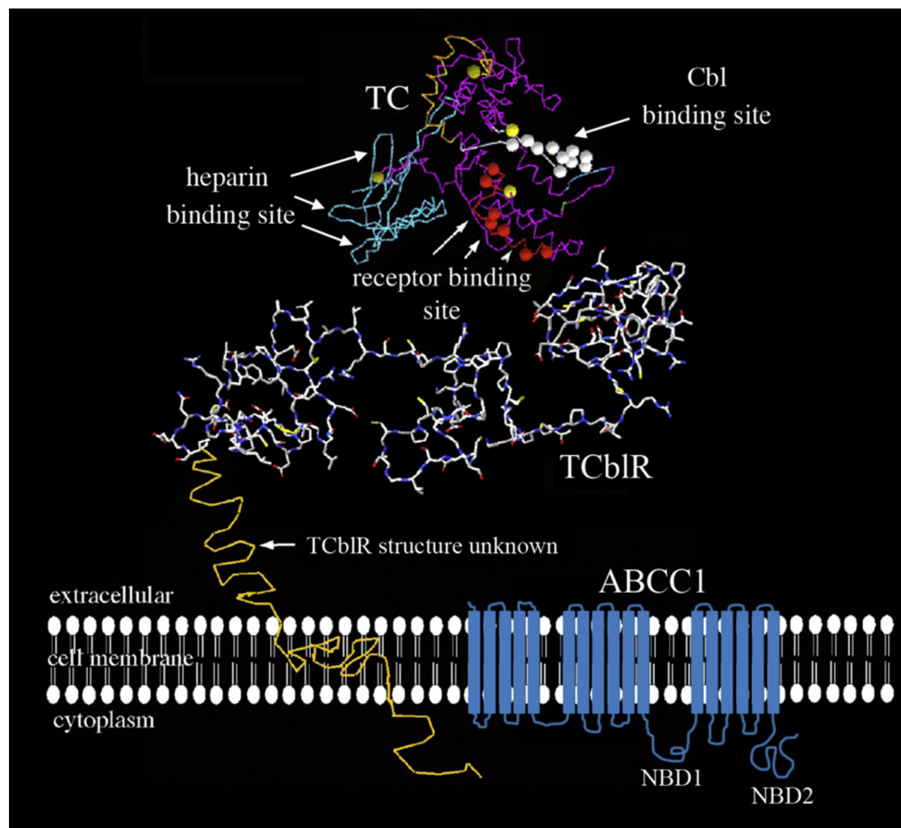

Fig. 1. The structure of proteins involved in cobalamin transport. The white circles on the TC molecule represent the Cbl binding region and the orange circles represent the receptor binding region as determined by epitope specific monoclonal antibodies that block these functions; the blue region represents the heparin-binding region likely involved in receptor binding. The TCblR molecule, with a partial theoretical 3- dimensional shape (Swiss Model) is shown oriented in the plasma membrane along with the transmembrane and cytoplasmic domains. The structure of the two LDLR-type A domains of TCblR is derived from the known structure of the LDL receptor. The two LDLR-A domains with regions involved in calcium binding are necessary for binding to holo TC. The ABCC1 transporter involved in efflux of cobalamin is depicted in blue with its numerous transmembrane domains and nucleotide binding domains (NBD1 and NBD2).

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