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Commentary Open Access

A New Strategy for the Treatment of Anemia

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Commentary

Being the most common type of blood cell, erythrocytes are the principal means of delivering oxygen (O_2) to tissues in the human body. In order to provide more space for hemoglobin, these cells lose nuclei during development as they mature. Additionally, erythrocytes lose all other cellular organelles such as their mitochondria, Golgi apparatus, and endoplasmic reticulum in mammals. Erythrocyte development lasts for around 7 days, starting as stem cells and becoming mature erythrocytes. Following development, the functional lifetime of mature erythrocytes is about 100-120 days [1].

These erythrocytes are crucial for the proper functioning of the human body, and improper function can result in devastating diseases, such as anemia. Anemia is the most common disease in blood cells, and is characterized by the low oxygen transport capacity of the erythrocytes. This is usually due to a low red cell count, or some abnormality of the red blood cells (RBCs) or hemoglobin. Based on WTO reports, almost 25% of the world population is affected by anemia. Diamond Blackfan anemia (DBA) is a rare form of anemia, which is diagnosed with inherited bone marrow failure syndrome. Glucocorticoid, a generic drug used to lower cholesterol, might help children with DBA. Glucocorticoids stimulate red blood cell formation by promoting self-renewal for early burst-forming unit-erythroid (BFU-E) progenitors [2]. Although glucocorticoid is an effective treatment on DBA, the side effects of the drug, such as stunted growth and osteoporosis, are dangerous for the patients. After a small meeting with patient families in 2007, the Whitehead Institute's Harvey Lodish decided to devote a portion of his lab's efforts to understand why glucocorticoids seemed to help DBA patients. In 2010, researchers in Lodish's lab found that glucocorticoids could increase RBCs in EPO-resistant anemias, including DBA. They demonstrated that the RNA-binding protein ZFP36L2, a transcriptional target of the glucocorticoid receptor (GR), is required for the glucocorticoids' effects. They further found that ZFP36L2 preferentially binds to messenger RNAs that act on burst-forming unit-erythroids (BFU-Es), inducing them to divide into and produce multiple colonies forming unit-erythroids (CFU-Es). Thus, patients have more BFU-Es and in turn produce more CFU-Es after treatment with glucocorticoids. Finally, these events result in a higher production of RBCs in patients [3]. Based on their data, glucocorticoids can increase red blood cell production over 20-fold in vitro. These findings clearly answer why glucocorticoid can promote the self-renewal of RBCs.

Because few CFU-Es are produced when the patient is also treated with erythropoietin (Epo) in many of the acute and chronic anemias, especially in DBA [4], Harvey Lodish's lab tried to find a drug that can act at an earlier stage of red blood cell formation and enhance the formation of Epo-sensitive CFU-E progenitors. They demonstrated that the activation of the peroxisome proliferator-activated receptor α (PPAR-α), along with its agonists GW7647 or fenofibrate, and its synergy with the GR, could promote BFU-E self-renewal. They found that GR agonists could greatly increase the production of mature red blood cells. This finding suggests that the clinical use of PPAR- α agonists may improve the efficacy of corticosteroids in treating Epo-resistant anemias, especially DBA. Their data showed that the combination of glucocorticoid and fenofibrate treatment significantly increase levels of red blood cell numbers in a mouse model of chronic anemia [5]. In fact, the synergy between the two drugs is so powerful that the mice do not require treatment with glucocorticoids. "The prospects of a clinical trial and better treatment options are exciting and anxiously anticipated by the entire DBA community," said DBA Foudation's Executive Director Dawn Baumgardner. Many diseases-treating drugs, especially for complex diseases related to metabolism and cancer, have side effects and rarely cure the patients completely. Combining different target drugs may provide a good research and clinical strategy for the treatment of these complex diseases.

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