Second Edition

HEMATOLOGY IN CLINICAL PRACTICE

A GUIDE TO DIAGNOSIS AND MANAGEMENT

血液学临床实践

世界图书出版公司

Robert S. Hillman / Kenneth A. Ault

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A Guide to DIAGNOSIS AND MANAGEMENT

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McGraw-Hill
HEALTH PROFESSIONS DIVISION

New York St. Louis San Francisco
Auckland Bogotá Caracas Lisbon London
Madrid Mexico City Milan Montreal New Delhi
San Juan Singapore Sydney Tokyo Toronto

(陕)新登字 014 号

陕版出图字 著作权合同登记 25-1998-361 号

ISBN 007-1164103

Hematology In Clinical Practice

血液学临床实践

by Hillman et.al.

任卫军 重印责任编辑

世界图书出版西安公司 重印发行

(西安市 南大街 17 号 邮编 710001)

中国人民解放军 7226 印刷厂印刷

787×1092 毫米 开本 1/32 印张 18.5

1999 年 6 月第 1 次重印

ISBN 7-5062-2256-6/R·394

定价:95.00 元

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世界图书出版公司

西安 北京 广州 上海

NOTICE

PREFACE

Hematology in Clinical Practice, Second Edition, is written specifically for the clinician—the student, resident in training, primary care internist or family practitioner, and the clinical hematologist/oncologist. It is a practical guide to the diagnosis and treatment of the most common disorders of red blood cells, white blood cells, and hemostasis. Each disease state is discussed in terms of the underlying pathophysiology, clinical features which suggest the diagnosis, the use of state-of-the-art laboratory tests in the diagnosis and differential diagnosis of the condition, and the current management.

We would like to thank James McArthur and John Bolles of the University of Washington's Health Sciences Center for Educational Resources for the color photographs selected from the American Society of Hematology National Slide Bank; Catherine Hartung for the artwork; Jacqueline Hedlund, Nancy Roy, and Gil Fraser for their editorial assistance; and Arlene Shatz for her superb secretarial support.

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PART ONE

RED BLOOD CELL DISORDERS

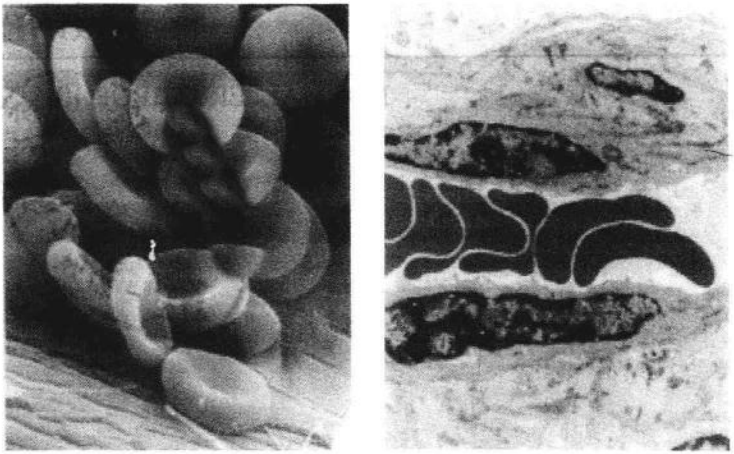
CHAPTER
ONE

NORMAL ERYTHROPOIESIS

The oxygen required by tissues for aerobic metabolism is supplied by the circulating mass of mature erythrocytes (red blood cells). The circulating red blood cell population is continually renewed by the erythroid precursor cells in the marrow, under the control of both humoral and cellular growth factors. This cycle of normal erythropoiesis is a carefully regulated process. Oxygen sensors within the kidney detect minute changes in the amount of oxygen available to tissue and by releasing erythropoietin are able to adjust erythropoiesis to match tissue requirements. Thus, normal erythropoiesis is best described according to its major components including red blood cell structure, function, and turnover; the capacity of the erythroid marrow to produce new red blood cells; and growth factor regulation.

STRUCTURE OF THE RED BLOOD CELL

The mature red blood cell is easily recognized because of its unique morphology. At rest, the red blood cell takes the shape of a biconcave disc with a mean diameter of 8 μm, a thickness of 2 μm, and a volume of 90 fl. It lacks a nucleus or mitochondria, and 33 percent of its contents are made up of a single protein, hemoglobin. Intracellular energy requirements are largely supplied by glucose metabolism, which is targeted at maintaining hemoglobin in a soluble, reduced state, providing appropriate amounts of 2,3-diphosphoglycerate (2,3-DPG), and generating ATP to support membrane function. Without a nucleus or protein metabolic pathway, the cell has a limited lifespan of 100 to 120 days. However, the unique structure of the adult red blood cell is perfect for its function, providing maximum flexibility as the cell travels through the microvasculature (Fig. 1-1).



(A) (B)

Figure 1-1 Red blood cell morphology. (*a*) Adult red blood cells are characterized by their lack of a nucleus, and biconcave disc shape. Each red blood cell has a diameter of approximately 8 μm and a width of 2 μm. Red blood cells are extremely pliable as they pass through small vessels and sinusoids. (*b*) The section of a small blood vessel demonstrates the ability of red blood cells to undergo major shape distortions. *(Scanning EM photographs used with the permission of Dennis Knuckel, Ph.D., copyright © 1993, American Society of Hematology National Slide Bank.)*

Membrane

The shape, pliability, and resiliency of the red blood cell is largely determined by its membrane. The structure of this membrane is illustrated in Fig. 1-2. It is a lipid sheath, just two molecules thick, that consists of closely packed phospholipid molecules. The external surface of the membrane is rich in phosphatidylcholine, sphingomyelin, and glycolipid, whereas the inner layer is largely phosphatidylserine, phosphatidylethanolamine, and phosphatidylinositol. This asymmetry is maintained by two transporters, ATP-dependent aminophospholipid translocase and floppase. Interference with these transporters results in a relocation of phosphatidylserine to the cell surface with a resulting increase in the thrombogenic potential of the cell surface. Accumulation of excess phosphatidylserine on the red cell surface as a part of aging may also be responsible for macrophage destruction.

Approximately 50 percent of the red blood cell membrane is made up of cholesterol that is in equilibrium with the unesterified cholesterol in the plasma. Because of this, the cholesterol content of the membrane is influenced by plasma cholesterol levels, as well as by the activity of the enzyme lecithin cholesterol acyltransferase (LCAT), and bile acids. Liver disease patients with impaired LCAT activity accumulate excess cholesterol on the red blood cell membrane, which results in abnormal red blood cell morphology (targeting) and at times a shortened survival.

The outer lipid membrane layer is affixed to a reticular protein network consisting of spectrin and actin. As shown in Fig. 1-2, the integral proteins glycophorin C and Band 3, which function as anion exchangers, extend vertically from the spectrin lattice work through the lipid layer to make contact with the cell surface. Spectrin heterodimers interact horizontally with protein 4.1 and complementary spectrin heterodimers to form a hexagonal lattice framework under the lipid bilayer. Defects in the vertical structure of the membrane (deficiency of spectrin, ankyrin, or band 3, or loss of lipid) result in spherocyte formation. Damage to the horizontal spectrin framework results in severe red cell fragmentation or mild elliptocytosis.

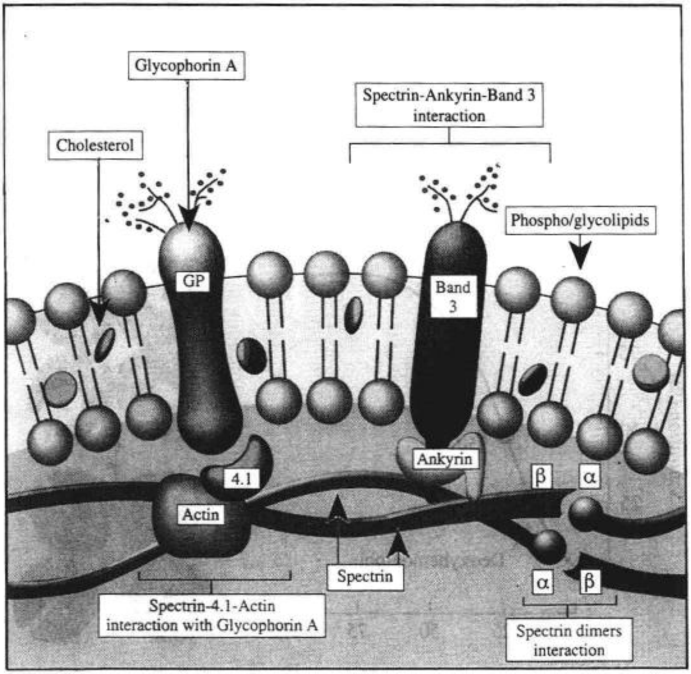


Figure 1-2 Red blood cell membrane structure. The red blood cell membrane consists of a two molecule thick lipid sheath fixed to an intracellular protein network. The outer lipid layer is rich in phosphatidylcholine, sphingomyelin, and glycolipid; the inner layer is made up of the phosphatides of serine, ethanolamine, and inositol. Almost half of the lipid layer is cholesterol. The membrane proteins, glycophorin C and band 3, penetrate the lipid sheath and make vertical contact with the reticuloproteins, spectrin, protein 4.1, actin, and in the case of band 3, ankyrin. Spectrin heterodimers provide a horizontal framework by bridging protein 4.1 to complementary spectrin dimers.

The integral proteins and surface glycosphingolipids are also responsible for the cell's antigenic structure. More than 300 red blood cell antigens have now been classified with the ABO and Rh blood group antigens, being of primary importance in typing blood for transfusion. Autoantibodies against minor blood group antigens can result in increased red blood cell destruction by the reticuloendothelial cells.

Hemoglobin

The red blood cell is, basically, a container for hemoglobin—a 68,000 dalton protein made up of 4 polypeptide chains, each containing an active heme group. Each heme group is capable of binding to an oxygen molecule. The respiratory motion of hemoglobin, that is, the uptake and release of oxygen to tissues, involves a specific change in molecular structure (Fig. 1-3). As hemoglobin shuttles from its deoxyhemoglobin to its oxyhemoglobin form, carbon dioxide and 2,3-DPG are expelled from their position between the beta chains. This situation opens the molecule to receive oxygen and has the effect of increasing its oxygen affinity. It is responsible for the sigmoid shape of the oxygen dissociation curve.

Inherited defects in hemoglobin structure can interfere with this respiratory motion. Most defects are substitutions of a single amino acid in either the alpha or beta

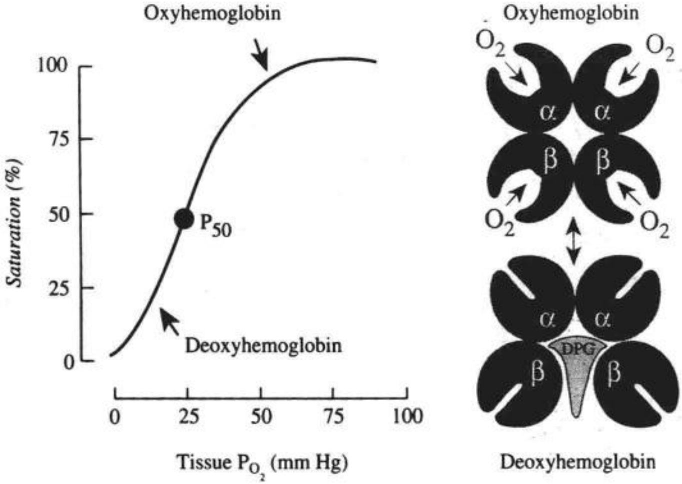


Figure 1-3 Hemoglobin-oxygen dissociation curve. Hemoglobin is capable of a respiratory motion where oxygen loaded at the lung is unloaded at the tissue level. To accept oxygen, 2,3-DPG and carbon dioxide are expelled, salt bridges are ruptured, and each of the four heme groups opens to receive a molecule of oxygen. Oxygen release to tissues reverses the process; salt bridges are reestablished and both 2,3-DPG and carbon dioxide are accepted. The complex interaction of the four heme groups is responsible for the sigmoid shape of the hemoglobin-oxygen dissociation curve.

polypeptide chains. Some interfere with molecular movement, restricting the molecule to either a low or high affinity state, whereas others either change the valency of heme iron from ferrous to ferric or reduce the solubility of the hemoglobin molecule. Hemoglobin S (sickle cell disease) is an example of a single amino acid substitution that results in a profound effect on solubility.

The normal red blood cell contains approximately 32 pg of hemoglobin [mean cell hemoglobin (MCH) = 32 ± 2 pg]. Normal hemoglobin synthesis requires an adequate supply of iron and normal production of both protoporphyrin and globin (Fig. 1-4). Protoporphyrin synthesis is initiated in the mitochondria with the formation of delta aminolevulinic acid from glycine and succinyl-CoA. Synthesis then moves to the cell cytoplasm for the formation of porphobilinogen, uroporphyrin, and coproporphyrin. The final assembly of the protoporphyrin ring is carried out by the mitochondria, after which iron is incorporated under the control of the cytoplasmic enzyme, ferrochelatase, to form heme.

Globin chains are assembled by the cytoplasmic ribosomes under the control of two clusters of closely linked genes on chromosomes 11 and 16. The final globin molecule is a tetramer of two alpha and two nonalpha chains. In the adult, 96 to 97 percent of the hemoglobin is made up of two alpha and two beta chains (hemoglobin A) with minor components of hemoglobin F and A_2. The final assembly of the hemoglobin molecule occurs in the cell cytoplasm. Small amounts of iron, protoporphyrin, and free globin chains remain after hemoglobin synthesis is complete. The iron is stored as ferritin, whereas the excess porphyrin is complexed to zinc.

This complex series of reactions is triggered by erythropoietin stimulation of red cell progenitors. With precursor differentiation, there is a coordinated transcriptional induction of heme biosynthesis, globin synthesis and transferrin receptor expression,

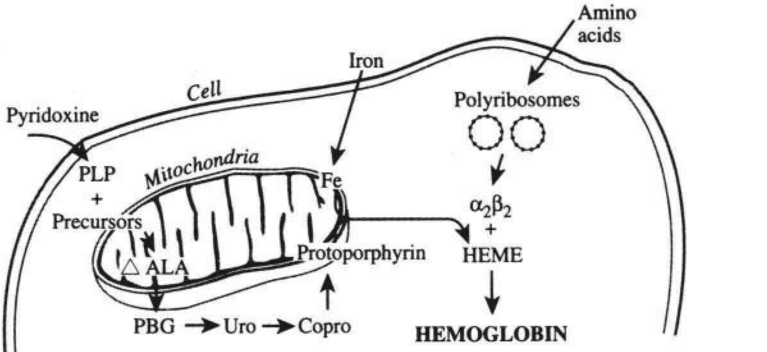


Figure 1-4 Hemoglobin synthesis. Normal hemoglobin synthesis requires an adequate supply of iron, amino acids, and pyridoxine (vitamin B_6). Porphyrin production is the responsibility of the mitochondria, whereas globin production is controlled by ribosomal RNA. The formation of the complete hemoglobin molecule involves the assembly of heme from protoporphyrin and iron and the union of a heme molecule with the two alpha and two beta chains that comprise the globin component.

which is required for iron transport (see Chap. 5). The rate of hemoglobin synthesis is determined by the availability of transferrin iron and level of intracellular heme. Hemoglobin synthesis is maximal in more mature marrow erythroblasts but persists to a lesser degree in the marrow reticulocytes. The cessation of heme synthesis is heralded by a decrease in membrane transferrin receptor expression, followed by a downregulation of heme and globin synthesis.

Cellular Metabolism

The stability of the red blood cell membrane and the solubility of intracellular hemoglobin depend on four glucose supported metabolic pathways (Fig. 1-5). The Embden-Meyerhoff pathway (nonoxidative or anaerobic pathway) is responsible for the generation of the ATP necessary for membrane function and the maintenance of cell shape and pliability. Defects in anaerobic glycolysis are associated with increased cell rigidity and decreased survival, which produces a hemolytic anemia.

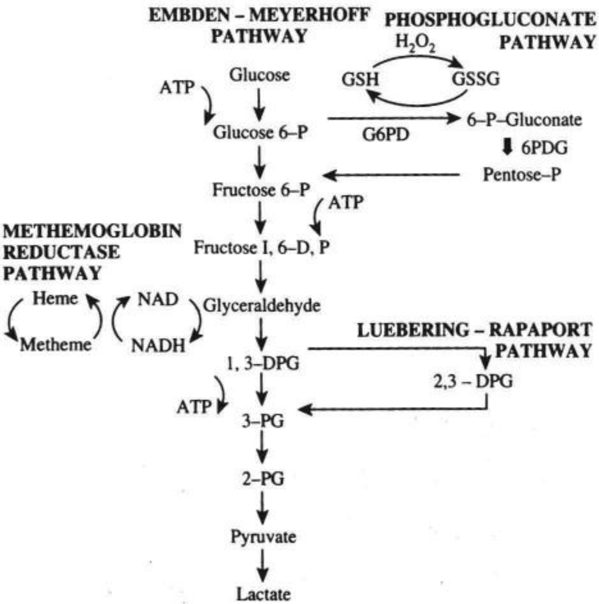


Figure 1-5 Red blood cell metabolic pathways. The red blood cell depends on four metabolic pathways to keep hemoglobin in solution and maintain membrane integrity. The Embden-Meyerhoff pathway is responsible for the generation of high energy phosphate (ATP) for membrane maintenance, whereas the other pathways support hemoglobin function. The methemoglobin reductase pathway is required to maintain hemoglobin in a reduced state. The phosphogluconate pathway helps counteract environmental oxidants and the Luebering-Rapaport pathway generates intracellular 2,3-DPG.

The Embden-Meyerhoff pathway also plays a role in supporting the methemoglobin reductase, phosphogluconate, and Luebering-Rapaport pathways. The methemoglobin reductase pathway uses the pyridine nucleotide-NADH generated from anaerobic glycolysis to maintain heme iron in its ferrous state. Inherited mutations in the methemoglobin reductase enzyme (NADH-cytochrome b_5 reductase) result in an inability to counteract oxidation of hemoglobin to methemoglobin, which is the ferric form of hemoglobin that will not transport oxygen. Patients with Type I b5 reductase deficiency accumulate small amounts of methemoglobin in circulating red cells, while the Type II patients suffer from severe cyanosis and mental retardation.

In a similar fashion, the phosphogluconate pathway couples oxidative metabolism with NADP and glutathione reduction. It counteracts environmental oxidants and prevents globin denaturation. When patients lack either of the two key enzymes, glucose 6 phosphate dehydrogenase (G6PD) or glutathione reductase (GSH), denatured hemoglobin precipitates on the inner surface of the red blood cell membrane, resulting in membrane damage and hemolysis.

Finally, the Luebering-Rapaport pathway is responsible for the production of 2,3-DPG. It is tied to the rate of anaerobic glycolysis and the action of the pH sensitive enzyme phosphofructokinase. The 2,3-DPG response is also influenced by the supply of phosphate to the cell. Severe phosphate depletion in patients with diabetic ketoacidosis or nutritional deficiency can result in a reduced 2,3-DPG production response.

REGULATION OF OXYGEN TRANSPORT

Red blood cells play a central role in oxygen transport. At the cellular level, oxygen supply is a function of red blood cells perfusing the tissue and their hemoglobin oxygen carrying capacity. The unique physiology of the hemoglobin-oxygen dissociation curve allows an onsite adjustment of oxygen delivery to match tissue metabolism. At the same time, components such as pulmonary function, cardiac output, blood volume, blood viscosity, and adjustments of regional blood flow are also important contributors to oxygen transport.

Hemoglobin-Oxygen Dissociation Curve

Under normal conditions, arterial blood enters tissues with an oxygen tension of 95 mmHg and a hemoglobin saturation of better than 97 percent. Pooled venous blood returning from tissues has an oxygen tension of 40 mmHg and a percent saturation of 75 to 80 percent. Thus, only the top portion of the hemoglobin-oxygen dissociation curve is used in the basal state (Fig. 1-6). This provides a considerable excess capacity for increased oxygen delivery to support increased oxygen requirements. The sigmoid shape of the hemoglobin-oxygen dissociation curve also helps in this regard by releasing oxygen more easily as the tissue PO_2 falls below 40 mmHg.

The affinity of hemoglobin for oxygen is also influenced by temperature, pH, CO_2 concentration, and by the level of red cell 2,3-DPG. As shown in Fig. 1-6, the position