Overview of Hemoglobin's Structure/Function Relationships

Hemoglobin's primary function is to bind oxygen that diffuses into the bloodstream from the lungs and then transport it to outlying tissues where it is released primarily for aerobic respiration. Hemoglobin (**Hb**) has to the capacity to bind between **1** and **4** O_2 molecules, ranging from fully "desaturated" Hb (**deoxyHb**) to fully "saturated" Hb (**oxyHb**). Oxygen transport is a highly dynamic process with oxygen continuously being exchanged between the lungs and the capillaries. As part of this process, Hb also serves to replenish the "oxygen stores" maintained by myoglobin (**Mb**), the O_2-binding protein in muscle which releases its oxygen in response to high levels of muscle activitiy. Hemoglobin also serves as the conduit for O_2 delivery to the fetus which carries a different form of hemoglobin in it circulation, **HbF**, or fetal hemoglobin, as distinquished from **HbA**, or adult hemoglobin, .

The dynamics of oxygen exchange is highly regulated by several metabolically-derived factors that collectively define the "oxygen demand" of an individual's tissues. Among the key metabolic factors regulating the dynamics of hemoglobin's oxygen exchange reactions is oxygen itself. When oxygen levels are high, the capacity of a partially saturated hemoglobin molecule to bind oxygen disproportionately increases with the number of oxygen molecules it has already bound. In other words, when environmental oxygen levels are high, partially saturated hemoglobin molecules exhibit enhanced affinity for binding additional oxygen molecules, a specialized behavior referred to as **cooperativity**. Equally important, hemoglobin also manifests cooperativity in the reverse direction: When environmental oxygen levels are low, hemoglobin's affinity for oxygen drops disproportionately as fewer and fewer oxygen molecules remain to bind to hemoglobin. Thus, the cooperative loading or unloading of oxygen from hemoglobin, depending on the environmental concentration of oxygen,. effectively enhances the oxygen uptake and delivery capactiy of hemoglobin. In this regard, hemoglobin is "**supersensitive**" to concentration of it ligand, O_2,

Cooperative ligand binding is no accident. Rather, it is the remarkable product of the evolutionary molding of hemoglobin's structure such that it can adopt more than one functional shape or conformation. In this regard, hemoglobin is an allosteric protein with an ability to change shapes, or undego allosteric conformational changes. This property allows hemoglobin to be more responsive to changes in the environmental oxygen levels. As discussed in detail later on, hemoglobin's cooperative ligand binding behavior can be mathematically approximated by the following Hill equation, named after its discoverer:

$$Ya = pO_2{}^3/(pO_2{}^3 + P_{50}{}^3) \qquad\qquad\qquad \text{Eq. (1)}$$

Ya, the "saturation fraction" of hemoglobin which is a quanitative measure of hemoglobin's capacity to bind oxygen. Simply stated, Ya is the average fraction of all available oxygen binding sites in hemoglobin with oxygen actually bound at equilibrium at a specific partial pressure of oxygen, pO_2. For example, when the saturation fraction equals one, each hemoglobin molecule is fully saturated with oxygen molecules bound to all four of the available sites in each molecule. The P_{50} term in the denominator of this equation is effectively an equilibrium constant unique to hemoglobin. Empirically, P_{50} equals the equilibrium pO_2 level where hemoglobin molecules are half-saturated, on the average, or 50% saturated with oxygen (Ya = 0.5).

Without the evolutionarily-molded structure of hemoglobin that allows for cooperative oxygen binding, it

can easily be shown that hemoglobin's saturation fraction for oxygen binding would quantitatively obey a different equation, one describing noncooperative ligand binding. Namely,

$$Ya = pO_2/(pO_2 + P_{50}) \hspace{6cm} \text{Eq. (2)}$$

Although Eqs. (1) and (2) may not appear to be that different, the difference has enormous physiological implications for the individual. As shown later, when the saturation behavior of hemoglobin (i.e., its oxygen binding capacity) is regulated according to the first equation above, each hemoglobin molecule is capable of transporting about twice as many oxygen molecules under normal physiological conditions than would be possible if the saturation behavior obeyed the second equation. Assuming an individual has 5 liters blood volume with about 5 billion red blood cells per milliliter, each containing about 280 million hemoglobin molecules, an individual's blood is estimated to contain about eight-tens of a kilogram of hemoglobin capable of transporting up to 5 hundreths of a mole of oxygen with each cycle through the lungs. Without hemoglobin's specialized cooperative ligand binding behavior, nearly twice as much hemoglobin would be needed to transport the same amount of oxygen and this requirement would presumably require twice the blood volume to accommodate a doubling of the number of red blood cells for housing the additional hemoglobin. A doubling of the blood volume and hemoglobin mass would add nearly 12 pounds to an individual's weight! Clearly, the evolution of hemoglobin's cooperative oxygen binding behavior serves to economize an individual's weight and this presumably improves the survivability of the species (as well as the self-esteem of its weight-concious members!).

Some of the important structural features of hemoglobin are highlighted in the following series of web pages.

Adult Hemoglobin HbA
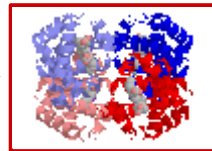
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