

# Why does natural selection maintain high G6PD activities?

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## ABSTRACT

High fitness of an organism relies on adequate performance of its metabolic networks. These performance requirements, in turn, are fulfilled only upon a suitable orchestration of the kinetic and composition parameters (enzyme activities,  $K_{MS}$ ,  $K_{IS}$ , etc.). So, natural selection prunes the parameter space of metabolic networks, leaving only the parameter sets that allow satisfactory organism performance. By considering metabolic parameters around their physiological values, one can determine how these parameters influence metabolic performance according to various criteria. From these results, one can infer the metabolic-level selective pressures that tuned those parameters and obtain insight on the functional roles of system components. In this work, we tested this approach on NADPH redox cycling in human erythrocytes. G6PD catalyses the first step of the hexose-monophosphate shunt (HMS), which supplies NADPH for repair of oxidative damage. Although patients with less than 1% of normal G6PD activity show chronic hemolytic anemia, individuals with as low as 10% of normal G6PD activity seem asymptomatic. Furthermore, in normal erythrocytes under oxidative stress, the rate of NADPH supply is limited upstream of G6PD. Why then does natural selection maintain high G6PD activities? We found that the steady-state concentration of NADPH, the rate of NADPH supply, the sensitivity of NADPH supply to demand and the robustness of this supply are not significantly affected by the activity of G6PD. The time ( $t_{1/2}$ ) for

half-adaptation of NADPH supply to steps of oxidative load, however, decreases with increasing G6PD activity. The physiological operating values of the total concentration of NADP, of the fraction of NADPH that is unbound, and of the inhibition constant of G6PD by NADPH lie near breakpoints of  $t_{1/2}$ , on the flat portions where  $t_{1/2}$  is minimal; and the operating value of the apparent  $K_M$  of glutathione reductase for NADPH lies near a local minimum of  $t_{1/2}$ . The physiological  $t_{1/2}$ , 0.1-0.2 s, is comparable to the estimated time (0.1 s) for half-equilibration between alveolar and erythrocytic  $O_2$  partial pressure as erythrocytes cross pulmonary capillaries. The oxidative load likely tracks the increasing  $O_2$  partial pressure with a small delay. So, the physiological concentration of G6PD is sufficient, but not excessive, to ensure a timely adaptation of NADPH supply to the oxygenated environment prevailing in lung capillaries. Delayed adaptation would lead to accumulation of oxidative damage, as erythrocytes circulate through the lungs about once every minute. Although too subtle to have acute clinical manifestations, such ineffective operation should negatively impact overall biological performance.

Our analysis of metabolic performance can thus explain the high physiological activity of G6PD. This aspect of the design for the oxidative portion of the HMS results from an important constraint. Namely, the timely adaptation of the NADPH supply to the increased oxidative load as erythrocytes enter the pulmonary capillaries.