Feedforward regulation:
* PK is activated by fructose 1,6-bisphosphate, the product of phosphofructokinase-1 reaction
* linking of the two kinase activities
* increased phosphofructokinase-1 activity results in elevated levels of fructose 1,6-bisphosphate, which activates PK

Covalent modulation of pyruvate kinase:
* Hepatic isoenzyme of PK is inactivated on phosphorylation by a cAMP-dependent protein kinase increased by glucagon. Therefore, PEP is unable to continue in glycolysis and, instead, enters the gluconeogenesis pathway - this explains the observed inhibition of hepatic glycolysis and stimulation of gluconeogenesis by glucagon
* dephosphorylation of PK by a phosphatase results in reactivation of the enzyme

Pyruvate kinase deficiency:
* mature RBCs are completely dependent on glycolysis for ATP production to meet their metabolic needs and to maintain their flexible, biconcave shape that allows them to squeeze through narrow capillaries
* PK deficiency --> reduced rate of glycolysis --> decreased ATP production --> alterations in the RBC membrane - --> changes in cell shape --> phagocytosis by macrophages of spleen + premature lysis of RBC --> nonospherocytic hemolytic anemia
* the effects of PK deficiency are restricted to RBCs (hepatic PK is encoded by the same gene as the RBC isozyme but liver cells show no effect because they have mitochondria and can generate ATP by oxidative phosphorylation)
* severity = depends on the degree of enzyme deficiency and the extent to which RBCs can compensate by synthesizing increased levels of 2,3-BPG
* individuals heterozygous for PK deficiency are resistant to the most severe forms of malaria

REDUCTION OF PYRUVATE TO LACTATE:
* pyruvate --> lactate dehydrogenase --> lactate (final product of anaerobic glycolysis)
* formation of lactate is minor, for fate of pyruvate in the lens and cornea of the eye, kidney medulla, testes, leukocytes of RBCs, these are all poorly vascularized (lack mitochondria)

Lactate formation in muscle:
* in exercising skeletal muscle, NADH production exceeds the oxidative capacity of respiratory chain resulting in an elevated NADH/NAD+ ratio, favoring reduction of pyruvate to lactate that accumulates in muscle, causing a drop in intracellular pH, and hence muscle cramps
* much of this lactate diffuses into bloodstream and is used by liver to produce glucose

Lactate utilization:
* the direction of lactate dehydrogenase reaction depends on the relative intracellular concentrations of pyruvate and lactate and on NADH/NAD+ ratio that is higher in exercising muscle as compared to liver and heart
* in liver --> lactate (obtained from blood) oxidized to pyruvate which is either converted to glucose (gluconeogenesis) or oxidized in the TCA cycle
* in heart --> lactate oxidized to carbondioxide and water via TCA cycle

Lactic acidosis:
* collapse of circulatory system such as MI, pulmonary embolism, uncontrolled hemorrhage, shock --> deficient delivery of oxygen to the tissues --> impaired oxidative phosphorylation and decreased ATP synthesis --> cells rely on anaerobic glycolysis for ATP generation --> lactic acid production and eventually its accumulation in bloodstream (called lactic acidosis)
* excess oxygen required to recover from a period when the availability of oxygen has been inadequate = oxygen debt
* measuring the blood levels of lactic acid allows the rapid, early detection of oxygen debt in patients and the monitoring of their recovery