Glucose is not only the main source for energy, but also a precursor for the synthesis of many biomolecules. On entering glycolysis, glucose is converted in three steps to fructose-1,6-bisphosphate (FBP), which is then split into triose phosphates by FBP aldolases. Glucose deprivation activates AMP-activated protein kinase (AMPK), a sensor of cellular energy that monitors levels of AMP, ADP and ATP and plays a primary role in adaptive responses to energy stress, but it had been unclear how glucose deprivation is sensed and signals to activate AMPK. We have found that it is the aldolase that senses the availability of glucose and directly links to AMPK activating complex on the lysosome in a manner independent of energy status change. These findings have redefined AMPK, in that the ancestral role of AMPK is to sense a fall of glucose availability prior to decrease of energy levels. Glucose starvation-induced AMPK activation may also prime the response to subsequent energy shortage in an AMP-dependent manner. Biological/pharmaceutical implications of our new discoveries will be also discussed.