Metabolic early-warning system: oxidative bursts instantly reroute glucose to safeguard NADPH

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C. Aburto[I]

[I]Centro de estudios científicos, Valdivia, Chile

Oxidative stress induced by H_2O_2 redirects glycolytic flux toward the pentose phosphate pathway (PPP). One proposed regulatory mechanism involves negative feedback through the tonic inhibition of glucose-6-phosphate dehydrogenase by NADPH. However, recent evidence shows that, in the presence of glucose, NADPH levels do not decrease during the first five seconds of incubation with H_2O_2. This finding is inconsistent with the negative feedback model, which requires a drop in NADPH levels. Here we propose that PPP regulation follows an anticipatory feedback phenomenon mediated by glucose metabolism, which anticipates the demand for NADPH under oxidative stress and increases its production. To test this, we employed HEK293 cells exposed to oxidative stress by exogenous H_2O_2. To measure key metabolite levels with resolution of seconds, genetically encoded fluorescent indicators were used. Our results show that H_2O_2 increases the rate of glucose uptake and consumption, keeping NADPH levels stable, while in the absence of glucose or when the first enzyme of the PPP is blocked, NADPH rapidly decreases. This NADPH decrease takes around six seconds after activation of glucose metabolism. Mathematical modeling ruled out the feasibility of negative feedback; instead, the data supports the presence of an anticipatory phenomenon.
Altogether, these findings open new perspectives on redox homeostasis and regulatory mechanisms of PPP associated with oxidative stress in health and disease.