# Control of the integrated stress response by a stochastic molecular switch

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Stress granules (SGs) are formed in the cytosol as an acute response to environmental cues, such as virus infections or exposition to chemotherapeutic drugs, that activate the integrated stress response (ISR), a central signaling pathway controlling protein synthesis. Using chronic virus infection as stress model, we previously uncovered a unique temporal control of the ISR resulting in recurrent phases of SG assembly and disassembly. Here, we elucidated the molecular network generating this fluctuating stress response, by integrating quantitative experiments with mathematical modeling, and found that the ISR operates as a stochastic switch. Key elements controlling this switch are the cooperative activation of the stress-sensing kinase PKR, the ultrasensitive response of SG formation to the phosphorylation of the translation initiation factor eIF2α, and negative feedback via GADD34, a stress-induced subunit of protein phosphatase 1. This negative feedback loop was responsible for adaptation to cellular stress as well as the dynamics of stress-induced apoptosis. We identified GADD34 mRNA levels as the molecular memory of the ISR that plays a central role in cell adaptation to acute and chronic stress.