Stress-response balance drives the evolution of a newcomer network and its host genome

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Newcomer stress response modules are major contributors to drug resistance in microbial infections and cancer. Yet, their evolution is poorly understood, partly because we lack appropriate model systems that allow the development of quantitative, experimentally testable predictions. To address this problem, we used a synthetic gene circuit integrated into the budding yeast genome to model the adaptation of a newcomer stress response module and its host in three different scenarios. In agreement with computational predictions, we found that (i) mutations target and eliminate the module if it gratuitously responds to harmless signals; (ii) mutations inside and outside the module activate the module if it initially fails to respond to stress; and (iii) a select set of intra- and extra module mutations may be required to fine-tune the module's response if initially suboptimal. These findings reveal predictable, environment-dependent routes of stress-response network evolution with implications for drug resistance development in the clinic.