MEK critically regulates cellular proteome homeostasis via HSF1

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The RAS-MEK-ERK signaling cascade is central to biology. ERK, canonically, is perceived as the only substrate for MEK. Herein we report that HSF1, the master regulator of the highly evolutionarily conserved proteotoxic stress response, is a new MEK substrate. Through physical interaction and phosphorylation, MEK mobilizes HSF1 to govern the cellular proteome. Surprisingly, ERK repressively phosphorylates MEK to inactivate HSF1. Beyond mediating cell-environment interactions, this MEK-HSF1 regulation critically impacts malignancy. In tumor cells, MEK blockade provokes protein destabilization, aggregation, and, strikingly, amyloidogenesis. Further, combinatorial proteotoxic insult potently exacerbates this proteomic chaos. Remarkably, amyloidogenesis is tumor-suppressive and evidently contributes to the therapeutic effects of proteotoxic stressors. Importantly, compared to their non-transformed counterparts, malignant cells are particularly susceptible to amyloidogenesis. Thus, our findings unveil a previously unrecognized key biological function of RAS-MEK-ERK signaling in guarding cellular proteome homeostasis. Conceptually, our findings suggest proteomic instability as an intrinsic feature of malignancy and, therefore, that perturbation of fragile tumor proteostasis may be a feasible therapeutic strategy.