A cholesterol precursor mediates sensitivity to cell death by ferroptosis

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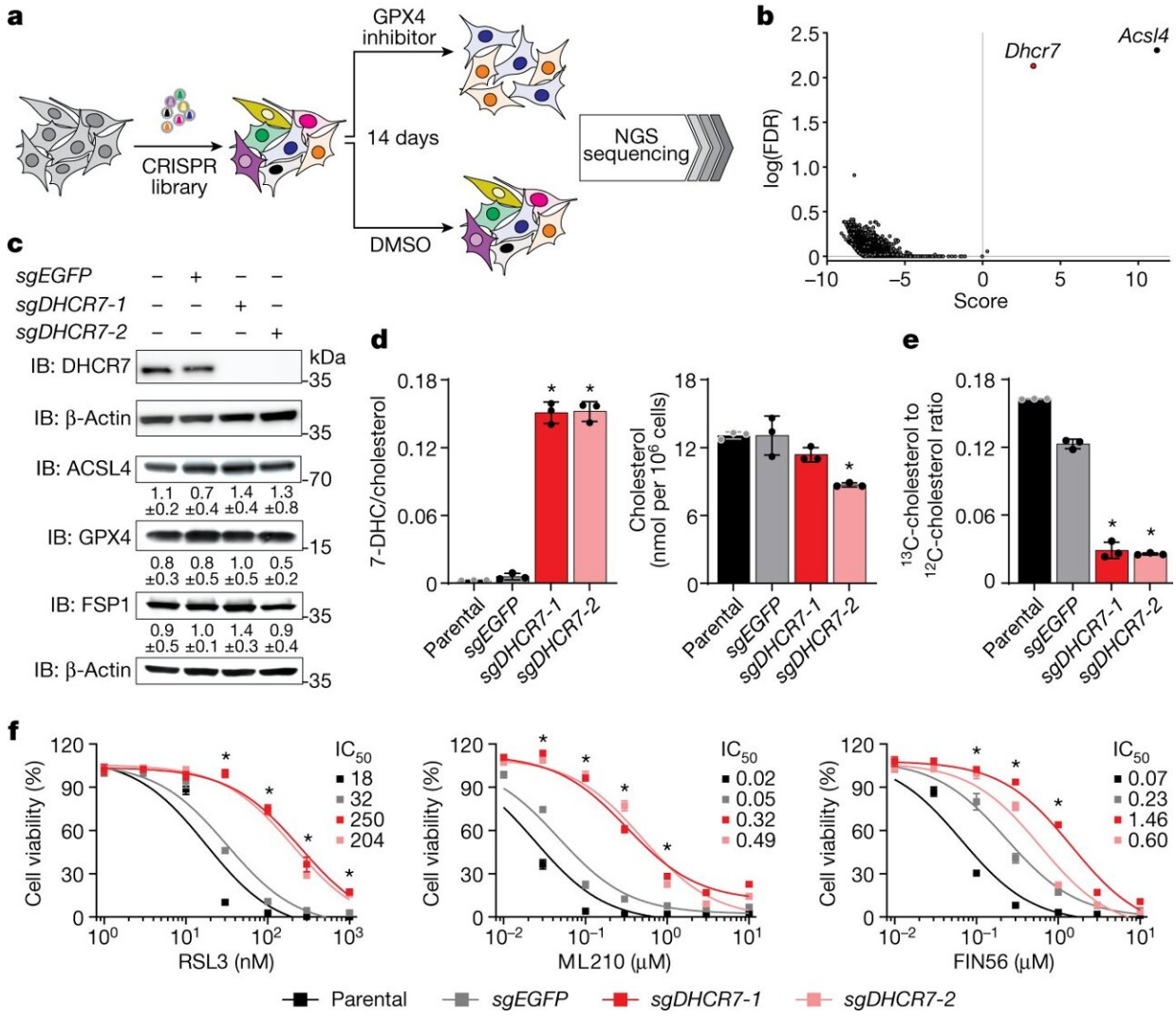

Identification and impact of DHCR7 deficiency on ferroptosis. a, Schematic of the identification of Dhcr7 as a proferroptotic gene, using CRISPR-KO library and GPX4 inhibition. b, Volcano plot of sgRNA enriched in cells selected with

RSL3 compared with untreated control cells. c, Immunoblot (IB) analysis of DHCR7 and key ferroptosis regulators, namely, FSP1, ACSL4 and GPX4 in cells expressing an sgRNA targeting DHCR7 and EGFP. Values represent mean ± s.d. of ratio of protein of interest in relation to β-actin, n = 3 independent experiments. d, Relative quantification of 7-DHC and cholesterol concentrations in HT1080 cell lines stably transduced with a vector expressing Cas9 and a sgRNA targeting DHCR7 and EGFP as a control. e, Assessment of de novo cholesterol biosynthesis, by means of the quantification of 13C-cholesterol originating from 13C-glucose in HT1080 cell expressing sgRNA targeting DHCR7 and EGFP as control. Data are the mean ± s.d. of n = 3 wells of a 6-well plate from one representative experiment (d,e). f, Dose-dependent toxicity of the ferroptosis inducers RSL3, ML210 and FIN56 in HT1080 cell lines stably transduced with a vector expressing Cas9 and an sgRNA targeting DHCR7 and EGFP as a control. Cell viability was monitored using Alamar blue after 48 h (f) and represented as the mean ± s.d. of triplicates from one representative of two independent experiments (f). *P