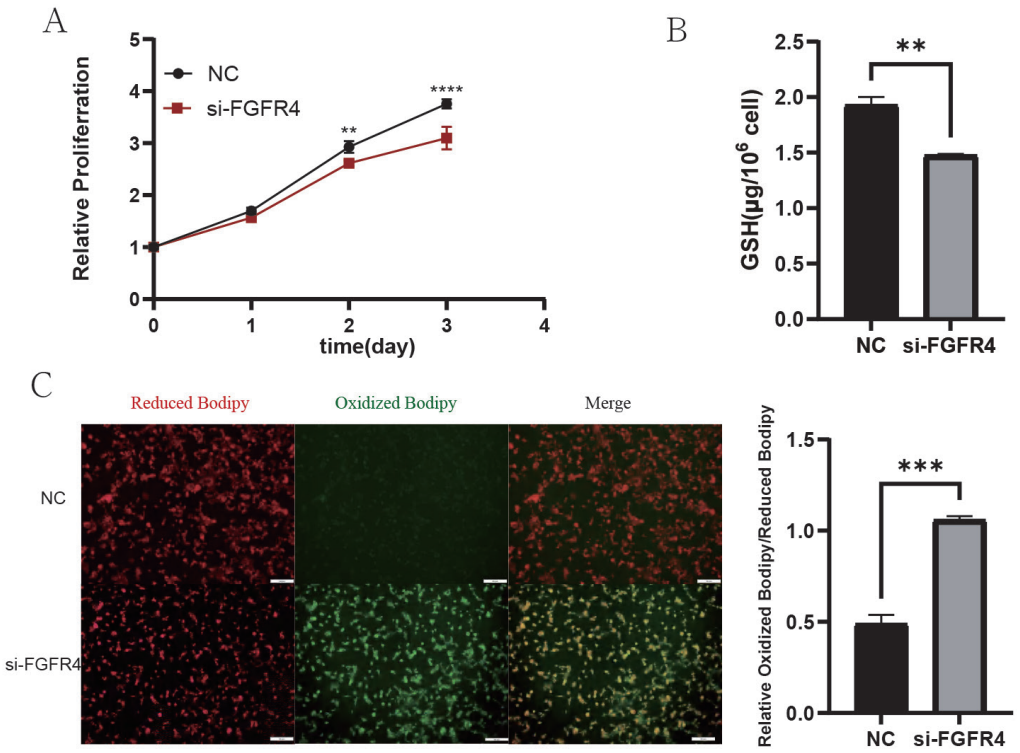

Figure S1 FGFR4 knockdown sensitizes colorectal cancer cells to erastin-induced ferroptosis. (A) Cell viability upon erastin induction was measured by CCK-8 assay. (B) Analysis of intracellular glutathione (GSH) levels. (C) Lipid peroxidation was detected by C11-BODIPY staining. *, P<0.05; **, P<0.01; ***, P<0.001; ****, P<0.0001.

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Table S1 Summary of ferroptosis pathways potentially regulated by FGFR4

Type	Regulatory axis	The logical chain of reasoning	Ferroptosis-related targets	Cancer type	Doi
Direct ferroptosis regulatory mechanisms	CYP26A1/RA-SLC7A11-GSH-GPX4 Axis	FGFR4↓→CYP26A1 (a member of the cytochrome P450 family)/RA (retinoic acid) accumulation axis↓ → SLC7A11-GSH-GPX4↓ → Fe^{2+}+ Lipid ROS ↑→ ferroptosis↑	SLC7A11, GSH, GPX4, Fe^{2+}, lipid ROS	Hepatocellular cancer	10.1186/s13046-025-03622-1
	FGF19/FGFR4-KLB-TFRC Axis	FGFR4↓→ FGF19-FGFR4-KLB↓ → TFRC↑ +Lipid ROS ↑→ferroptosis↑	TFRC, lipid ROS	Hepatocellular cancer	10.1016/j.ajg.2024.11.001
	HMOX1-Fe^{2+} Axis	FGFR4↑→ HMOX1↑→Fe^{2+}↑ + GSH ↓→Lipid ROS ↑→ferroptosis↑	Fe^{2+}, GSH, lipid ROS	Hepatocellular cancer	10.1016/j.ejphar.2024.176493
	SLC7A11-GSH-GPX4 Axis	FGFR4-ADC (Pharmacological inhibition context) specifically binds to FGFR4 →release sulfasalazine→FGFR4↓→ SLC7A11-GSH-GPX4 ↓→ Fe^{2+}+ Lipid ROS ↑→ ferroptosis↑	SLC7A11, GSH, GPX4, Fe^{2+}, lipid ROS	Hepatocellular cancer	10.1016/j.isci.2025.113718
Upstream signaling regulation of ferroptosis	PI3K-AKT/MAPK Axis	FGFR4↑ →PI3K-AKT/MAPK Axis↑→GPX4↑→Fe^{2+}+Lipid ROS ↑→ferroptosis↓	GPX4, ACSL4, MDA, Fe^{2+}, lipid ROS	Oral squamous cell cancer	10.1038/s41598-024-78552-7
	β-catenin/TCF4 Axis	FGFR4↓→β-catenin/TCF4 ↓→SLC7A11/FPN1→GSH ↓ + Fe^{2+}+ Lipid ROS ↑ → ferroptosis↑	SLC7A11, FPN1, GSH, GPX4, Fe^{2+}, lipid ROS	Breast cancer	10.1038/s41467-022-30217-7
Oxidative stress and metabolic context-related pathways	NRF2-KEAP1 Axis	FGFR4↓ →KEAP1↑ → NRF2↓→HO1↓ → ROS↑→ cell death	ROS level	Gastric cancer	10.1016/j.redox.2023.102998
	FGFR4-ERK-NRF2 Axis	FGFR4↓ → block the FGFR4–ERK signaling axis↓ → Inactivation of the NRF2/HO1 antioxidant axis→ decreased cellular antioxidant capacity→ ROS ↑ → Apoptosis	ROS level	Ovarian cancer	10.3389/fcell.2025.1626938
	AKT/STAT3/ERK Axis	FGFR4↓→ Inhibition of downstream AKT/STAT3/ERK signaling↓ → impairs the antioxidant system, ROS↑→and induces DNA damage→ Apoptosis	ROS level	Triple-negative breast cancer	10.1186/s13058-025-02086-7

Direct ferroptosis regulatory mechanisms: including pathways directly involved in lipid peroxidation and iron metabolism (e.g., SLC7A11/GPX4 axis and iron regulatory systems). Upstream signaling regulation of ferroptosis: such as PI3K/AKT and Wnt signaling, which influence cellular survival and redox adaptation. Oxidative stress and metabolic context-related pathways: Oxidative stress and metabolic context–related pathways shape the intracellular redox environment. Such pathways indirectly affect ferroptosis susceptibility.

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