Table SI. Shared lactylation mechanisms in digestive cancer.

A, Histone lactylation				
Lactylation event	Regulatory axis	Cancer types	Core function	(Refs.)
H3K18la-glycolytic positive feedback loop	HCC, H3K18la-YBX1; PC, H3K18la-TTK/BUB1B-P300; PC, H3K18la-TTK(Y239p)-LDHA	HCC and PC	Promotes glycolytic positive feedback loop	(44,45)
H3K9la-mediated immunosuppression	EC, H3K9la-LAMC2-VEGFA; CRC, H3K9la-PKM2	EC and CRC	Promotes immunosuppressive microenvironment formation	(47,48)
B, Non-histone lactylation				
Lactylation event	Regulatory axis	Cancer types	Core function	(Refs.)
β-catenin/Wnt pathway activation via lactylation	EC, Axin1 K147la; CRC, direct β-catenin lactylation	EC and CRC	Activates Wnt pathway, promotes stemness/proliferation	(55,56)

Axin1, axis inhibition protein 1; BUB1B, BUB1 mitotic checkpoint serine/threonine kinase B; CRC, colorectal cancer; EC, esophageal cancer; HCC, hepatocellular carcinoma; LAMC2, laminin subunit γ 2; LDHA, lactate dehydrogenase A; PC, pancreatic cancer; PKM2, pyruvate kinase M2; TTK, TTK protein kinase; VEGFA, vascular endothelial growth factor A; YBX1, Y-box binding protein 1.

Table SII. Cancer-specific lactylation mechanisms in digestive cancer.

A, EC		
Lactylation event/regulatory axis	Core function	(Refs.)
SHMT2 lactylation	Promotes glycolysis, stemness and migration	(71)
B, GC		
Lactylation event/regulatory axis	Core function	(Refs.)
H3K18la-METTL3-PD-L1 axis	T-cell immunosuppression	(49)
H3K18la-VCAM-1-AKT/mTOR axis	Promotes EMT and M2 recruitment	(50)
AARS1-YAP-TEAD lactylation circuit	Promotes proliferation	(30)
High copper-AARS1/2-METTL16 K229la-cuproptosis axis	Promotes cuproptosis	(81,82)
Lactate-PCBP2-H3K14la-LDHA positive feedback loop	Promotes glycolytic positive feedback and ferroptosis resistance	(83)
C, CRC		
Lactylation event/regulatory axis	Core function	(Refs.)
CAF-lactate-H3K18la-ANTXR1 dual activation axis	Promotes stemness and chemoresistance	(95)
RARγ-TRAF6/NF-κB/IL-6/STAT3 signaling axis	Promotes macrophage protumor polarization and chemotherapy resistance	(96)
SIRT3-ME2 lactylation-redox homeostasis axis	Regulates redox homeostasis to promote tumor growth	(18)
MRE11 K673 lactylation-DNA repair axis	Promotes HR repair leading to chemoresistance	(90)
DNA damage-ATM-GCN5-XLF K288la-NHEJ repair axis	Promotes NHEJ repair leading to chemoresistance	(91)
HDAC1 K412 lactylation-ferroptosis resistance axis	Induces ferroptosis resistance	(94)
eEF2 K439/K594 lactylation-translation efficiency axis	Enhances translation efficiency	(58)
NOP2 lactylation-m^5C-glycolysis positive feedback	Promotes glycolytic positive feedback	(92)
NOL6 lactylation-NOL6-Y1-c-Myc transcriptional positive feedback	Promotes c-Myc transcriptional positive feedback	(93)
D, HCC		
Lactylation event/regulatory axis	Core function	(Refs.)
H3K18la-HECTD2-KEAP1-NRF2 antioxidant axis	Promotes antioxidant response leading to lenvatinib resistance	(53)
AARS1-AKR1B10 K173la-LDHA Y10p-glycolysis positive feedback	Enhances glycolytic positive feedback leading to lenvatinib resistance	(57)
Lactylation-IGF2BP3-PCK2/NRF2-m^6A-lenvatinib resistance	Stabilizes PCK2/NRF2 mRNA promoting lenvatinib resistance	(59)
PARK7-IGF2BP3 K76la-FSP1-ferroptosis resistance-HAIC resistance	Induces ferroptosis resistance leading to HAIC resistance	(60)
Lactate-H3K18la-NUPR1-immunotherapy resistance	Promotes M2 polarization and T-cell exhaustion leading to immunotherapy resistance	(101)

Lactate-TWIST1 K33la-EMT	Promotes EMT	(104)
Xklp2l-PP1-AURKA-cell cycle	Promotes cell cycle progression	(99)
LDHA-lactate-YAP K102la-malignant progression	Activates YAP promoting malignant progression	(103)
H3K14la-NEDD4-PTEN-PI3K/Akt/mTOR-glycolysis positive feedback	Activates PI3K/Akt/mTOR promoting glycolysis	(106)
ABCF1 lactylation-nuclear translocation-KDM3A-HIF1α-glycolysis positive feedback	Activates HIF1α promoting glycolytic positive feedback	(105)
ZNF207-PRDX1 K67la-NRF2-ferroptosis resistance-regorafenib resistance	Activates NRF2 promoting ferroptosis resistance leading to regorafenib resistance	(107)
H3K56la-OCT4-Stemness	Promotes stemness	(102)
H2B K58la-NDRG1-GSK-3β-p53-senescence escape-survival	Inhibits p53 promoting senescence escape	(100)
Lactate-MOESIN lactylation-TGF-β/SMAD3-Treg differentiation-immune evasion	Promotes Treg differentiation leading to immune evasion	(24)
H3K18la/H3K9la-USP34-DNA repair-chemoresistance	Promotes DNA repair leading to chemoresistance	(52)
E, PC		
Lactylation event/regulatory axis	Core function	(Refs.)
Matrix stiffness-LDHA-lactate-FOXO3-sustained autophagy	Induces sustained autophagy	(61)
Lactate-EP300-NMNAT1 K128la-NAD^+ salvage-Sirt1-apoptosis inhibition	Inhibits apoptosis	(13)
Macrophage-ENSA K63la-PP2A-STAT3-CCL2-TAM recruitment-immunotherapy resistance	Promotes TAM recruitment leading to immunotherapy resistance	(112)
TFEB K91la-WWP2-ubiquitination (decreases) -autophagy/lysosomal activity (increases)	Promotes autophagy	(114)
RHOF-c-Myc-PKM2-glycolysis-lactate-Snail1 lactylation-EMT	Induces EMT	(111)
H3K18la-m^6A-TRAF6/ALDH1A3-autophagy-drug resistance	Stabilizes TRAF6/ALDH1A3 mRNA promoting autophagy-mediated drug resistance	(51)
CTCF-IGF2BP2-CSF1-M2 polarization	Promotes M2 polarization	(113)
NUSAP1 lactylation-c-Myc/HIF1α-LDHA positive feedback	Enhances glycolytic positive feedback	(110)

AARS1, alanyl-tRNA synthetase 1; AARS2, alanyl-tRNA synthetase 2; ABCF1, ATP binding cassette subfamily F member 1; AKR1B10, aldo-keto reductase family 1 member B10; AKT, protein kinase B; ALDH1A3, aldehyde dehydrogenase 1 family member A3; ANTXR1, anthrax toxin receptor 1; ATM, ataxia telangiectasia mutated; AURKA, aurora kinase A; CAF, cancer-associated fibroblast; CCL2, C-C motif chemokine ligand 2; CRC, colorectal cancer; CSF1, colony stimulating factor 1; CTCF, CCCTC-binding factor; EC, esophageal cancer; eEF2, eukaryotic elongation factor 2; EMT, epithelial-mesenchymal transition; ENSA, endosulfine α; EP300, E1A binding protein P300; FOXO3, forkhead box O3; FSP1, ferroptosis suppressor protein 1; GC, gastric cancer; GCN5, general control of amino acid synthesis 5; GSK-3β, glycogen synthase kinase 3 β; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; HDAC1, histone deacetylase 1; HECTD2, HECT domain E3 ubiquitin protein ligase 2; HIF1α, hypoxia-inducible factor 1 α; HR, homologous recombination; IGF2BP2, insulin-like growth factor 2 mRNA binding protein 2; IGF2BP3, insulin-like growth factor 2 mRNA binding protein 3; IL-6, interleukin 6; KDM3A, lysine demethylase 3A; KEAP1, kelch-like ECH-associated protein 1; LAMC2, laminin subunit γ 2; LDHA, lactate dehydrogenase A; ME2, malic enzyme 2; METTL3, methyltransferase-like 3; METTL16, methyltransferase-like 16; MOESIN, moesin; MRE11, meiotic recombination 11 homolog; mRNA, messenger ribonucleic acid; m^5C, 5-methylcytosine; m^6A, N6-methyladenosine; mTOR, mechanistic target of rapamycin; NAD^+, nicotinamide adenine

dinucleotide; NDRG1, N-Myc downstream-regulated gene 1; NEDD4, neural precursor cell expressed developmentally down-regulated 4; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NHEJ, non-homologous end joining; NMNAT1, nicotinamide mononucleotide adenylyltransferase 1; NOL6, nucleolar protein 6; NOP2, NOP2 nucleolar protein; NRF2, nuclear factor erythroid 2-related factor 2; NUPR1, nuclear protein 1; NUSAP1, nucleolar and spindle-associated protein 1; OCT4, octamer-binding transcription factor 4; P300, E1A binding protein P300; PARK7, parkinsonism associated deglycase; PC, pancreatic cancer; PCBP2, poly(rC)-binding protein 2; PCK2, phosphoenolpyruvate carboxykinase 2; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; PKM2, pyruvate kinase M2; PP1, protein phosphatase 1; PP2A, protein phosphatase 2A; PRDX1, peroxiredoxin 1; PTEN, phosphatase and tensin homolog; RARγ, retinoic acid receptor γ; RHOF, Ras homolog family member F; RNA, ribonucleic acid; SIRT1, sirtuin 1; SIRT3, sirtuin 3; SMAD3, SMAD family member 3; Snail1, snail family transcriptional repressor 1; STAT3, signal transducer and activator of transcription 3; TAM, tumor-associated macrophage; TEAD1, TEA domain transcription factor 1; TFEB, transcription factor EB; TGF-β, transforming growth factor β; TRAF6, TNF receptor-associated factor 6; Treg, regulatory T cell; TTK, TTK protein kinase; TWIST1, twist family BHLH transcription factor 1; Ub, ubiquitin; USP34, ubiquitin-specific protease 34; VCAM-1, vascular cell adhesion molecule-1; VEGFA, vascular endothelial growth factor A; WWP2, WW domain containing E3 ubiquitin protein ligase 2; XLF, XRCC4-like factor; Xklp2, Xenopus kinesin-like protein 2; YAP, Yes-associated protein; ZNF207, zinc finger protein 207.