Table S1. Evidence-tagged references used in Section 2

No.	Authors	Title	Year	Journal	Key content	Tissue	Species	Modality	Evidence level
11	Miao **et al.**	DDIT4 Licenses Only Healthy Cells to Proliferate During Injury-induced Metaplasia	2021	*Gastroenterology*	DDIT4 gates mTORC1/QC to permit healthy-cell cell-cycle re-entry after injury	Stomach/Chief	Mouse	in vivo, LT, genetic perturbation	**E1**
12	Sáenz **et al.**	ADAR1 licenses metaplastic reprogramming in gastric epithelium	2022	*JCI Insight*	ADAR1 modulates dsRNA response to license metaplastic reprogramming	GastricChief	Mouse	in vivo (± organoid), genetic perturbation (± LT)	**E1**
13	Radyk **et al.**	ATF3 induces RAB7 to govern autodegradation in paligenosis	2021	*EMBO Reports*	ATF3→RAB7 drives autodegradation/autophagy in early paligenosis	Stomach/Chief	Mouse	in vivo, LT, genetic perturbation	**E1**
14	Meyer **et al.**	xCT Is Required for Chief Cell Plasticity After Gastric Injury	2019	*CMGH*	Chief-cell plasticity requires xCT (cystine/glutamate antiporter)	Stomach/Chief	Mouse	in vivo, genetic perturbation (± LT)	**E1**
15	Miao **et al.**	Metaplastic regeneration in the mouse stomach requires a ROS pathway	2024	*Developmental Cell*	ROS pathway required for metaplastic regeneration; aligns with S1 stress axis	Stomach/Chief	Mouse	in vivo, LT, genetic perturbation	**E1**
16	Miao **et al.**	A Conserved Molecular Network Licenses Differentiated Cells to Return to the Cell Cycle	2020	*Developmental Cell*	Conserved licensing network enables differentiated cells to re-enter the cycle	Stomach/Chief	Mouse	in vivo, LT, genetic perturbation	**E1**
17	Lee **et al.**	p57(Kip2) imposes the reserve stem cell state of gastric chief cells	2022	*Cell Stem Cell*	p57^Kip2^ enforces a reserve-stem state in chief cells	Stomach/Chief	Mouse	in vivo (± LT), genetic perturbation, organoid	**E1**
18	Ma **et al.**	Single-cell transcriptomics reveals a conserved metaplasia	2021	*Gastroenterology*	Conserved metaplasia program in pancreatic injury (scRNA-seq)	Pancreas/Acinar	Mouse & Human	in vivo injury, scRNA-seq, organoid	**E2**

No.	Authors	Title	Year	Journal	Key content	Tissue	Species	Modality	Evidence level
		program in pancreatic injury							
19	Johnson **et al.**	Autophagic state prospectively identifies facultative stem cells in the intestinal epithelium	2022	*EMBO Reports*	Autophagic state prospectively marks facultative stem cells in intestine	Intestine/Epithelium	Mouse (± Human organoid)	in vivo, reporter/FACS, organoid	**E2**
22	Toshima **et al.**	Suppression of autophagy during liver regeneration impairs energy charge and causes senescence	2014	*Hepatology*	Autophagy inhibition impairs liver regeneration and energy homeostasis	Liver/Hepatocyte	Mouse	in vivo, autophagy inhibition (pharm./genetic)	**E2**
24	Sundaram **et al.**	Adipo-glial signaling mediates metabolic adaptation in peripheral nerve regeneration	2023	*Cell Metabolism*	Metabolic adaptation via adipo-glial signaling in nerve regeneration	Peripheral nerve/Schwann	Mouse	in vivo ± genetic, imaging/omics	**E2**
26	Rodgers **et al.**	mTORC1 controls the adaptive transition of quiescent stem cells from G0 to G(Alert)	2014	*Nature*	mTORC1 drives G0→G(Alert) transition in quiescent stem cells	Skeletal muscle/Satellite	Mouse	in vivo, genetic ± pharmacologic	**E1**
27	Yang **et al.**	The mTORC1 effectors S6K1 and 4E-BP play different roles in CNS axon regeneration	2014	*Nat Communications*	Distinct roles of S6K1 vs 4E-BP in CNS axon regeneration	CNS/Neuron	Mouse (rodent)	in vivo ± ex vivo, genetic perturbation	**E2**
29	Bohin **et al.**	IGF-1 and mTORC1 promote the intestinal regenerative response after irradiation injury	2020	*CMGH*	IGF-1/mTORC1 enhance intestinal regeneration post-irradiation	Intestine/Epithelium	Mouse	in vivo, genetic ± pharmacologic	**E1**
31	Wang **et al.**	Transient activation of autophagy via Sox2-mediated mTOR	2013	*Cell Stem Cell*	Early reprogramming: Sox2 suppresses mTOR to trigger autophagy	Reprogramming/MEF	Mouse	in vitro, genetic perturbation	**E2**

No.	Authors	Title	Year	Journal	Key content	Tissue	Species	Modality	Evidence level
		suppression in early pluripotency							

Abbreviations: LT, lineage tracing; scRNA-seq, single-cell RNA-seq; CMGH, Cellular and Molecular Gastroenterology and Hepatology.

Table S2. Stage-anchored intervention candidates across paligenosis (hypothesis-generating).

Target node	Stage targeted	Expected effect on repair/tumor risk	Tractable tools (status/examples)	Clinical caveats/notes
Sestrin2 → mTORC1 sensing (amino-acid stress)	**S1** (autophagy/QC induction)	↑ QC stringency, ↑ autophagy; may reduce unscheduled proliferation; potential ↓ tumor risk if confined to S1	Nutrient deprivation or **leucine restriction**; **NV-5138** (leucine mimetic; experimental)	Systemic catabolism; CNS effects for NV-5138; imprecise tissue targeting; needs **time-locked** dosing
DDIT4/REDD1 → mTORC1 suppression	**S1**	Enforce S1 "brake": mTORC1 off, autophagy on; predicted ↓ early oncogenic drift	**Rapalogs** (everolimus, temsirolimus; approved), ATP-competitive mTOR inhibitors; genetic up-modulation (preclinical)	Over-suppression impairs healing; immunometabolic adverse effects; diabetogenic tendencies
ATF3–RAB7 / Autophagy axis	**S1**	Promote organelle clearance & QC pass; support orderly plasticity	**mTORC1 inhibition** (induces autophagy); **Trehalose** (autophagy enhancer, off-label), **Spermidine** (nutraceutical), **HCQ/CQ** (autophagy blockade, for testing opposite hypothesis)	Autophagy inhibition (HCQ/CQ) may increase toxicity yet be useful against DTP; context-specific
xCT/SLC7A11 (cystine importer) / GPX4 axis (ferroptosis defense)	**S1–S2**	xCT inhibition may **sensitize DTP** and reduce malignant persistence; short pulses could stress damaged cells	**Sulfasalazine** (xCT inhibitor; approved for other indications), **Erastin/Imidazole-ketone erastin** (tool/experimental), **RSL3** (GPX4 inhibitor; tool)	Mucosal and neurotox risks; redox crisis in normal tissue; careful **timing** & dosing
IFRD1 → mTORC1 reactivation licensing	**Late S2**	Proper reactivation → orderly proliferation; blockade may keep DTP from exiting	RNAi/ASO or CRISPR interference (preclinical); no specific small-molecule yet	Target validation ongoing; off-target transcriptional effects; may delay repair if over-blocked
mTORC1 (reactivation)	**S2–S3**	Reactivation is required for regeneration; premature or chronic activation ↑ tumor risk	**Leucine/AA re-feed**, **Insulin/IGF/PI3K–AKT** pathway activators (context), **Rapalog withdrawal**	Only after **QC pass**; risk of fueling neoplasia; monitor **pS6/p4EBP1** closely
p53 axis (arrest/apoptosis)	**S1 (fail) / S2 fail**	Enforces elimination of damaged cells; prevents erroneous re-entry	No direct activator; **MDM2 inhibitors** (e.g., **idasanutlin**, experimental)	p53 wild-type dependence; toxicity (myelosuppression); may impair repair if over-activated
ADAR1 (dsRNA editing, QC)	**S1**	Proper editing supports QC; inhibition may expose damaged cells to immune clearance	Experimental **ADAR1 inhibitors/ASO**; **IFN** pathway modulation	Hematopoietic/autoimmunity liabilities; hypothesis-generating in paligenosis
Epigenetic regulators (examples): **EZH2**, **BRD4/BET**, **HDACs**, **DNMTs**	**S2–S3** (plasticity maintenance / lineage restoration)	Tuning chromatin may steer repair vs malignant drift; BET/EZH2 blockade can restrain aberrant stemness	**Tazemetostat** (EZH2i), **BET inhibitors** (JQ1, birabresib—exp.), **HDAC inhibitors** (vorinostat), **DNMT inhibitors** (azacitidine/decitabine)	Broad effects; cytopenias; use **short pulses** and combine with stage biomarkers
EMT/motility nodes (TGF-β/Snail/ZEB)	**Off-path / risk mitigation**	Limiting EMT-like drift may reduce fibrosis/invasion during chronic injury	**TGF-β inhibitors** (galunisertib—exp.), **ALOX/FAO** modulators（context）	Anti-fibrotic benefit vs wound healing delay; patient selection critical

Notes: Evidence in paligenosis per se is variable and often indirect; many agents are experimental or context-dependent. Species/tissue differences and model constraints limit generalizability. Clinical translation will require prospective validation, dosing/timing windows, and safety evaluation.

Emergence (DTP entry, S1-like)

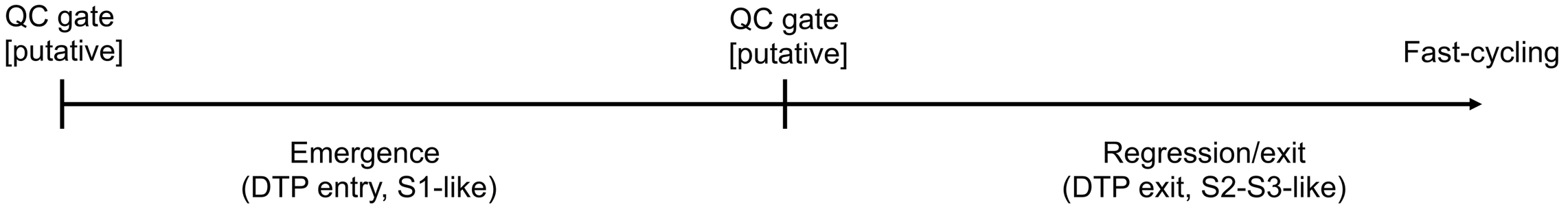
mTORC1 suppression • ISR/translation down • Autophagy

- pS6↓ / p4EBP1↓ (mTORC1 inhibition)
- p-eIF2α↑ / ATF4↑ (integrated stress response)
- LC3-II flux↑ / p62↓ (autophagy active)
- Assays: phospho-IHC/IF (pS6/p4EBP1, p-eIF2α/ATF4); LC3/p62 dual-stain; GFP–mCh–LC3 reporters

Regression/exit (DTP exit, S2-S3-like)

mTORC1 reactivation • fast-cycling re-entry

- pS6↑ / p4EBP1↑ (mTORC1 reactivation)
- c-MYC rebound; global translation ↑
- Ki-67, Cyclin–CDK; EdU/BrdU
- Assays: phospho-IHC/flow; short-term ex vivo EdU/BrdU; serial biopsy/organoid time-course



Biomarker panel & longitudinal readout

Emergence: DDIT4↑, pS6↓/p4EBP1↓, LC3-flux↑/p62↓, p-eIF2α↑/ATF4↑, ATF3/RAB7, xCT [±GPX4]

Exit: IFRD1↑ with pS6/p4EBP1↑, Ki-67 & EdU/BrdU, c-MYC, SOX9/LGR5/CD44v

Fig. S1. Drug-tolerant persister alignment with the paligenosis framework in colorectal cancer.

Chemo-surviving colorectal cancer cells enter a diapause-like DTP entry (S1-like) state characterized by mTORC1 inhibition (pS6 ↓/p4EBP1 ↓), translation down/ISR activation (p-eIF2α ↑/ATF4 ↑), and autophagy (LC3-II flux ↑/p62 ↓), with stress/QC markers (ATF3, RAB7) and xCT/SLC7A11 (±GPX4) upregulation. A putative QC gate separates this phase from DTP exit (S2–S3-like), during which mTORC1 reactivates (pS6 ↑/p4EBP1 ↑), c-MYC and cell-cycle programs resume (Ki-67, Cyclin–CDK; EdU/BrdU). Suggested assays include phospho-IHC/IF or phospho-flow, LC3/p62 dual staining, and organoid LC3 reporters; serial biopsies/organoids enable longitudinal tracking. The biomarker panel at the bottom summarizes emergence vs exit readouts (e.g., DDIT4/ATF3/RAB7/xCT with mTORC1 metrics for entry; IFRD1 with mTORC1 reactivation and proliferation markers for exit). Relationships are hypothesis-generating and require prospective validation.