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Conditional pyrimidine salvage dependence and a catabolism-associated adverse state in cancer

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Abstract

Pyrimidine nucleotide supply is a metabolic dependency of cancer cells, and inhibitors of de novo synthesis are under renewed investigation. We used publicly available data to characterize the salvage and catabolism arms of pyrimidine metabolism in relation to de novo synthesis, drug response, genetic dependency, survival, and the tumor microenvironment, framed as a pan-cancer survey with a colorectal focus. In an ovarian cancer model, acute inhibition of de novo synthesis increased the salvage kinases UCK1, TK1, and DCK, and the catabolism marker UPP1 rose in the established resistant state. In colorectal tumors, catabolism genes formed a co-expression module separate from de novo and proliferation genes. Higher catabolism-gene expression was associated with reduced 5-fluorouracil sensitivity across cancer cell lines. In CRISPR screens, de novo genes were essential in colorectal cells while salvage genes were non-essential and showed no buffering of de novo loss. Across cancers, a catabolism composite score was associated with shorter overall survival (hazard ratio 1.21 per +1 standard deviation, 95% CI 1.14–1.28) and with a macrophage-rich tumor signal. These convergent results indicate that de novo synthesis is a standing dependency, that the salvage kinases represent a candidate conditional dependency engaged by de novo blockade, and that catabolism-gene expression marks adverse tumor states. The findings define testable targets for functional study.

Keywords: pyrimidine metabolism, nucleotide salvage, 5-fluorouracil, colorectal cancer, in silico analysis

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Introduction

Pyrimidine nucleotides are required for DNA and RNA synthesis, and their supply is a recognized dependency of proliferating cancer cells [1]. Cellular pyrimidine pools are maintained by three connected routes: de novo synthesis (CAD, DHODH, and UMPS), which builds nucleotides from small precursors; the salvage pathway, in which kinases (UCK1, UCK2, TK1, and DCK) re-phosphorylate preformed nucleosides; and catabolism (including UPP1, CDA, DPYD, and TYMP), which degrades and interconverts pyrimidines [2]. These four enzymes are referred to as the catabolism genes throughout. These same enzymes govern the activity of pyrimidine-analogue chemotherapeutics: 5-fluorouracil, a mainstay of colorectal and other cancers, is activated and

Availability of data and material
The data analyzed in this study were obtained from the TCGA database, the GDSC and DepMap portals, and the GSE283381 and GSE28702 datasets in the GEO database.

Authors' contributions
The article is prepared by a single author.

Ethics approval and consent to participate
Not applicable.

degraded through these routes and acts on thymidylate synthase (TYMS) [3].

Inhibitors of de novo synthesis, in particular DHODH inhibitors such as brequinar, are being re-examined as anticancer agents [4,5]. A recurring limitation of such agents is that cells can sustain pyrimidine supply through the salvage pathway, which may blunt de novo blockade and support resistance [6,7]. When de novo synthesis is constrained, tumor cells may rely on salvage kinases that are otherwise dispensable, making these enzymes candidate vulnerabilities. How far this idea is supported by existing large-scale data, and how the catabolism arm relates to it, has not been systematically assessed.

Here we address these questions through analysis of publicly available datasets. We characterize the pyrimidine salvage and catabolism arms in relation to de novo synthesis, 5-fluorouracil response, genetic dependency, prognosis and the tumor immune microenvironment. Analyses were framed as a pan-cancer survey with a colorectal focus, given the central role of 5-fluorouracil in colorectal cancer. The aim was to identify, from convergent public data, which pyrimidine enzymes show features of a candidate conditional dependency and which track adverse tumor states.

Materials and Methods

Datasets

This study is an *in silico* analysis of publicly available datasets and generated no new experimental data. Transcriptional response to de novo pyrimidine blockade was examined in the ovarian cancer line OVCAR5 (GEO: GSE283381; RNA-seq) [8]. Gene co-expression was analyzed in a colorectal cancer cohort (GEO: GSE28702; n = 83; Affymetrix HG-U133 Plus 2.0) [9]. Drug-sensitivity associations used the Genomics of Drug Sensitivity in Cancer resource (GDSC1 and GDSC2; fitted dose-response, release 27 Oct 2023, with matched RNA-seq) [10,11]. Gene essentiality used CRISPR–Cas9 screens from the Cancer Dependency Map (DepMap Public 26Q1; Chronos gene-effect) [12]. Survival and tumor-microenvironment analyses used The Cancer Genome Atlas (TCGA) pan-cancer cohort obtained through UCSC Xena [13,14].

Differential expression

Raw gene counts (GSE283381) were analyzed with DESeq2 [15]. Two contrasts were computed: acute brequinar (a DHODH inhibitor) versus vehicle in parental cells, and the chronically brequinar-resistant versus sensitive state at baseline. Log2 fold-changes are reported for a predefined pyrimidine-metabolism gene panel, with Benjamini–Hochberg-adjusted significance.

Co-expression

Expression from the GSE28702 series matrix was summarized to gene level from mapped probes, and pairwise Spearman correlation coefficients were computed across the 83 samples for 15 pyrimidine-pathway genes.

Drug-sensitivity correlation

Spearman correlations were computed between gene expression (RNA-seq, TPM) and 5-fluorouracil sensitivity (natural-log IC_{50}) across GDSC cell lines: pan-cancer (GDSC2, n = 943; replicated in GDSC1, n = 887) and a colorectal subset (n = 48). Positive coefficients indicate association with resistance. *P*-values were adjusted by the Benjamini–Hochberg method across

the gene panel.

Dependency and buffering

Median CRISPR gene-effect (Chronos) scores were summarized across colorectal cell lines (n = 63); a median below –0.5 was taken as a dependency. To test for latent salvage buffering, Spearman correlations were computed between each salvage/catabolism gene's gene-effect and a composite de novo gene-effect score (mean of DHODH, CAD, and UMPS) across the same lines; coefficients within the two-sided $p = 0.05$ critical value ($|\rho| \approx 0.25$ at n = 63) were treated as non-significant.

Survival analysis

A catabolism composite score was defined as the mean of z-scored UPP1, CDA, and DPYD expression. TYMP was not included in this score. The score was used only in the TCGA analyses, whereas the GDSC and DepMap analyses were performed on individual genes. All TCGA analyses used tumor samples with available expression data, and normal-tissue samples were excluded. Survival models were further restricted to samples with available overall-survival follow-up, which gave 9,525 samples for the pan-cancer model. Cox proportional-hazards models related this score to overall survival, reporting the hazard ratio per +1 standard deviation. A pan-cancer model stratified by cancer type (n = 9,525) and per-tumor-type models were fitted.

Macrophage-signal association

A macrophage signal was defined as the mean of z-scored CD68, CD163, MRC1, and CSF1R expression. Partial Spearman correlations were computed between this signal and each pyrimidine composite score (the catabolism composite score defined above, and a de novo composite score calculated as the mean of z-scored DHODH, CAD, and UMPS) and, separately, UCK1 and TK1 individually adjusting for proliferation (MKI67), in TCGA tumor samples. Because this analysis does not require survival follow-up, it included all tumor samples with the necessary expression values, giving 11,768 samples pan-cancer and 651 for colorectal cancer (TCGA-COAD and TCGA-READ combined).

Statistical analysis

Analyses were performed in Python 3.11 (pandas 3.0, NumPy 2.4, SciPy 1.17, statsmodels 0.14) and R (DESeq2). Monotonic associations were assessed by Spearman rank correlation (SciPy); Cox proportional-hazards models were fitted with statsmodels using the Efron method for ties; differential expression was computed with DESeq2. Multiple testing was controlled by the Benjamini–Hochberg false-discovery rate where multiple genes were tested. The tumor-type-specific survival models were not adjusted for multiple comparisons and are reported as nominal p-values, and these analyses are therefore considered exploratory. The pan-cancer stratified model is the primary survival analysis. Significance is denoted * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, and ns denotes not significant. In Figs. 1 and 3 these refer to Benjamini–Hochberg-adjusted p-values. Hazard ratios are reported as HR (95% CI).

Results

Transcriptional response to de novo pyrimidine blockade

To test whether inhibiting de novo pyrimidine synthesis engages the salvage route, we re-

analyzed OVCAR5 transcriptomes under acute brequinar treatment and in the chronically resistant state. Acute brequinar decreased de novo genes (DHODH, CAD, RRM2) and increased the salvage kinases UCK1, TK1 and DCK, while the catabolism marker UPP1 was not significantly changed (Fig. 1A). In the established resistant state, UPP1 was increased, together with UCK1 and DCK. Salvage-kinase induction accompanies acute de novo blockade, whereas the UPP1 marker rises in the stabilized resistant state (Fig. 1B).

Co-expression structure in colorectal tumors

To ask whether these genes behave coherently in patient tumors, we computed pairwise co-expression across colorectal cancers (Fig. 2). De novo and proliferation-associated genes

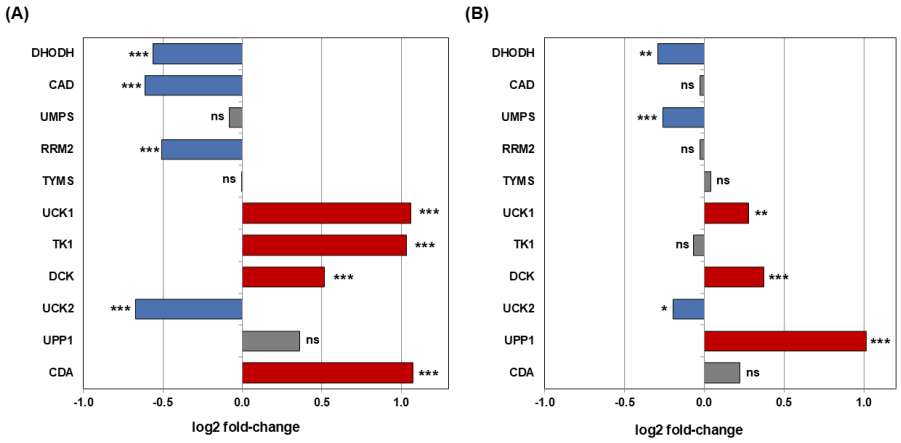

Fig. 1. Acute de novo pyrimidine blockade induces salvage kinases in an ovarian cancer model. Differential expression (DESeq2 log2 fold-change) of pyrimidine-metabolism genes in OVCAR5 cells (GSE283381). (A) Acute brequinar (DHODH inhibitor) treatment versus vehicle control. (B) Chronic brequinar-resistant versus sensitive cells. Bars are colored by the direction of change (red, increased; blue, decreased; gray, not significant). Asterisks denote Benjamini–Hochberg-adjusted significance ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$), and ns denotes not significant. n = 3 biological replicates per group.

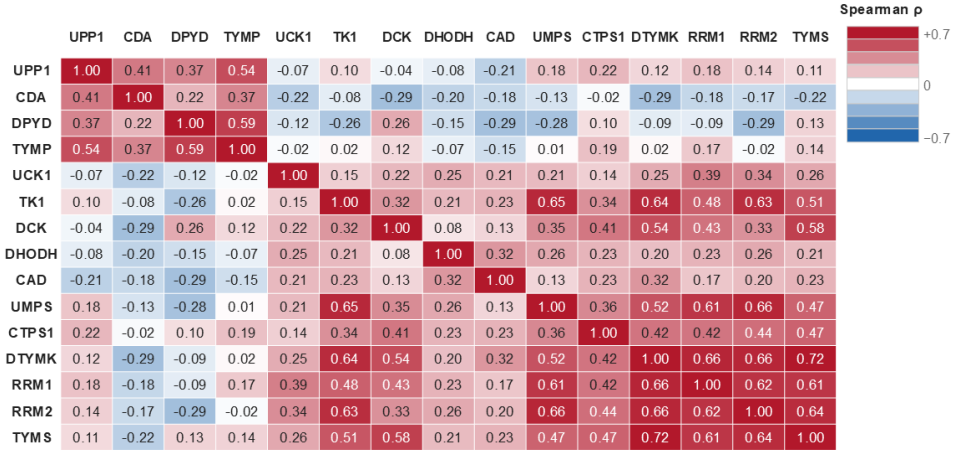

Fig. 2. Co-expression structure of pyrimidine-metabolism genes in colorectal tumors. Pairwise Spearman correlation coefficients (ρ) among 15 pyrimidine-pathway genes across 83 colorectal cancer samples (GSE28702; Affymetrix HG-U133 Plus 2.0, GPL570; FOLFOX cohort). Cell shading encodes ρ (red, positive; blue, negative; color scale at right); the diagonal (self-correlation, ρ = 1.00) is shown for reference.

(DHODH, CAD, UMPS, RRM1/2, TYMS, DTYMK) formed one strongly correlated group, and the catabolism genes (UPP1, CDA, DPYD, TYMP) formed a separate group, hereafter the catabolism co-expression module with the two groups largely uncorrelated. Pyrimidine metabolism resolves into separable catabolism and de novo/proliferation modules.

Association with 5-fluorouracil sensitivity

To relate expression to drug response, we correlated pyrimidine-gene levels with 5-fluorouracil sensitivity across cancer cell lines. Higher expression of UPP1, CDA, TK1, and UCK1 was associated with resistance, and higher DCK, UCK2, CAD, and DHODH with sensitivity (pan-cancer, n = 943) (Fig. 3A). The UCK1 and UCK2 associations reproduced in an independent GDSC release, and most associations were directionally consistent in the colorectal subset (n = 48) without reaching significance at that sample size (Fig. 3B and C). Expression of the individual catabolism genes UPP1, CDA, and DPYD is associated with reduced 5-fluorouracil sensitivity across datasets.

Genetic dependency and buffering

To distinguish constitutive from conditional requirements, we examined CRISPR gene-effect scores in colorectal cell lines. The de novo genes DHODH, CAD, UMPS and RRM2 were essential (gene effect below −0.5), whereas the salvage kinases (UCK1, TK1, DCK), UCK2 and the catabolism genes (UPP1, CDA, and DPYD) were non-essential at baseline (Fig. 4A). No salvage or catabolism gene's dependency co-varied with the de novo dependency score, in contrast to the de novo internal control (Fig. 4B). Salvage genes are dispensable at baseline and show no latent buffering of de novo loss.

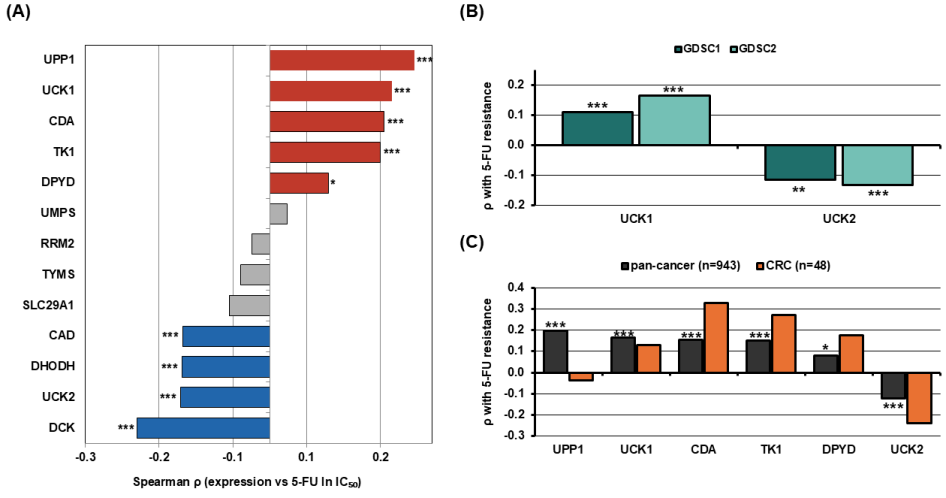

Fig. 3. Association of pyrimidine-gene expression with 5-fluorouracil sensitivity across cancer cell lines. Spearman correlation (ρ) between gene expression (RNA-seq, TPM) and 5-fluorouracil ln(IC_{50}) in the Genomics of Drug Sensitivity in Cancer (GDSC) panel; positive ρ indicates association with resistance. (A) Pan-cancer correlations for 13 genes (GDSC2; n = 943), colored by direction (red, positive; blue, negative; gray, not significant). (B) Replication of UCK1 and UCK2 across GDSC1 (n = 887) and GDSC2 (n = 943). (C) Pan-cancer (n = 943) versus colorectal-only (n = 48) correlations for six genes. Asterisks denote Benjamini–Hochberg-adjusted significance ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$).

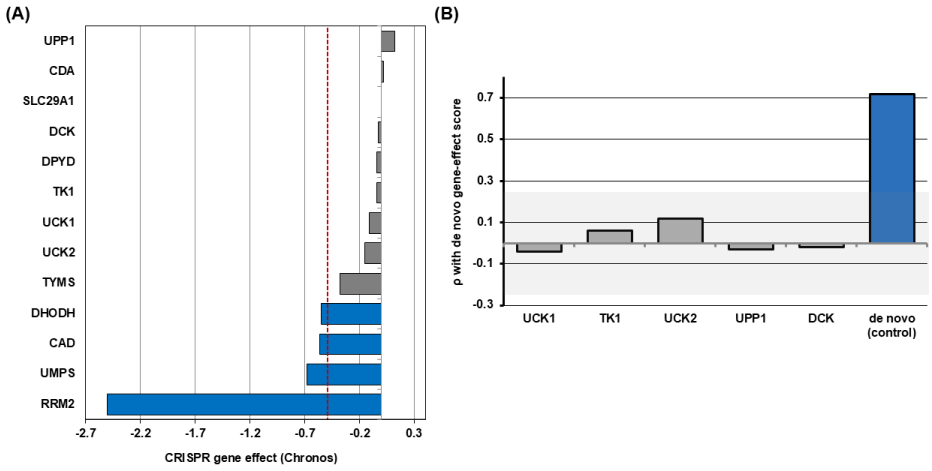

Fig. 4. Baseline essentiality and absence of latent salvage buffering in colorectal cell lines. CRISPR–Cas9 loss-of-function screens from the Cancer Dependency Map (DepMap; Chronos gene-effect). (A) Median gene-effect for pyrimidine-metabolism genes across colorectal cell lines (n = 63); more negative values indicate stronger dependency. The dashed line marks the −0.5 dependency threshold; genes crossing it are colored blue, the remainder gray. (B) Spearman correlation between each salvage/catabolism node's gene-effect and the composite de novo gene-effect score across the same lines. The shaded band marks the non-significant range (|ρ| below the two-sided $p = 0.05$ critical value, ≈0.25 at n = 63); the de novo internal control is shown for comparison.

Association with overall survival

To assess clinical relevance, we related pyrimidine expression to overall survival across cancers (Fig. 5). A catabolism composite score (UPP1, CDA, DPYD) was associated with shorter overall survival pan-cancer (HR 1.21 per +1 SD, 95% CI 1.14–1.28, n = 9,525) and, in exploratory analyses that were not adjusted for multiple comparisons, was adverse in several individual cancer types at a nominal $p < 0.05$. A higher catabolism composite score marks worse outcome.

Association with macrophage signal

To place the program in the tumor microenvironment, we correlated a macrophage signal with the pyrimidine modules while adjusting for proliferation (Fig. 6). The macrophage signal correlated positively with the catabolism composite score and negatively with the de novo composite score, in both colorectal and pan-cancer cohorts. The catabolism composite score is associated with macrophage-rich tumors independently of proliferation, opposite to the de novo composite score.

Discussion

This study combined several independent public datasets to describe how the salvage and catabolism arms of pyrimidine metabolism relate to de novo synthesis, drug response, genetic dependency, survival, and the tumor microenvironment. The salvage kinases behaved as a candidate conditional resource engaged by de novo blockade, and the catabolism genes behaved as a marker of adverse tumor states. Both patterns fit the established view that pyrimidine supply is a targetable dependency in cancer [2].

The conditional character of the salvage arm agrees with earlier work showing that cells can maintain pyrimidine pools through salvage when de novo synthesis is inhibited, for example by taking up extracellular uridine [16]. Acute inhibition of de novo synthesis increased the salvage kinases UCK1, TK1, and DCK, consistent with an adaptive shift toward salvage. These

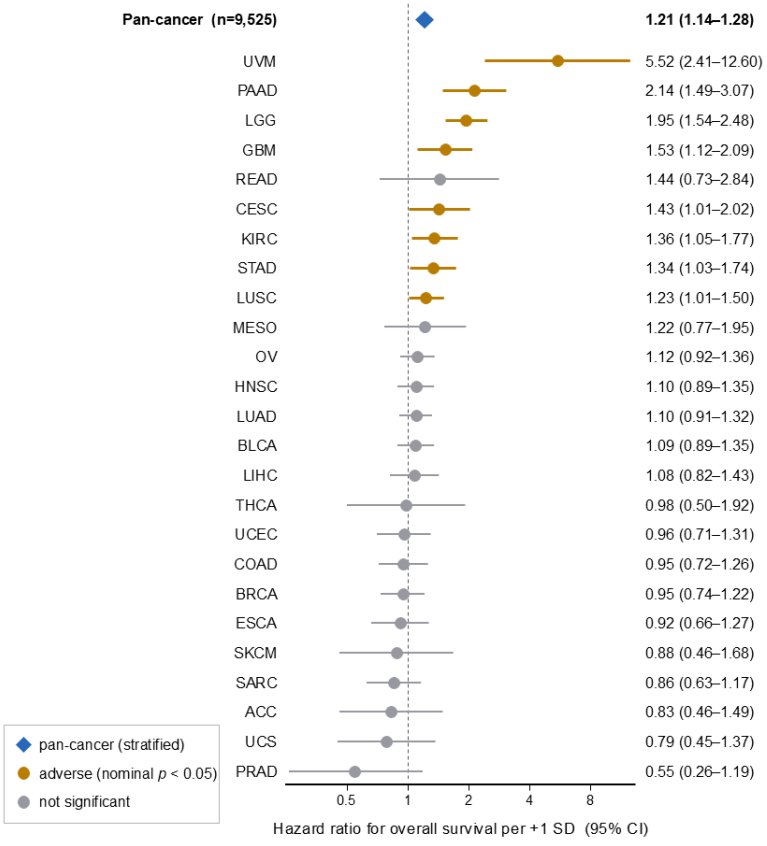

Fig. 5. The pyrimidine-catabolism score is an adverse overall-survival factor across cancers. Forest plot of hazard ratios (HR; 95% CI) for overall survival per +1 standard deviation of the catabolism composite score (UPP1, CDA, DPYD), from Cox proportional-hazards models (TCGA; UCSC Xena). The pan-cancer estimate (stratified by cancer type; n = 9,525) is shown as a diamond; per-tumor-type estimates are points with 95% CI. Markers are gold where adverse at a nominal $p < 0.05$ and gray where not significant, and the dashed line marks HR = 1. Per-tumor-type estimates were not adjusted for multiple comparisons and are exploratory. TCGA, The Cancer Genome Atlas.

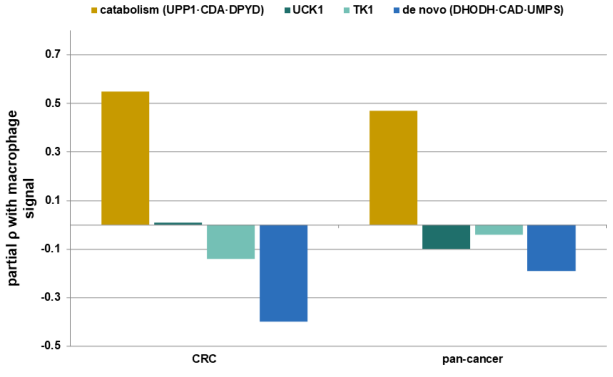

Fig. 6. Pyrimidine-catabolism expression tracks tumor-associated macrophage signal independently of proliferation. Partial Spearman correlation (ρ) between pyrimidine-gene modules and a tumor-associated macrophage signature (CD68, CD163, MRC1, and CSF1R) adjusted for proliferation (MKI67), in colorectal (CRC) and pan-cancer cohorts (TCGA; UCSC Xena). Composite scores: catabolism (UPP1·CDA·DPYD) and de novo (DHODH·CAD·UMPS); UCK1 and TK1 were analyzed individually. CRC n = 651 (COAD + READ tumors); pan-cancer n = 11,768 (TCGA tumor samples). TCGA, The Cancer Genome Atlas.

kinases were not essential at baseline in genome-wide screens, while the de novo enzymes were. And the dependency on salvage genes did not covary with the dependency on de novo genes, which argues against a standing buffering relationship. Together these results are consistent with a potential conditional dependency, in which salvage kinases would matter when de novo synthesis is constrained and are otherwise dispensable, a pattern that resembles collateral metabolic vulnerabilities reported for other pathways [17]. Under this view UCK1 and the other salvage kinases are candidate partners for combination with de novo inhibitors and not standalone essentials.

The catabolism arm showed a distinct and internally consistent behavior. The catabolism genes formed a co-expression module separate from the de novo and proliferation genes. Higher expression of these genes was associated with reduced 5-fluorouracil sensitivity, which fits the known roles of these enzymes in fluoropyrimidine handling, including degradation of 5-fluorouracil by DPYD [18]. The same genes, summarized as a composite score, were associated with shorter overall survival and with a macrophage-rich tumor signal. These associations are in line with reports linking catabolism enzymes such as UPP1 to nutrient scavenging and an immunosuppressive microenvironment in other tumor types [19,20], and with the broad association between tumor-associated macrophages and poor outcome [21]. Taken together, the catabolism genes are a candidate biomarker of an adverse tumor state.

We used a published ovarian cancer dataset for the perturbation analysis because it provided matched acute and chronic de novo blockade in sensitive and resistant cells, which is the design needed to observe induction of the salvage kinases. De novo pyrimidine dependence is itself relevant in ovarian cancer, and the de novo and salvage relationship is a general feature of pyrimidine wiring, so this model is a reasonable setting in which to examine this relationship [8]. Clinical relevance was then examined in patient tumors across many cancer types and in colorectal cancer, where 5-fluorouracil is central.

Several limitations should be stated plainly. Most of the patient-level findings are associations and do not establish causation. In particular, salvage-gene dependency under de novo inhibition was not tested functionally, and the conditional dependency described here therefore remains a candidate that requires experimental confirmation. The perturbation evidence comes from a single ovarian cell model, so generalization depends on the patient and pan-cancer analyses. The colorectal drug-sensitivity subset was small (n = 48), so those estimates are directional only. The link between the catabolism genes and the macrophage signal was measured in bulk tissue, which cannot resolve the cellular source of the signal or the direction of the relationship, and this question will need single-cell and functional work. Finally, the study relies on the accuracy and annotation of the source datasets, and one gene of interest (UCK2) lacked a mapped probe in the co-expression platform.

Within these limits, the convergent results outline a simple and testable picture. De novo synthesis is a standing dependency, the salvage kinases are a candidate conditional resource that de novo blockade may bring into play, and the catabolism genes mark tumors with poorer drug response, poorer survival, and a macrophage-rich environment. These conclusions give a defined starting point for functional studies, including a direct test of salvage-kinase dependence under de novo inhibition.

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