

HNF1A is a novel BRD4 target and critical for BET-inhibitor response in pancreatic ductal adenocarcinoma

Corresponding Author: Dr Ethan Abel

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

This is a valuable carrying diseases significance. The manuscript is well-written, and the data clearly presented. For the most part, the data is supportive of the main conclusions of the manuscript. However, there are some additional results needed to fully support them and enhance the rigor of the experimental design. First, in Figure 1, the authors should molecular markers flanking the band of interest. The MYC (cMYC, I presume) and HIF1A blots should be accompanied by the mRNA expression of target genes regulated these transcription factors (beyond the ones included in Figure 3). This will be a better read out of the targeting BRDs. Second, the experiments of Figures 1 and 3 should be repeated in hypoxic conditions. Third, the mechanism of regulation of HIF1A by BRD4 should be expanded. How BRD4 is recruited to this promoter? Is it MYC dependent and hypoxia-independent? Also, the authors should determine if the BETi and BRD4 knockdown changes the chromatin landscape of the HIF1A promoter. Fourth, the direct regulation of members ERBB signaling should be validated in PDAC lines by ChIP-PCR. Also, the chromatin landscape in these regulatory sequences should be examined in the presence of BETi and HIF1i.

Reviewer #2

(Remarks to the Author)

In this manuscript, Humphrey and colleagues demonstrate that HNF1A is a central mediator of the response to BET inhibitors (BETi) in pancreatic ductal adenocarcinoma (PDAC). The authors first establish that BETi treatment negatively correlates with HNF1A expression across multiple PDAC cell lines. Subsequently, they demonstrate that HNF1A is necessary for acquired resistance to BETi, as HNF1A re-expression rescues cells from BETi-induced growth suppression. Mechanistically, the authors show that HNF1A expression is directly controlled by BRD4 binding to its promoter. At the cellular level, HNF1A promotes cell cycle progression and maintains cancer stem cell properties under BETi treatment. At the molecular level, the authors identify that HNF1A exerts its pro-tumorigenic effects through the EGFR/ERBB signaling axis, with EGFR inhibitors abrogating the protective effects of HNF1A re-expression. Overall, the authors convincingly demonstrate a critical role for HNF1A in BETi resistance during PDAC progression and suggest a potential therapeutic strategy combining BETi with RTK inhibitors. The manuscript is well-executed and the conclusions are largely supported by the data; however, several points should be addressed to strengthen the manuscript prior to publication.

1. Clarify drug concentrations: The rationale for selecting the specific concentrations of OTX-015 (0.5 μ M) and ABBV-744 (0.1 μ M) used throughout the study is not clearly stated. While the authors show dose-response western blots, providing IC50 values for these inhibitors in the PDAC cell lines used would strengthen the justification for the chosen concentrations.
2. Refine conclusions to better align with the data: Several conclusions extend beyond the direct evidence presented. The authors should carefully revise the language in the following instances to ensure conclusions are strictly supported by the data:
 - a. Relationship between MYC and HNF1A (lines 359-360): The authors conclude that HNF1A acts "beyond control of MYC expression." While the data clearly show that MYC re-expression does not rescue BETi effects and that MYC is necessary for proliferation, the relationship between these two factors remains incompletely characterized. Specifically, it is unclear whether MYC is required for the HNF1A-mediated rescue effect. The authors could address this either by performing additional experiments (e.g., HNF1A rescue in the context of MYC knockdown) to definitively establish the epistatic relationship, or by softening the claim to reflect that while HNF1A restoration rescues MYC expression, the data currently do not establish whether this is the primary mechanism or a parallel event.

b. BRD4 specificity in regulating HNF1A (line 393): The authors state that BRD4 is "the BET protein most responsible for regulation of HNF1A." However, the siRNA data in Figure 4A show that BRD2 knockdown also reduces HNF1A expression in AsPC-1 and UM15 cells. While the BRD4 degrader data support a dominant role for BRD4, the possibility that BRD2 contributes to HNF1A regulation in a context-dependent manner cannot be excluded. The authors should revise the text to acknowledge this potential redundancy, rather than presenting BRD4 as the sole or primary regulator.

c. HNF1A-dependent metastasis genes (lines 452-453): The authors conclude that BETi "target metastasis associated genes and drivers in an HNF1A-dependent manner." This statement is stronger than the data support. Of the 252 metastasis-associated transcripts overlapping with HNF1A-upregulated genes, only 62 were downregulated by BETi, and only 40 of those 62 were rescued by HNF1A re-expression. Thus, only a subset of the metastasis-associated genes shows clear HNF1A-dependent regulation by BETi. The authors should revise this conclusion to reflect that BETi suppress a subset of metastasis-associated genes, some of which are regulated in an HNF1A-dependent manner.

3. TAM IF staining: Were adjacent normal tissues available for comparison, and if so, did they reflect similar or different staining patterns for HNF1A, BRD4, and the RTKs? In Figure 8B, the representative core shows minimal BRD4 expression. Clarifying whether this core is representative of a specific PDAC subtype, a particular clinical characteristic, or simply a region of tumor heterogeneity would aid interpretation. Given the ubiquitous expression of BRD4 in mammalian epithelium, confirming that the lack of signal is biological rather than technical (e.g., antigen degradation) would strengthen the figure.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

Not further comments.

Reviewer #2

(Remarks to the Author)

I have completed my re-review of the revised manuscript. The authors have provided comprehensive and satisfactory responses to all of my previous critiques. The revised text, figures, and justifications are clear and convincing. I am pleased to recommend the manuscript for acceptance without further revision.

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We sincerely thank both Reviewers for their enthusiasm for the initial draft of our manuscript and for their critiques that have allowed us to further strengthen our story. We have done our best to address each concern in a point-by-point manner below:

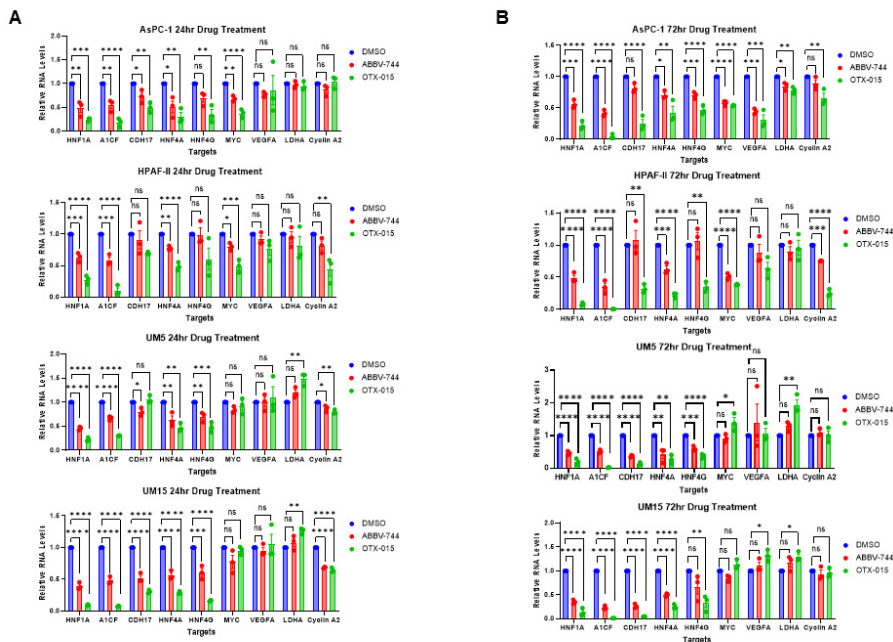
Reviewers' comments:

Reviewer #1 (Remarks to the Author):

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First, in Figure1, the authors should molecular markers flanking the band of interest. The MYC (cMYC, I presume) and HIF1A blots should be accompanied by the mRNA expression of target genes regulated these transcription factors (beyond the ones included in Figure 3). This will be a better read out of the targeting BRDs.

We thank the Reviewer for their requests, the inclusion of which has added rigor to our study. Molecular weights for proteins have been added throughout the manuscript as well as uncropped western blots in supplemental, per the Journal's requirements. MYC does refer to c-MYC; we've clarified this in line 365. We performed qRT-PCR for multiple HNF1A (HNF4A, HNF4G, CDH17, A1CF¹) and MYC (LDHA^{2,3}, Cyclin A2^{3,4}, VEGFA⁵) target genes (and HNF1A and MYC themselves) following 24 and 72 hours of BETi treatment. As previously shown in the original manuscript, *HNF1A* mRNA was significantly decreased by both BETi at 24 hours and this was also seen at 72 hours in all 4 cell models (AsPC-1, HPAF-II, UM5, and UM15). By contrast, *MYC* mRNA only decreased in AsPC-1 and HPAF-II cells, both at 24 and 72 hours. *A1CF* and *HNF4A* mRNAs decreased significantly in all cells at both 24 and 72 hours, while *CDH17* and *HNF4G* mRNAs decreased in most cells at both time points with cell-specific and inhibitor-specific variability observed. Neither *VEGFA* nor *LDHA* mRNAs decreased at 24 hours but were significantly decreased in AsPC-1 only at 72 hours. *Cyclin A2* mRNA decreased in AsPC-1 only with OTX-015 at 72 hours, HPAF-II only with OTX-015 at 24 hours but both inhibitors at 72 hours, and with both inhibitors in UM5 and UM15 at 24 hours but neither inhibitor at 72 hours. These data are consistent with literature supporting that MYC (and presumably MYC target genes) does not consistently respond to BETi in PDAC⁶. We conclude from these experiments that HNF1A as well as its targets (with some variability) are downregulated by BET-inhibitors, while MYC and its targets are downregulated in a cell-specific manner. These data are shown below and have been incorporated into the revised manuscript (Supplemental Figure 1B and lines 393-405).

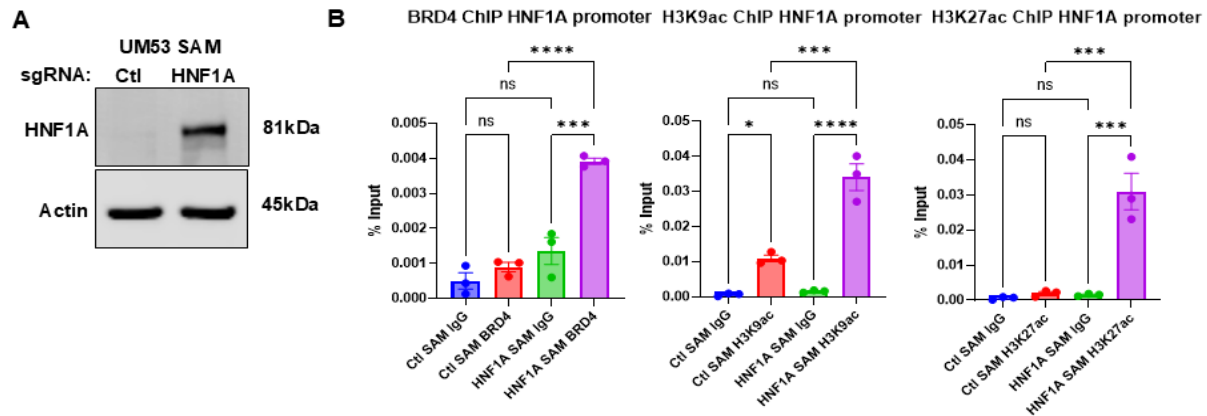


Second, the experiments of Figures 1 and 3 should be repeated in hypoxic conditions.

We would like to respectfully clarify that the focus of our manuscript is HNF1A (hepatocyte nuclear factor 1 alpha) and not HIF1A (hypoxia induced factor 1 alpha). As such, we feel that exploring the role of hypoxia in such extensive detail is beyond the scope of this manuscript, although we do believe that exploring any potential crosstalk between HNF1A, hypoxia, and HIF1A would be interesting for future studies.

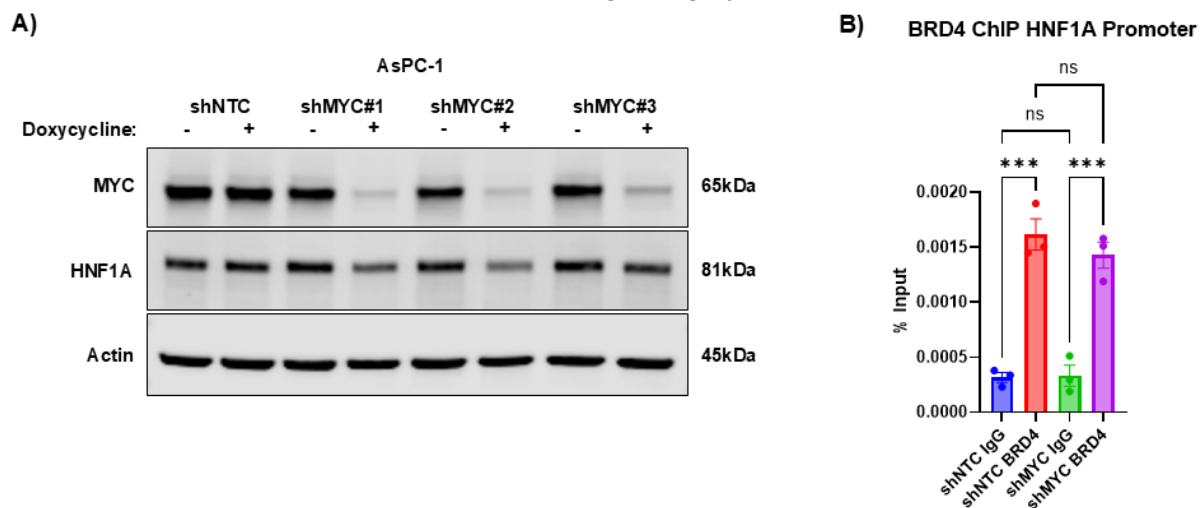
Third, the mechanism of regulation of HIF1A by BRD4 should be expanded. How BRD4 is recruited to this promoter?

BRD4 is known to be an “epigenetic reader,” binding to a number of acetylated histone marks on active promoters and enhancers⁷. We hypothesize that as a pancreas transcription factor (please see scRNA-seq data addressing Reviewer #2’s comments), HNF1A’s promoter bears active histone marks that recruit BRD4. To test this, we used an HNF1A-negative PDX line UM53⁸ and activated the HNF1A promoter and induced HNF1A expression (**A**) using a CRISPRa (synergistic activation mediator or SAM) system⁹. Using this system, we found that HNF1A promoter sgRNAs promoted acetylation of histone H3 at lysines 9 and 27 and the recruitment of BRD4 (**B**). We believe that these data support that BRD4 is recruited to the HNF1A promoter by the presence of activating histone marks. We have included most of these data in the revised manuscript (Supplemental Figure 3B), including language that acknowledges the limitations of our findings highlighted in yellow (lines 482-492).



Is it MYC dependent and hypoxia-independent?

We found that knockdown of MYC (which was substantially more complete than what we observed with BETi treatment in this study) modestly reduced the expression of HNF1A (to a much lesser extent than what we observed with BETi treatment) (A), suggesting that MYC may regulate HNF1A, either directly or indirectly. Nonetheless, we found that knockdown of MYC did not affect the recruitment of BRD4 to the HNF1A promoter (assayed by ChIP-PCR) (B). Because these data were negative in nature, we have chosen to not include them in the revised manuscript. Please see the above comment regarding hypoxia.

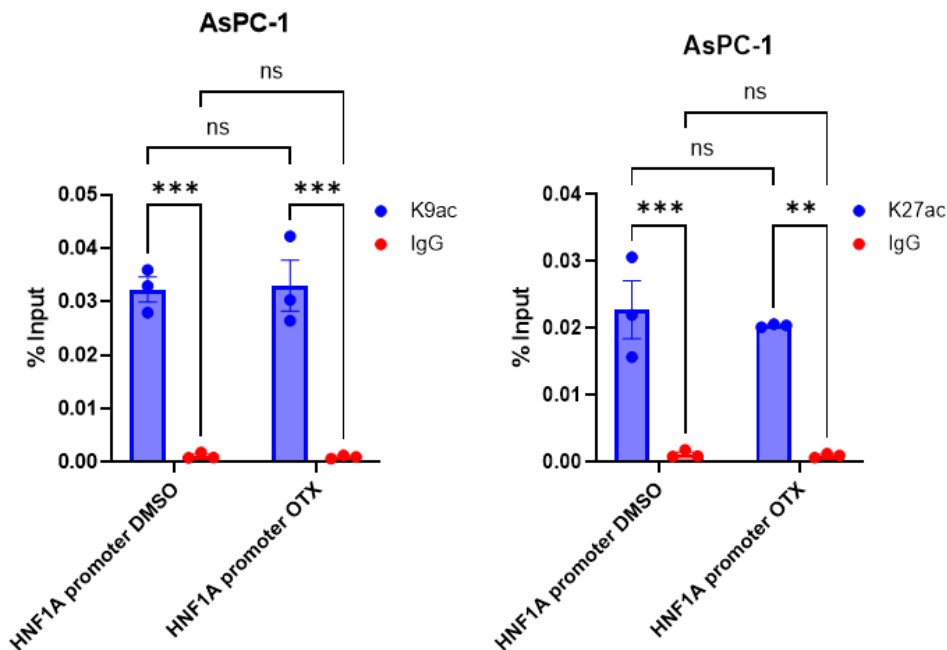


Also, the authors should determine if the BETi and BRD4 knockdown changes the chromatin landscape of the HIF1A promoter.

To address this critique, we performed ChIP-PCR for histone H3 acetyl-lysines 9 and -27 in AsPC-1 cells treated with 500nM OTX-015 for 72 hours. We did not observe a change in the acetylation-state of either residue at the HNF1A promoter. While we cannot conclude that there are no epigenetic changes that occur at the HNF1A promoter in response to BETi, we can conclude that these known activating marks do not change within the timeframe of most experiments in this study. These data are consistent with a previous study showing that while BETi disrupt transcription, they do not disrupt the interactions between enhancers and promoters¹⁰, and presumably the related chromatin landscape. Because these data were

negative in nature, we have chosen to not include them in the revised manuscript. A more in-depth analysis (e.g., Hi-C and ATAC-seq) of how chromatin dynamics are controlled by HNF1A in PDAC is warranted and will be the focus of future studies in our lab.

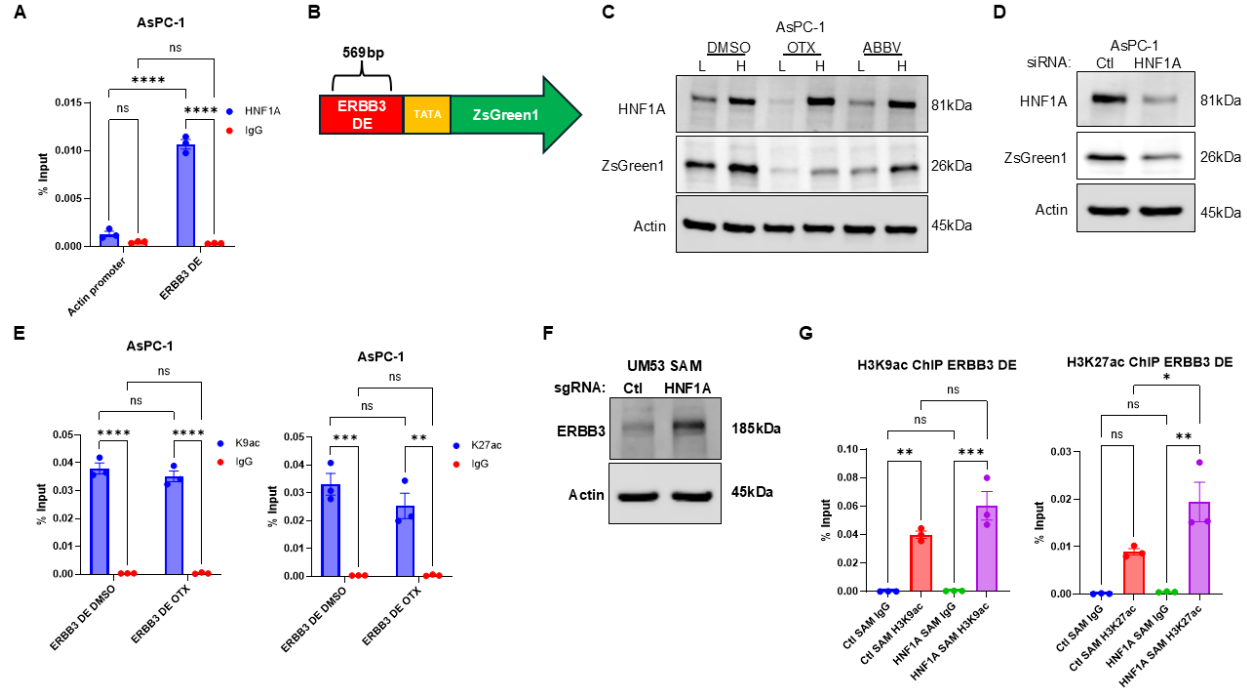
A



Fourth, the direct regulation of members ERBB signaling should be validated in PDAC lines by ChIP-PCR. Also, the chromatin landscape in these regulatory sequences should be examined in the presence of BETi and HIF1i.

As presented in the original manuscript, we identified an HNF1A ChIP-seq peak ~75kbp upstream of the ERBB3 promoter region in UM5 and UM15 cells, which we speculated may serve as a distal enhancer (DE). To further validate this region, we performed HNF1A ChIP-PCR and confirmed enrichment of the ERBB3 DE in AsPC-1 compared to normal IgG (A). Notably, we did not see enrichment of the β -actin promoter. To determine whether the ERBB3 DE region has HNF1A-dependent enhancer activity, we cloned a 569bp fragment flanking the original HNF1A ChIP-seq peak we identified upstream of a minimal promoter driving ZsGreen1 (B). We transduced our LacZ- and HNF1A- overexpressing AsPC-1 cells with lentivirus encoding this reporter construct and treated the cells for 72 hours with DMSO, 500nM OTX-015, or 100nM ABBV-744. We found that the expression of the ZsGreen1 reporter was increased in HNF1A-overexpressing cells compared to LacZ-overexpressing cells, ZsGreen1 expression was reduced by treatment with either BETi, and that overexpression of HNF1A partially rescued ZsGreen1 expression in BETi treated cells (C). Furthermore, knockdown of HNF1A reduced the expression of ZsGreen1 in reporter expressing parental AsPC-1 cells (D). Similar to the HNF1A promoter we found that the acetylation of histone H3 was not responsive to BETi within 72 hours based on ChIP-PCR analysis (E), again possibly because BETi may not affect enhancer/promoter dynamics¹⁰. Finally, using our UM53 SAM cells, we found that activation of HNF1A expression corresponded to both increased ERBB3 expression (F) and increased acetylation of histone H3 K27 at the ERBB3 DE. Collectively, these data support that the ERBB3 DE is bound by and regulated by HNF1A and responsive to BETi, although more in-depth analysis such as Hi-C would be necessary to definitively demonstrate that it is directly regulating ERBB3's promoter. We have included most of these data in the revised manuscript

(Supplemental Figure 6D-I), including language that acknowledges the limitations of our findings highlighted in yellow (lines 591-602).



Reviewer #2 (Remarks to the Author):

In this manuscript, Humphrey and colleagues demonstrate that HNF1A is a central mediator of the response to BET inhibitors (BETi) in pancreatic ductal adenocarcinoma (PDAC). The authors first establish that BETi treatment negatively correlates with HNF1A expression across multiple PDAC cell lines. Subsequently, they demonstrate that HNF1A is necessary for acquired resistance to BETi, as HNF1A re-expression rescues cells from BETi-induced growth suppression. Mechanistically, the authors show that HNF1A expression is directly controlled by BRD4 binding to its promoter. At the cellular level, HNF1A promotes cell cycle progression and maintains cancer stem cell properties under BETi treatment. At the molecular level, the authors identify that HNF1A exerts its pro-tumorigenic effects through the EGFR/ERBB signaling axis, with EGFR inhibitors abrogating the protective effects of HNF1A re-expression. Overall, the authors convincingly demonstrate a critical role for HNF1A in BETi resistance during PDAC progression and suggest a potential therapeutic strategy combining BETi with RTK inhibitors. The manuscript is well-executed and the conclusions are largely supported by the data; however, several points should be addressed to strengthen the manuscript prior to publication.

1. Clarify drug concentrations: The rationale for selecting the specific concentrations of OTX-015 (0.5 μ M) and ABBV-744 (0.1 μ M) used throughout the study is not clearly stated. While the authors show dose-response western blots, providing IC50 values for these inhibitors in the PDAC cell lines used would strengthen the justification for the chosen concentrations.

We thank the Reviewer for the opportunity to add greater detail and clarity to this part of the manuscript. We have provided IC50 values for both OTX-015 and ABBV-744 based on their inhibition of HNF1A protein expression at 72 hours (Figures 1A and 1C). For all 4 cell lines, the IC50 of OTX-015 was ~30nM and the rationale for 500nM being used henceforth was based on

that being the dose that fully inhibited HNF1A expression in all cells tested. The IC50 for ABBV-744 varied across cell lines: 5.624nM (AsPC-1), 238.8nM (HPAF-II), 20.62nM (UM5), and 1.515nM (UM15). We chose to use 100nM throughout the manuscript because that concentration balanced high levels of HNF1A inhibition and high selectivity of BD2 over BD1 (the IC50 for BRD4 BD1 is 520nM)¹¹. Statements of the IC50s for each cell line and inhibitor, as well as our rationale for using 500nM OTX-015 and 100nM ABBV-744 have been added to the revised manuscript and are highlighted (lines 370-371, 386-387, 390-392).

2. Refine conclusions to better align with the data: Several conclusions extend beyond the direct evidence presented. The authors should carefully revise the language in the following instances to ensure conclusions are strictly supported by the data:

a. Relationship between MYC and HNF1A (lines 359-360): The authors conclude that HNF1A acts "beyond control of MYC expression." While the data clearly show that MYC re-expression does not rescue BETi effects and that MYC is necessary for proliferation, the relationship between these two factors remains incompletely characterized. Specifically, it is unclear whether MYC is required for the HNF1A-mediated rescue effect. The authors could address this either by performing additional experiments (e.g., HNF1A rescue in the context of MYC knockdown) to definitively establish the epistatic relationship, or by softening the claim to reflect that while HNF1A restoration rescues MYC expression, the data currently do not establish whether this is the primary mechanism or a parallel event.

We thank the Reviewer for affording us the flexibility to perform additional experiments or revise our claim. As noted, HNF1A overexpression does not rescue direct knockdown of MYC, while MYC overexpression is not sufficient to rescue the effects of BETi. Based on these observations we can only conclude that 1) MYC is necessary for PDAC proliferation and 2) HNF1A overexpression rescues both MYC expression and something that MYC alone cannot rescue. We previously acknowledge that regulation of MYC by HNF1A may, in concert with RTKs, contribute to HNF1A's oncogenic function in PDAC. As such, we have *strengthened* our statement acknowledging this in the Discussion from "possibly bolstering HNF1A oncogenic activity in conjunction with RTK upregulation" to "likely bolstering..." We have also *softened* our claims in the Results section with the conclusion "although we cannot conclude that the rescued expression of MYC by HNF1A does not contribute to the rescued proliferation observed." These additions are highlighted in revised manuscript (lines 433-434).

b. BRD4 specificity in regulating HNF1A (line 393): The authors state that BRD4 is "the BET protein most responsible for regulation of HNF1A." However, the siRNA data in Figure 4A show that BRD2 knockdown also reduces HNF1A expression in AsPC-1 and UM15 cells. While the BRD4 degrader data support a dominant role for BRD4, the possibility that BRD2 contributes to HNF1A regulation in a context-dependent manner cannot be excluded. The authors should revise the text to acknowledge this potential redundancy, rather than presenting BRD4 as the sole or primary regulator.

We acknowledge that the knockdown of BRD2 reduces the expression of HNF1A in some cell models and have added the following line to the results section: "although BRD2 likely also contributes to the regulation of HNF1A in some contexts (e.g., cell-line specific) and may possibly be redundant with BRD4." This addition is highlighted in revised manuscript (lines 467-469).

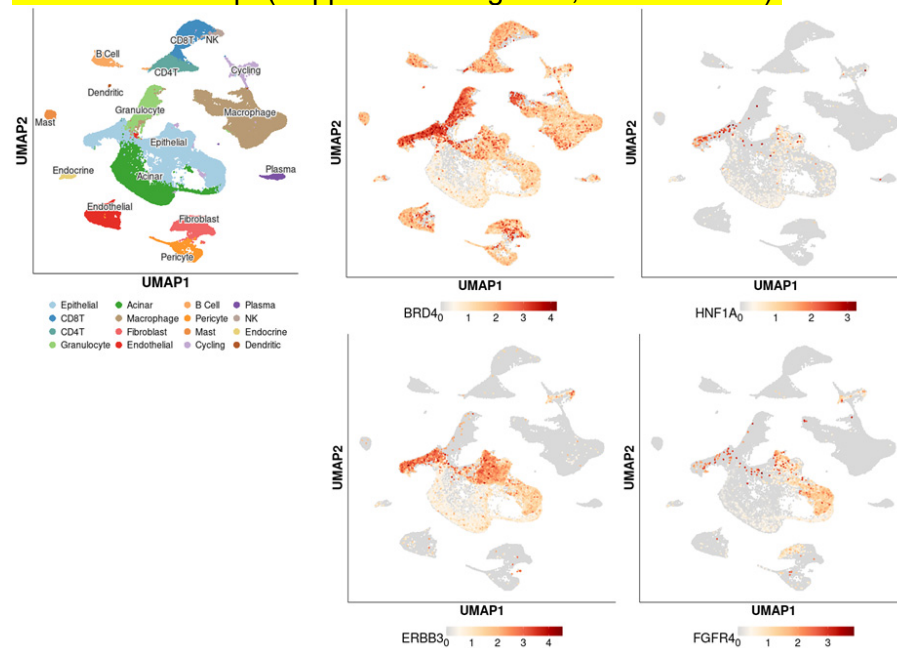
c. HNF1A-dependent metastasis genes (lines 452-453): The authors conclude that BETi "target metastasis associated genes and drivers in an HNF1A-dependent manner." This statement is stronger than the data support. Of the 252 metastasis-associated transcripts overlapping with

HNF1A-upregulated genes, only 62 were downregulated by BETi, and only 40 of those 62 were rescued by HNF1A re-expression. Thus, only a subset of the metastasis-associated genes shows clear HNF1A-dependent regulation by BETi. The authors should revise this conclusion to reflect that BETi suppress a subset of metastasis-associated genes, some of which are regulated in an HNF1A-dependent manner.

We agree that the original statement was too strong and have revised the last line of the paragraph to read “This would indicate that BETi downregulate a subset of metastasis-associated genes and drivers in an HNF1A-dependent manner.” We have also added the percent (15.9%) of rescued metastasis-associated transcripts to make the degree of overlap between gene sets clearer to readers. These changes are highlighted in revised manuscript (lines 536-538).

3. TAM IF staining: Were adjacent normal tissues available for comparison, and if so, did they reflect similar or different staining patterns for HNF1A, BRD4, and the RTKs?

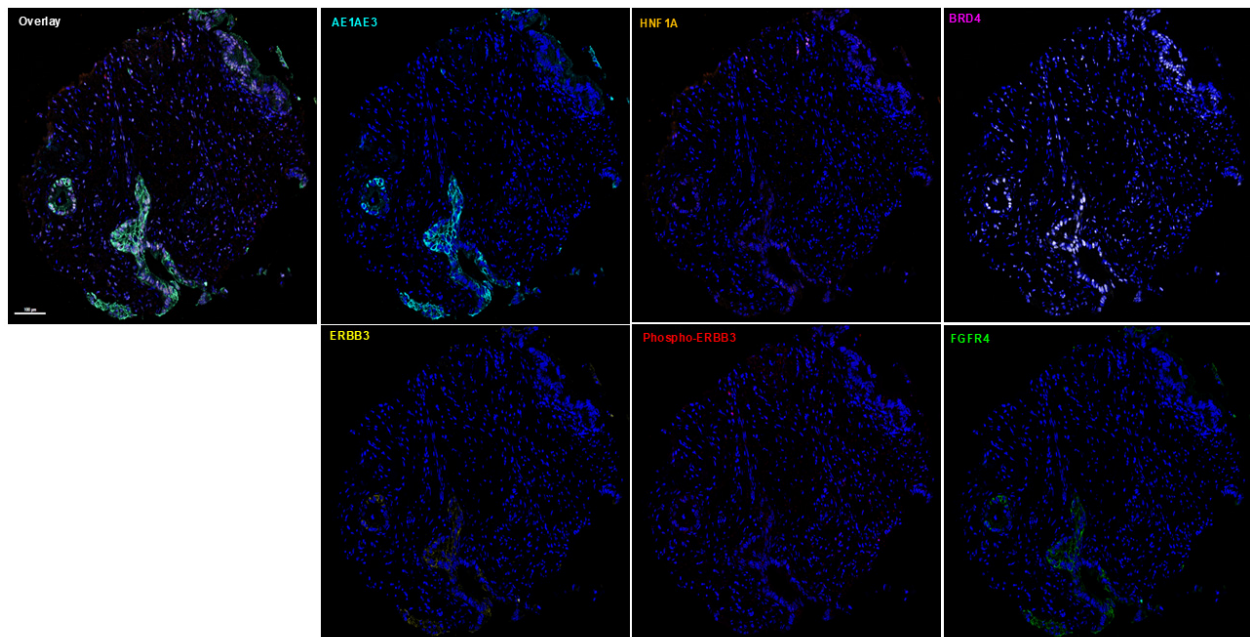
Unfortunately, the TMA used did not include normal pancreas for comparison. However, as an orthogonal approach to address the questions of expression of the BRD4-HNF1A-RTK axis in PDAC and normal cells of the pancreas, we examined publicly available scRNA-seq from 30 PDAC patients¹². In this data set we found that BRD4 was expressed in most cells in the tumor microenvironment/pancreas (as the Reviewer pointed out) but was generally highest in PDAC cells (labeled Epithelial). HNF1A expression was primarily limited to PDAC cells, acinar cells (probable cell of origin for PDAC) and endocrine cells, with the highest levels being in the PDAC cells. Similarly, ERBB3 and FGFR4 were primarily expressed in PDAC and acinar cells, with levels of both being markedly higher in PDAC cells compared to acinar cells. These data would suggest that the BRD4-HNF1A-RTK axis is primarily active PDAC and acinar cells and is elevated in PDAC versus its normal cell counterpart. These data have been included in the revised manuscript (Supplemental Figure 7, lines 622-631).



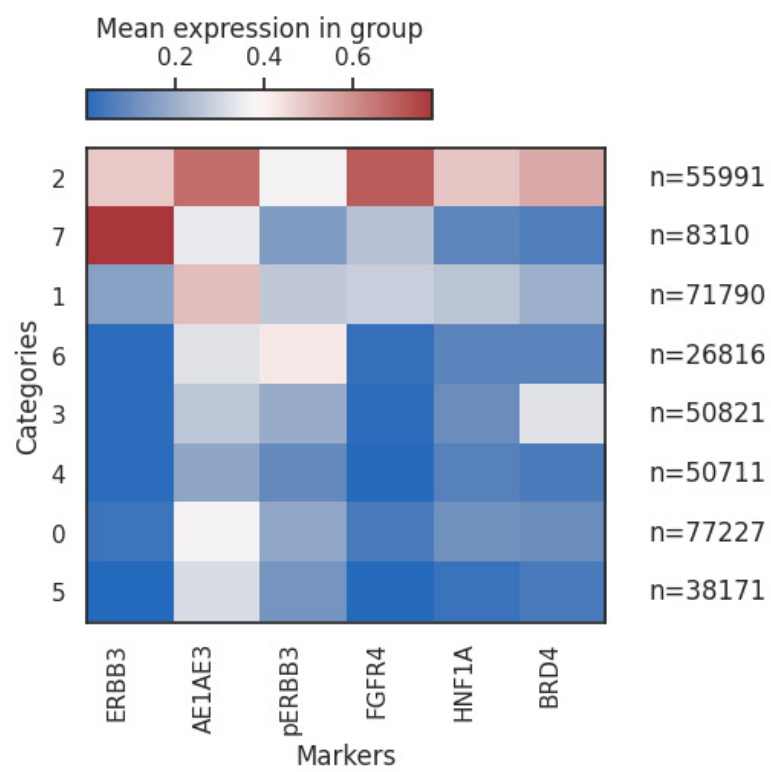
In Figure 8B, the representative core shows minimal BRD4 expression. Clarifying whether this core is representative of a specific PDAC subtype, a particular clinical characteristic, or simply a

region of tumor heterogeneity would aid interpretation. Given the ubiquitous expression of BRD4 in mammalian epithelium, confirming that the lack of signal is biological rather than technical (e.g., antigen degradation) would strengthen the figure.

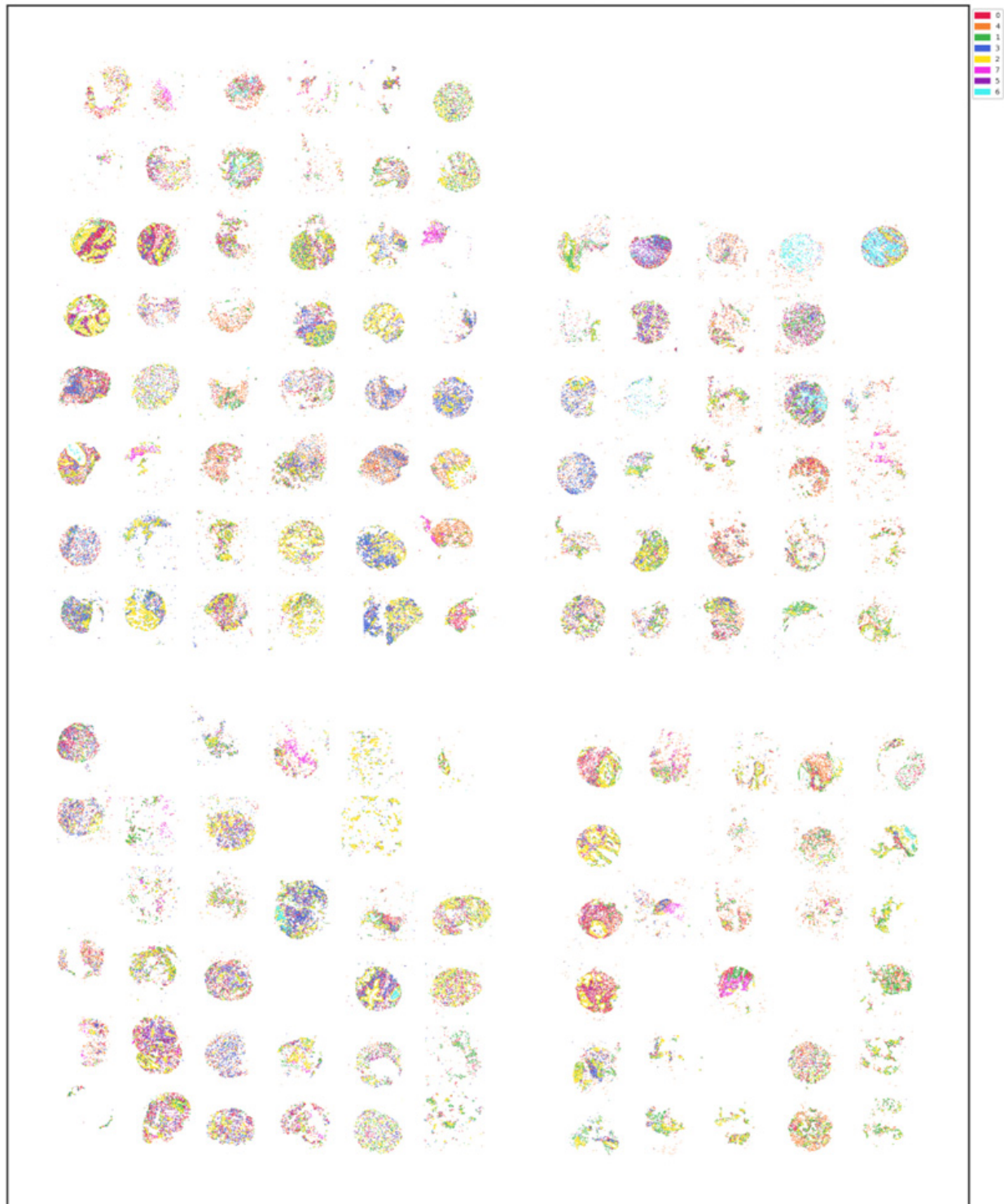
The Reviewer raises a fair point about the degree of marker negativity in the representative core from Figure 8B, although we initially selected it because AE1/AE3 staining was strong and abundant, arguing against but not proving that antigen degradation was not an issue. There was also, albeit very faint, staining for ERBB3, phospho-ERBB3, and FGFR4 in the representative core. However, as BRD4 should be present in most cases (as the Reviewer pointed out), we have replaced that representative image with a different core that has low BRD4 staining (comparable level between the PDAC cells and the stromal cells), HNF1A-negative/AE1/AE3-positive cells, low ERBB3/low phospho-ERBB3/low FGFR4/AE1/AE3-positive cells, and a few HNF1A-positive but AE1/AE3-negative cells visible (unknown cell type, but arguing against antigen degradation). The new images are below and in the revised manuscript. While Figure 8A and 8B are only representative images, the heatmap in Figure 8C shows the full spectrum of marker staining across the TMA and shows that while BRD4, HNF1A, and the RTKs are significantly correlated and clustered, there is a great deal of heterogeneity.



To further aid the Reviewer and readers this work in their interpretation of the TMA staining, we have provided Sci-MAP analysis of unique spatial single cell protein expression signatures of all 220 cores from the TMA (below and in Supplementary Information). Below is a category key describing the respective marker expressions for 7 categories of cells identified. Below the key are images of each core pseudocolored on a single-cell level for each category, showing the heterogeneity of staining categories across all cores.



leiden



leiden



Regarding details of PDAC subtypes or clinical characteristics; unfortunately, we do not have information for this particular TMA beyond the survival data originally provided.

- 1 Abel, E. V. *et al.* HNF1A is a novel oncogene that regulates human pancreatic cancer stem cell properties. *Elife* **7**, e33947 (2018). <https://doi.org:10.7554/eLife.33947>
- 2 Shim, H. *et al.* c-Myc transactivation of LDH-A: Implications for tumor metabolism and growth. *Proceedings of the National Academy of Sciences* **94**, 6658-6663 (1997). <https://doi.org:10.1073/pnas.94.13.6658>
- 3 Miller, D. M., Thomas, S. D., Islam, A., Muench, D. & Sedoris, K. c-Myc and cancer metabolism. *Clin Cancer Res* **18**, 5546-5553 (2012). <https://doi.org:10.1158/1078-0432.Ccr-12-0977>
- 4 Dang, C. V. c-Myc target genes involved in cell growth, apoptosis, and metabolism. *Mol Cell Biol* **19**, 1-11 (1999). <https://doi.org:10.1128/mcb.19.1.1>
- 5 Gao, K., Wu, C., Li, Y., Lu, J. & Jiang, Y. Transcriptome Analysis Reveals the Anti-Tumor Mechanism of Eucalyptol Treatment on Neuroblastoma Cell Line SH-SY5Y. *Neurochem Res* **47**, 3854-3862 (2022). <https://doi.org:10.1007/s11064-022-03786-8>
- 6 Garcia, P. L. *et al.* The BET bromodomain inhibitor JQ1 suppresses growth of pancreatic ductal adenocarcinoma in patient-derived xenograft models. *Oncogene* **35**, 833-845 (2016). <https://doi.org:10.1038/onc.2015.126>
- 7 Filippakopoulos, P. *et al.* Histone Recognition and Large-Scale Structural Analysis of the Human Bromodomain Family. *Cell* **149**, 214-231 (2012). <https://doi.org:https://doi.org/10.1016/j.cell.2012.02.013>
- 8 Crawford, K. J. *et al.* Targeting FGFR4 abrogates HNF1A-driven metastasis in pancreatic ductal adenocarcinoma. *Mol Cancer* **24**, 208 (2025). <https://doi.org:10.1186/s12943-025-02408-5>
- 9 Konermann, S. *et al.* Genome-scale transcriptional activation by an engineered CRISPR-Cas9 complex. *Nature* **517**, 583-588 (2015). <https://doi.org:10.1038/nature14136>
- 10 Crump, N. T. *et al.* BET inhibition disrupts transcription but retains enhancer-promoter contact. *Nature Communications* **12**, 223 (2021). <https://doi.org:10.1038/s41467-020-20400-z>
- 11 Faivre, E. J. *et al.* Selective inhibition of the BD2 bromodomain of BET proteins in prostate cancer. *Nature* **578**, 306-310 (2020). <https://doi.org:10.1038/s41586-020-1930-8>
- 12 Carpenter, E. S. *et al.* Analysis of Donor Pancreata Defines the Transcriptomic Signature and Microenvironment of Early Neoplastic Lesions. *Cancer Discovery* **13**, 1324-1345 (2023). <https://doi.org:10.1158/2159-8290.Cd-23-0013>