Tumor-associated macrophages promote PD-L1 expression in tumor cells by regulating PKM2 nuclear translocation in pancreatic ductal adenocarcinoma

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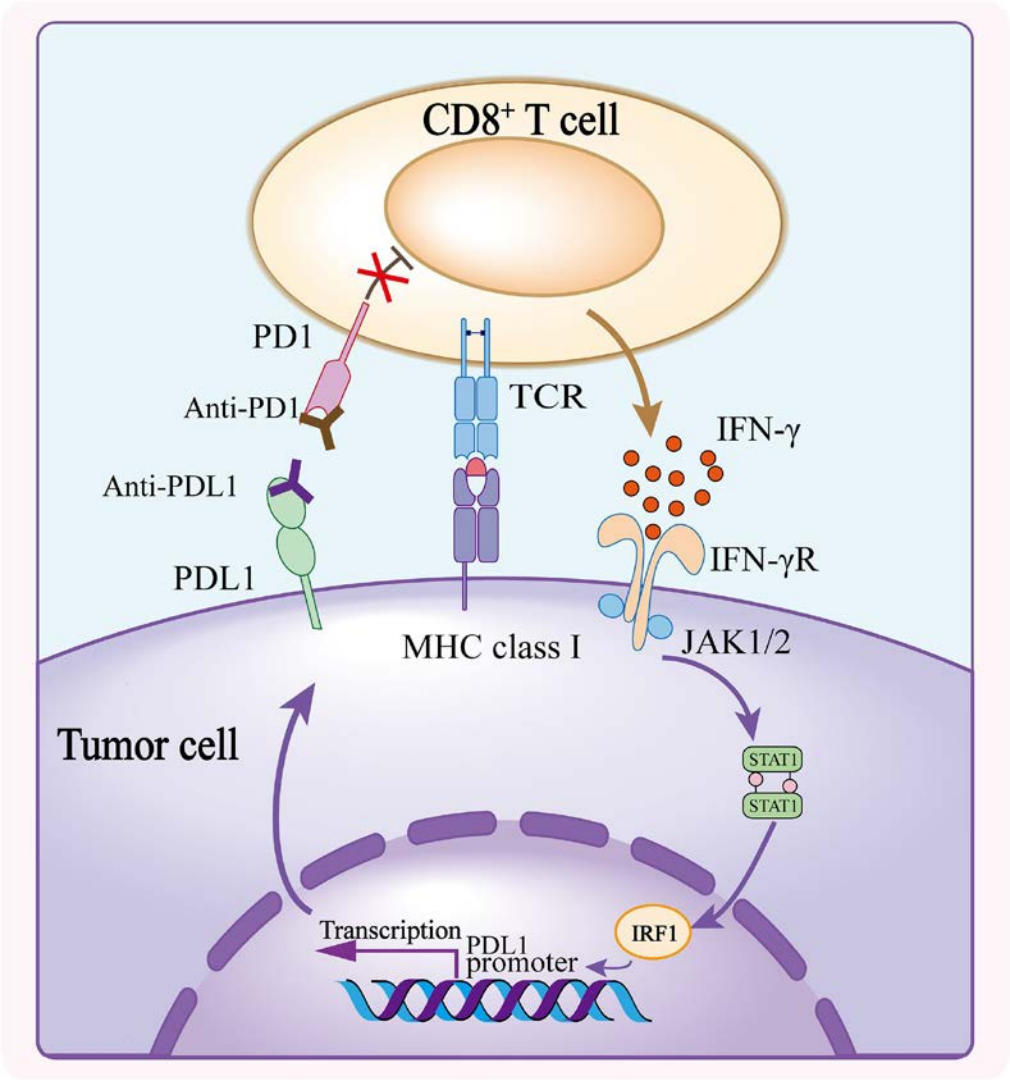
Presentation Structure

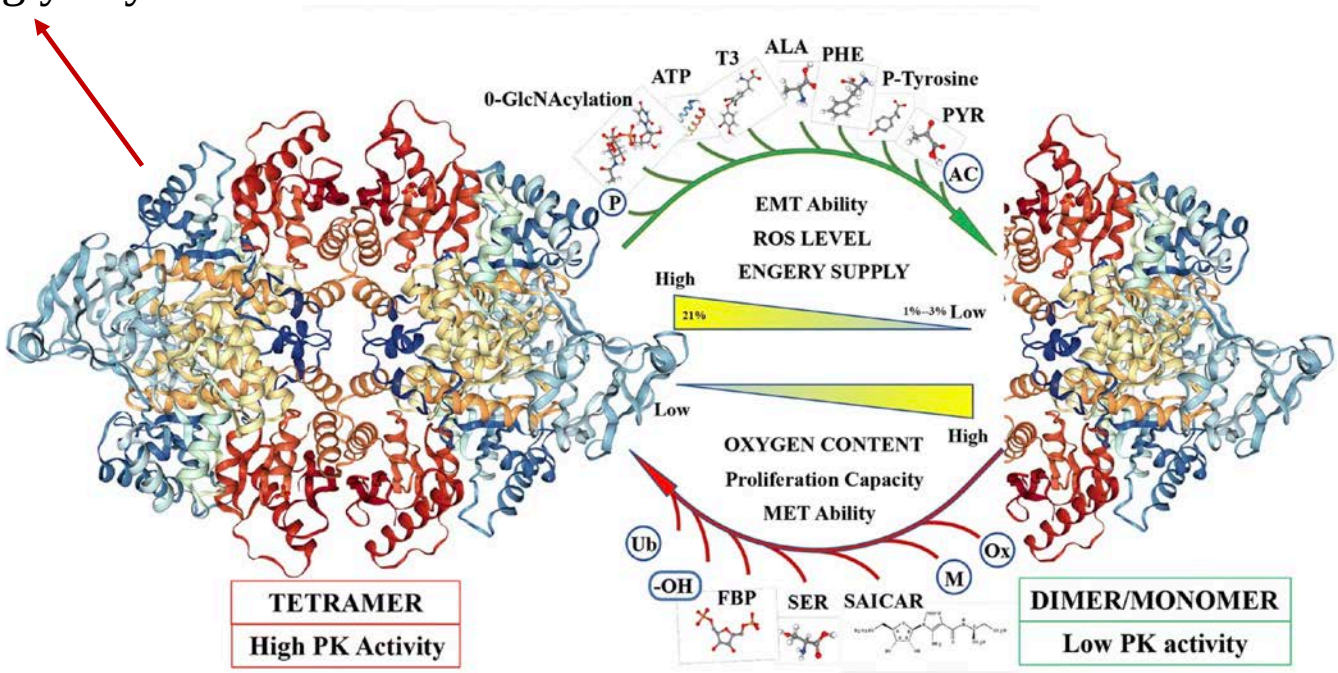
1) Introduction
2)Results
3) Proposed Working Model
4) Take-Home Messages
5) Discussion

PD-1 / PD-L1 immune checkpoint



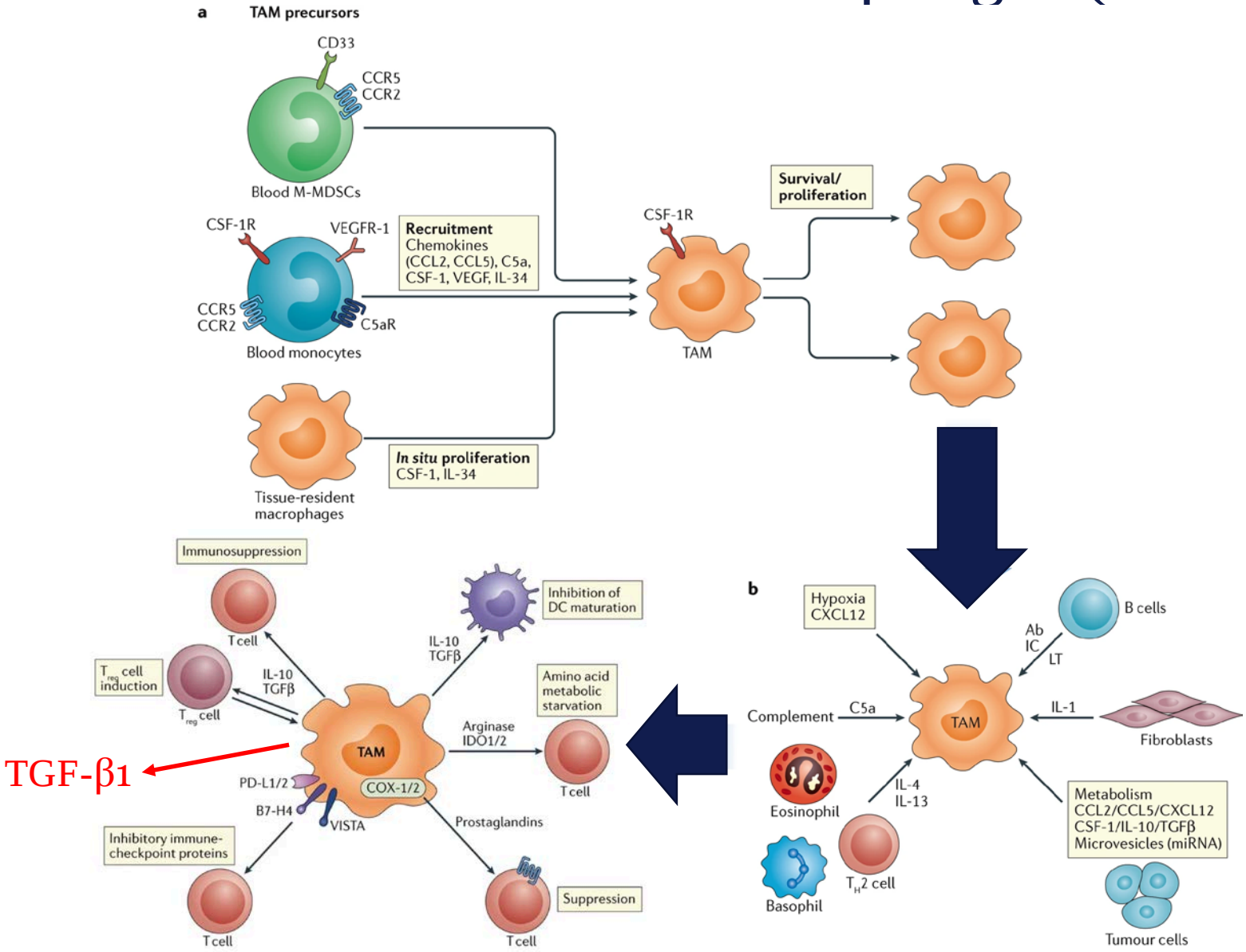
Pyruvate kinase isozyme M2 (=PKM2)

Tetramer: high PK activity - glycolysis



Dimer: nuclear factor invoved in PD-L1 upregulation

Tumor-associated macrophages (TAMs)



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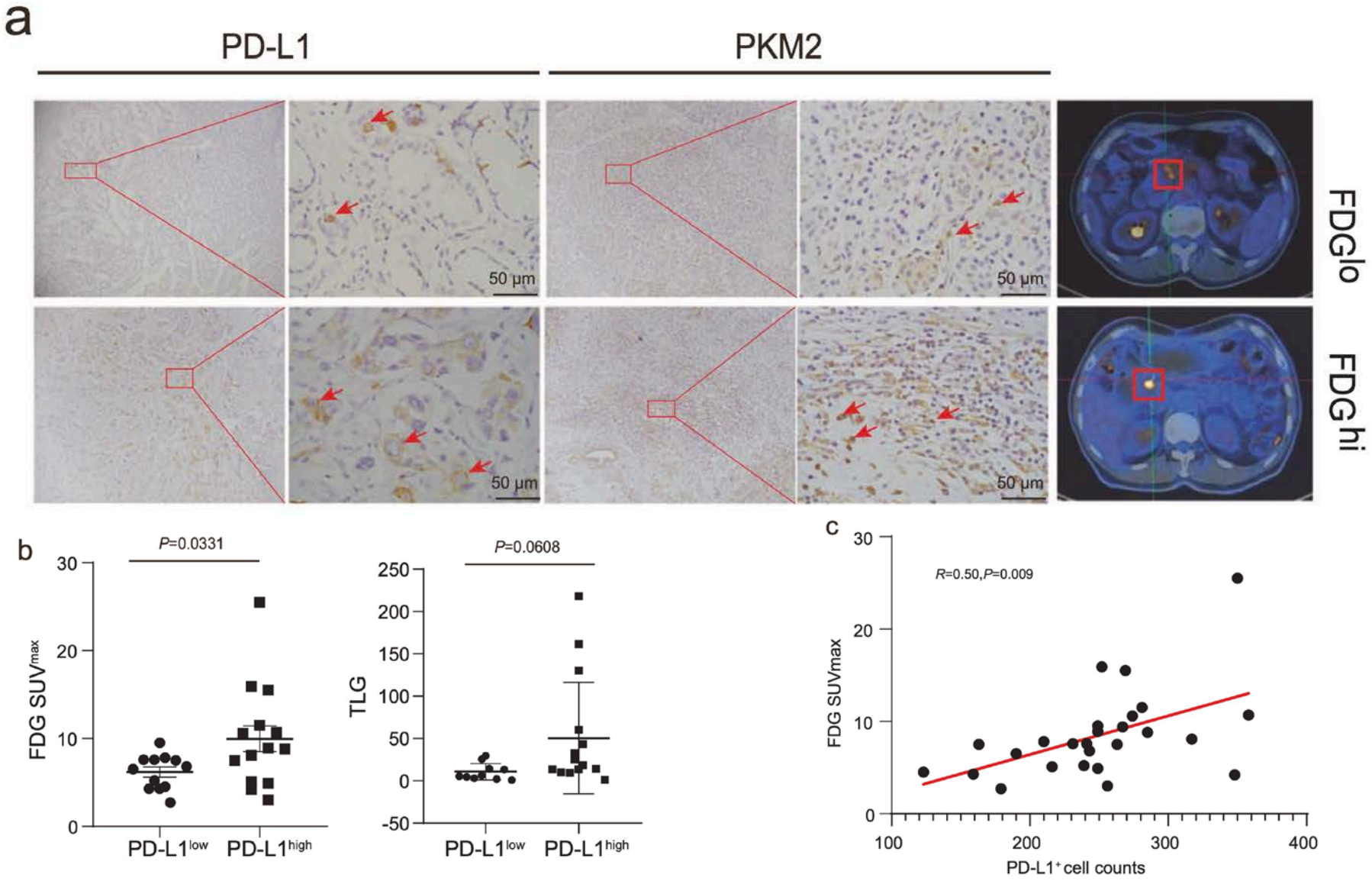
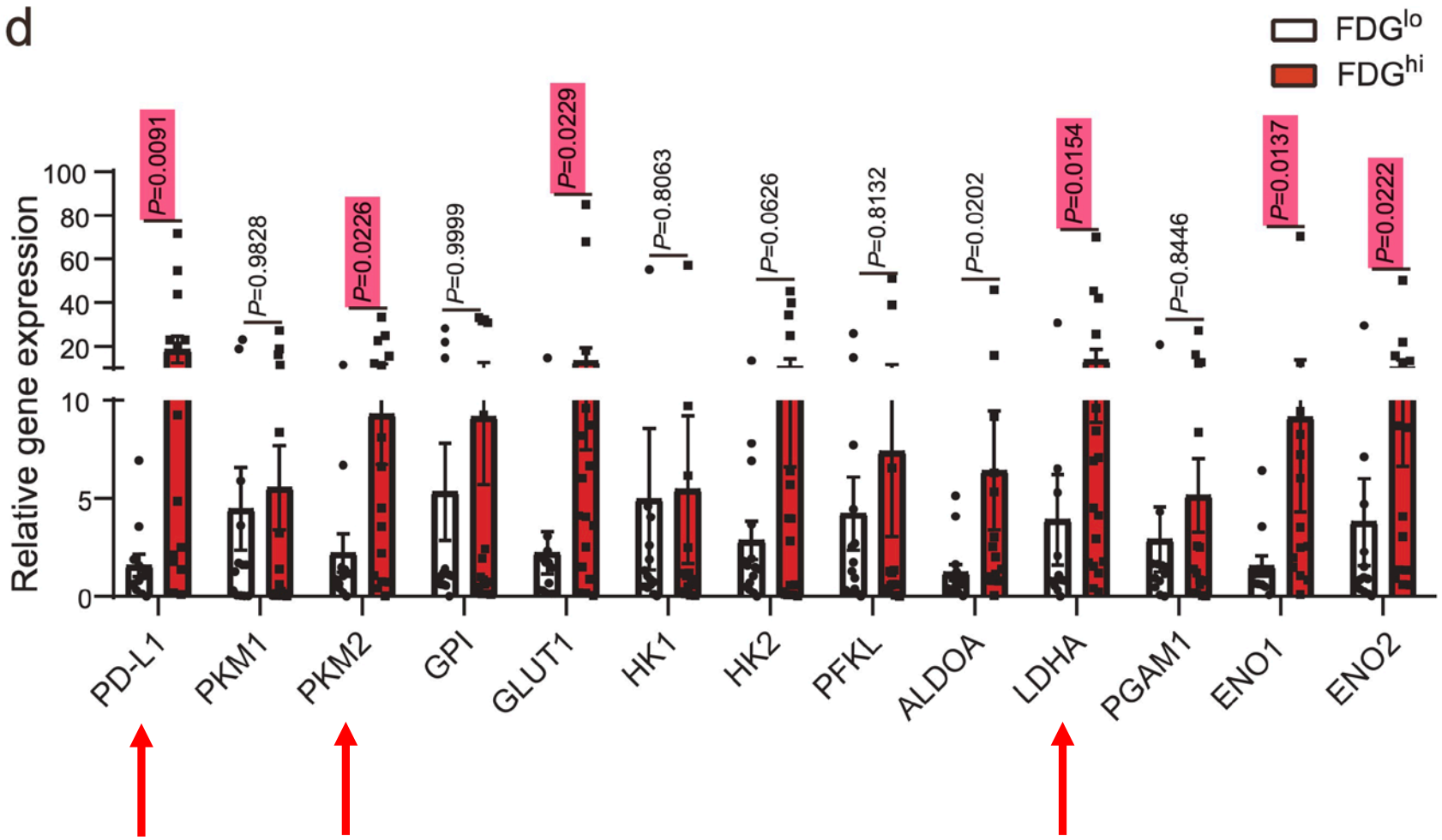
1.Is there a clinical correlation between PD-L1 and PKM2 expression to predict poor prognosis in patients with PDAC?

Does tumor glycolysis facilitate PD-L1 expression in PDACs?



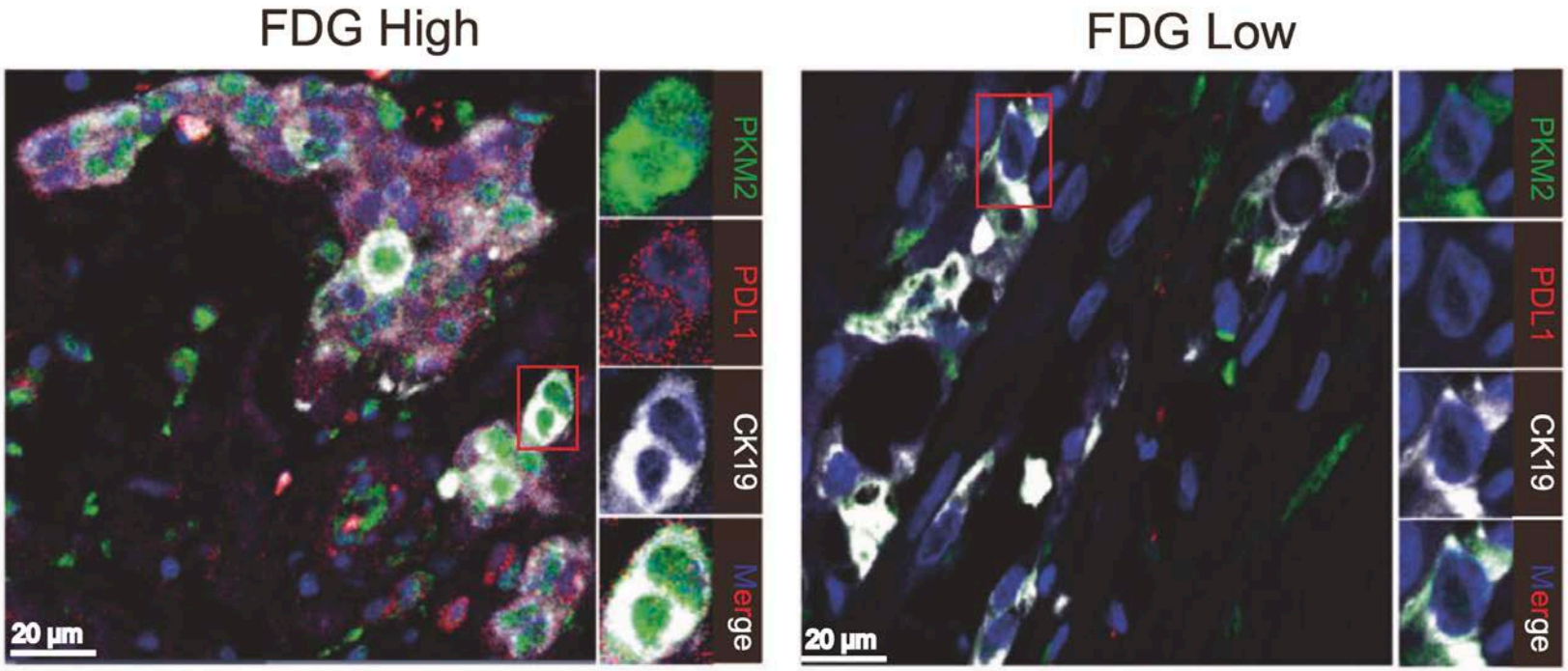
Which key glycolytic genes might be involved in the regulation of PD-L1 ?

→ qRT-PCR

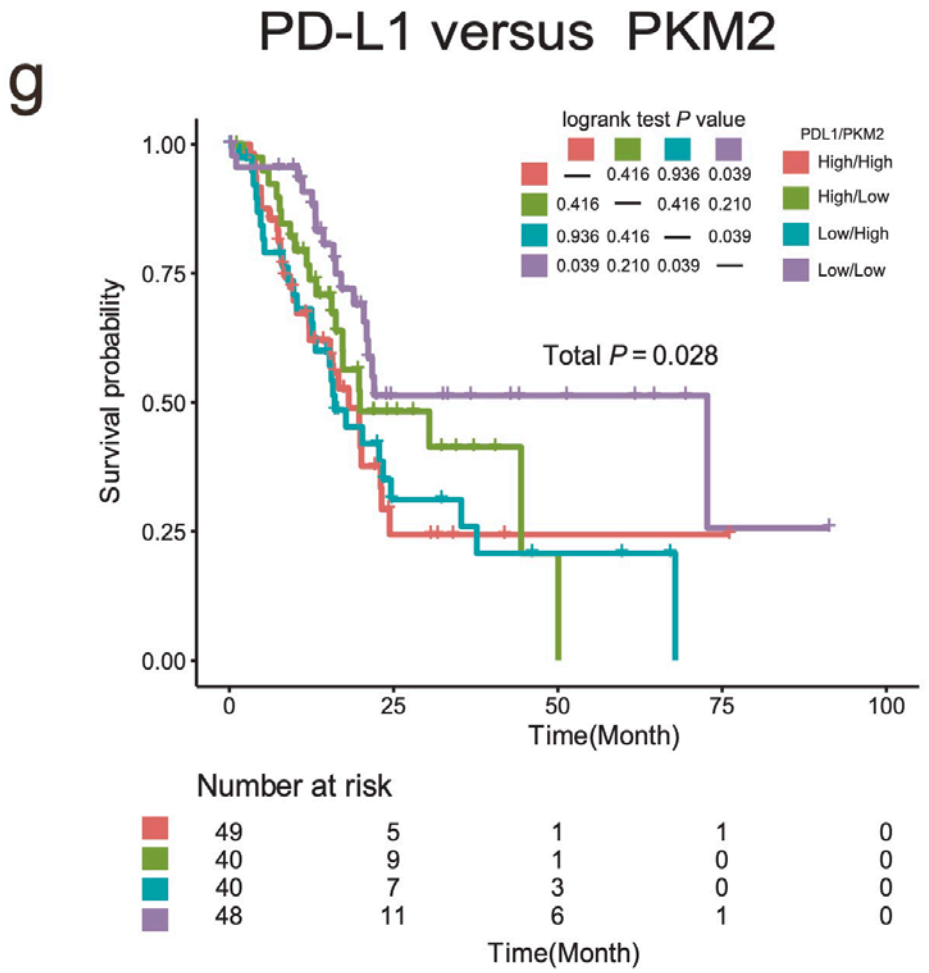


The expressions of PKM2 and PD-L1 were higher in „FDGhigh“ patients than „FDGlow“ patients.

f



Overall survival of patients with PDAC based on PKM2 and PD-L1 expression



PD-L1hi + PKM2hi VS.

PD- L1lo + PKM2lo

P = 0.039;

HR, 3.019;

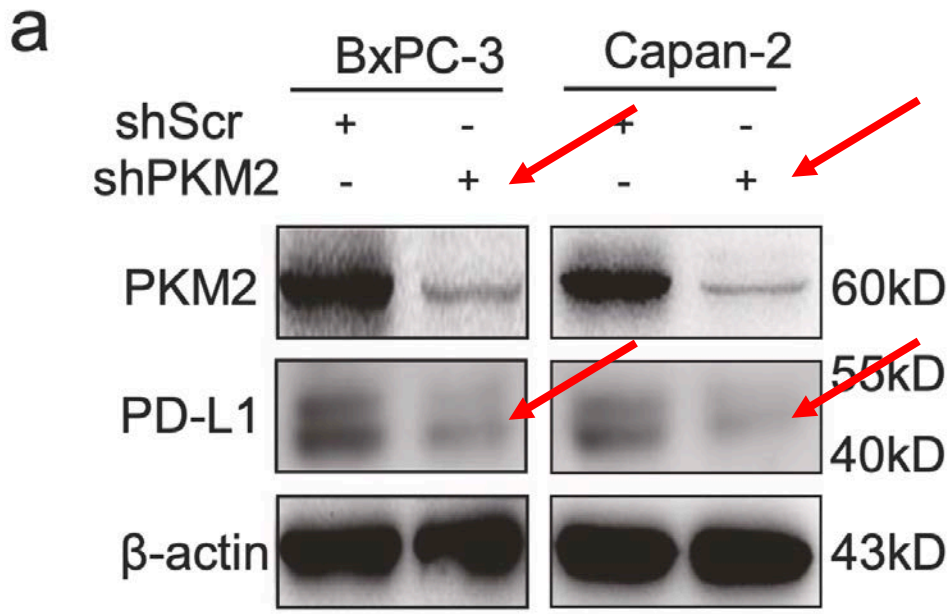
95% CI, 1.348–1.775

1.Is there a clinical correlation between PD-L1 and PKM2 expression to predict poor prognosis in patients with PDAC?

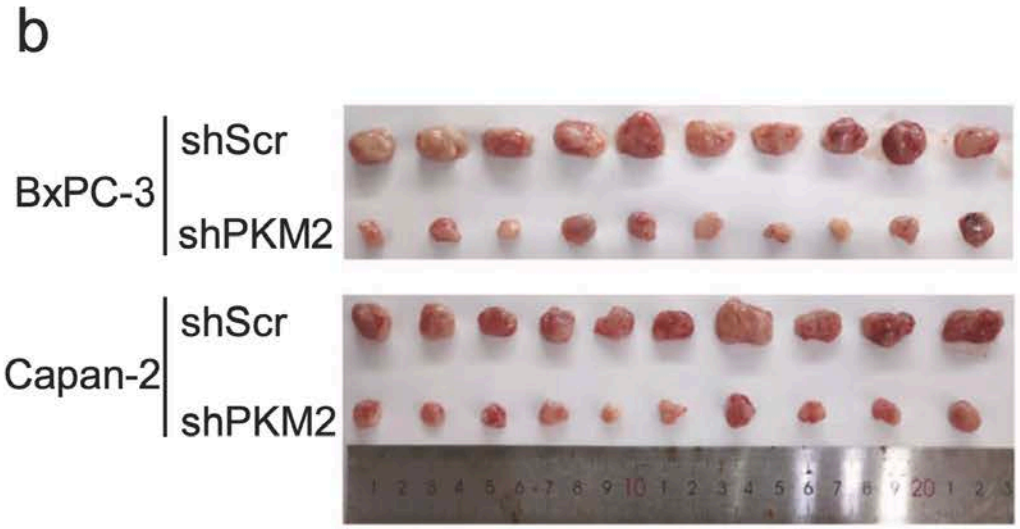
→PD-L1 is associated with high glycolysis activity and its combination with PKM2 predicts a worse prognosis in PDAC

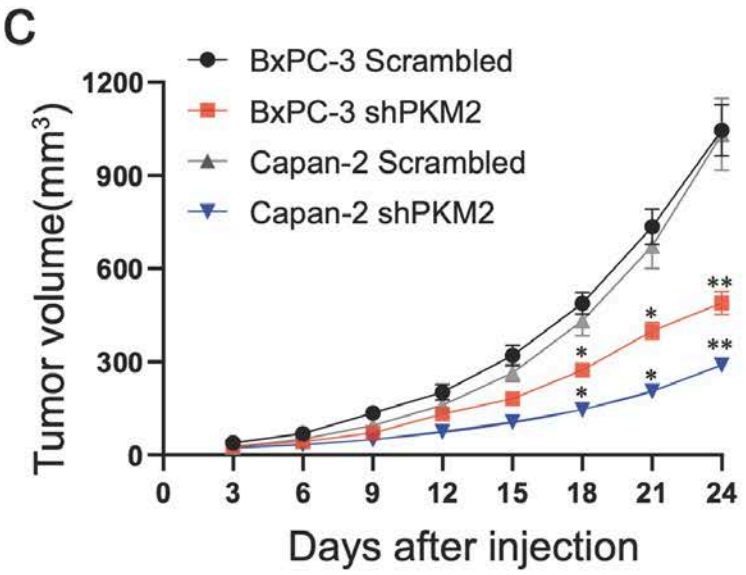
2.Does PKM2 knockdown decrease PD-L1 expression and hence induce antitumor immunity?

PKM2 knockdown decreases PD-L1 expression



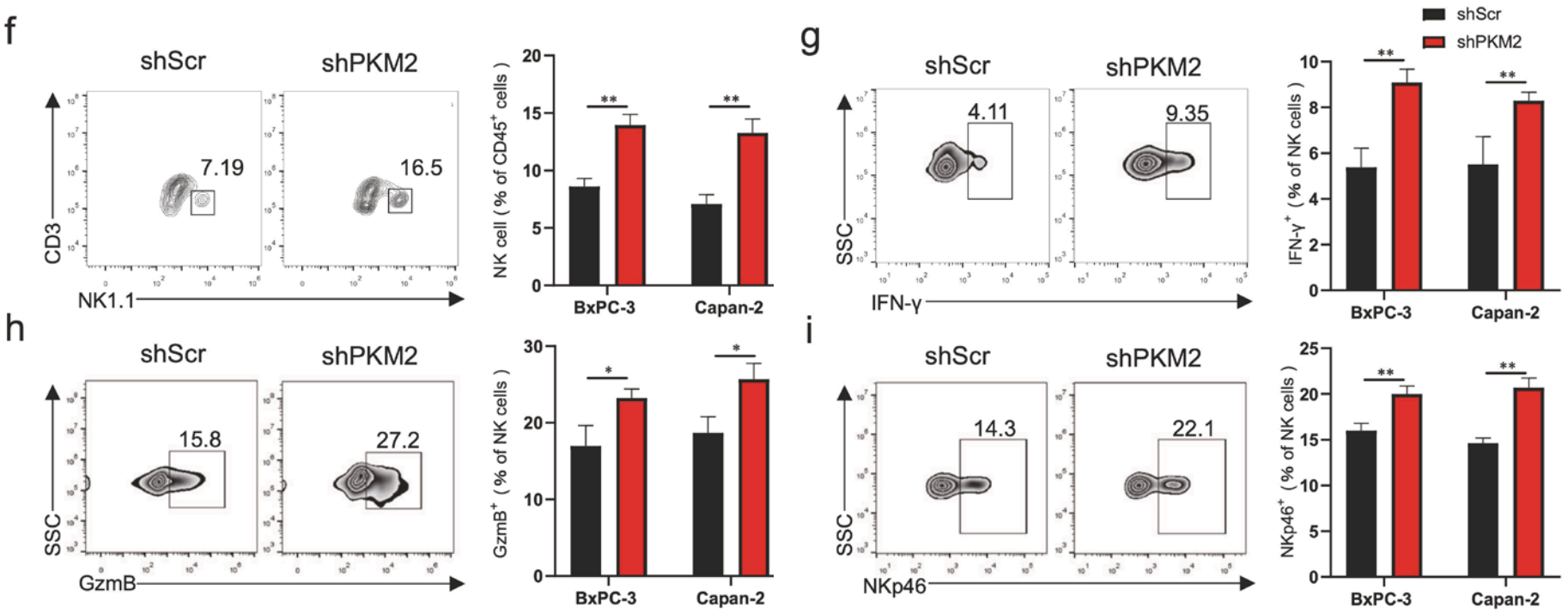
PKM2 knockdown decreases PD-L1 expression





Does PKM2 induce changes in tumor-infiltrating immune cells (in nude mice with PDAC) ?

NKs only

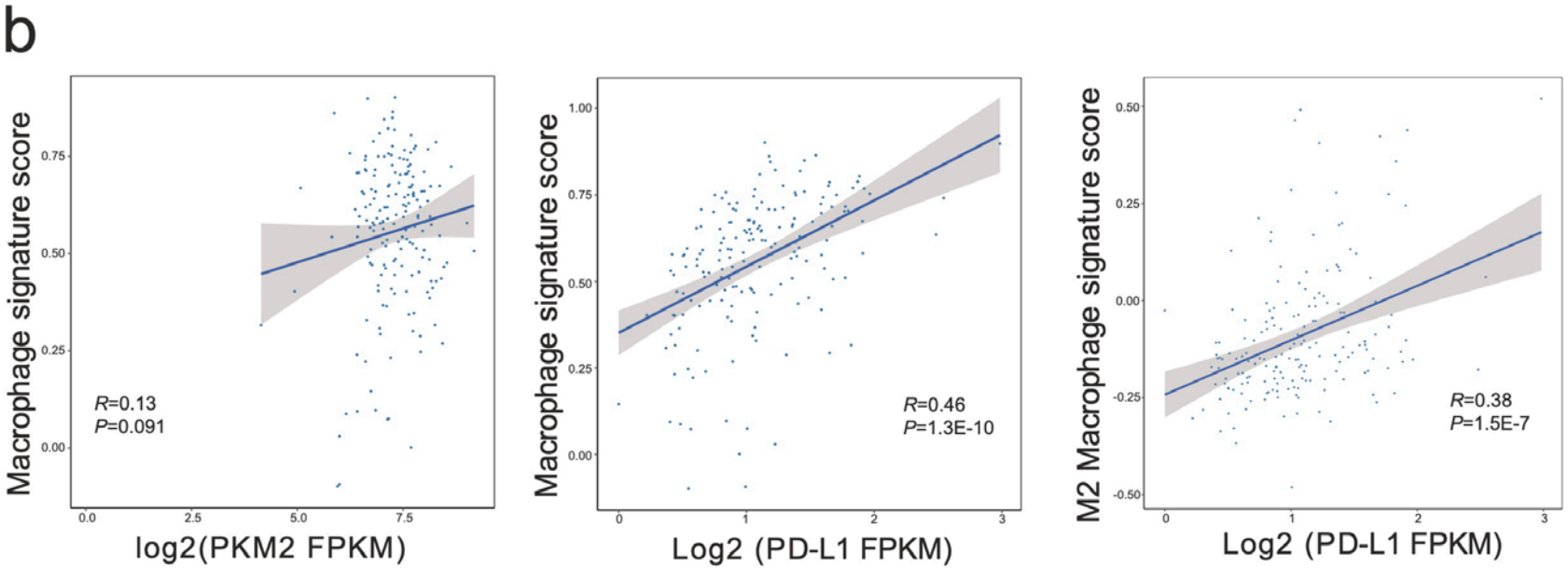


2.Does PKM2 knockdown decrease PD-L1 expression and hence induce antitumor immunity?

→The results suggest that PKM2 knockdown decreases the expression of PD- L1 and might elicit potent antitumor immunity by activating NK cells

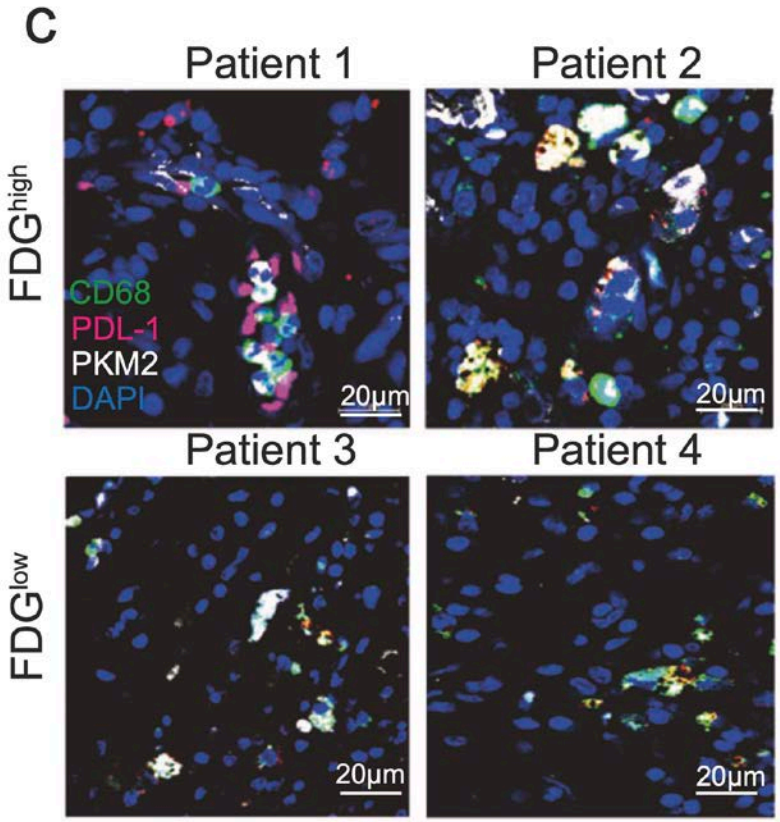
3.What is required for PKM2 mediated (and TAM- induced) PD-L1 expression in PDAC?

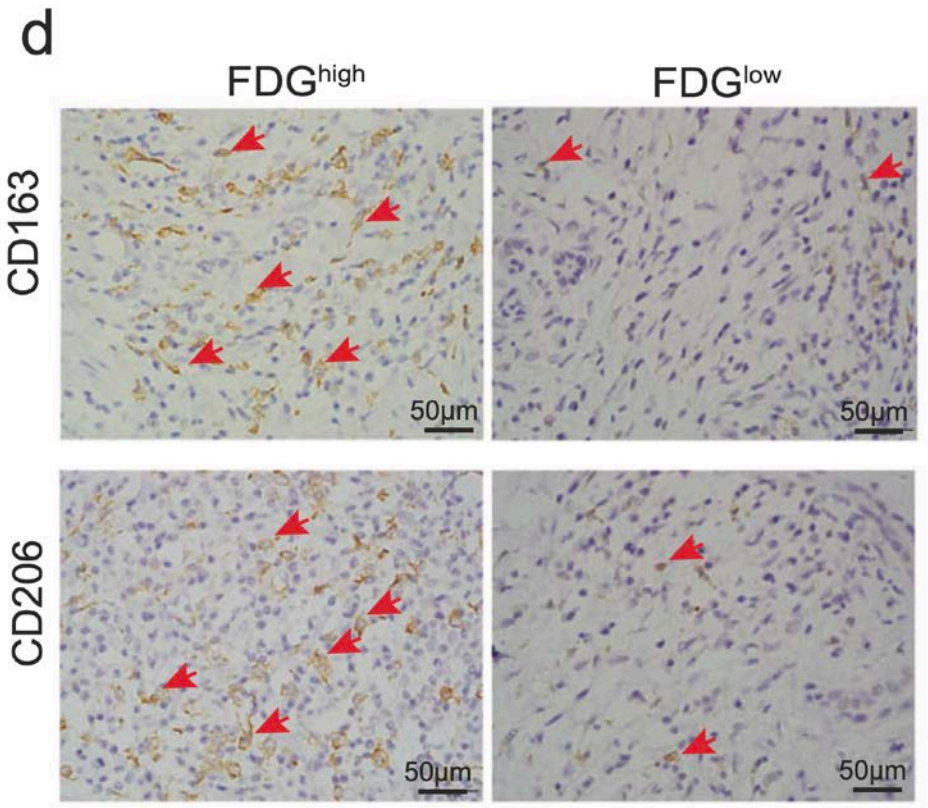
Is there a correlation between PD-L1, PKM2 and TAMs?



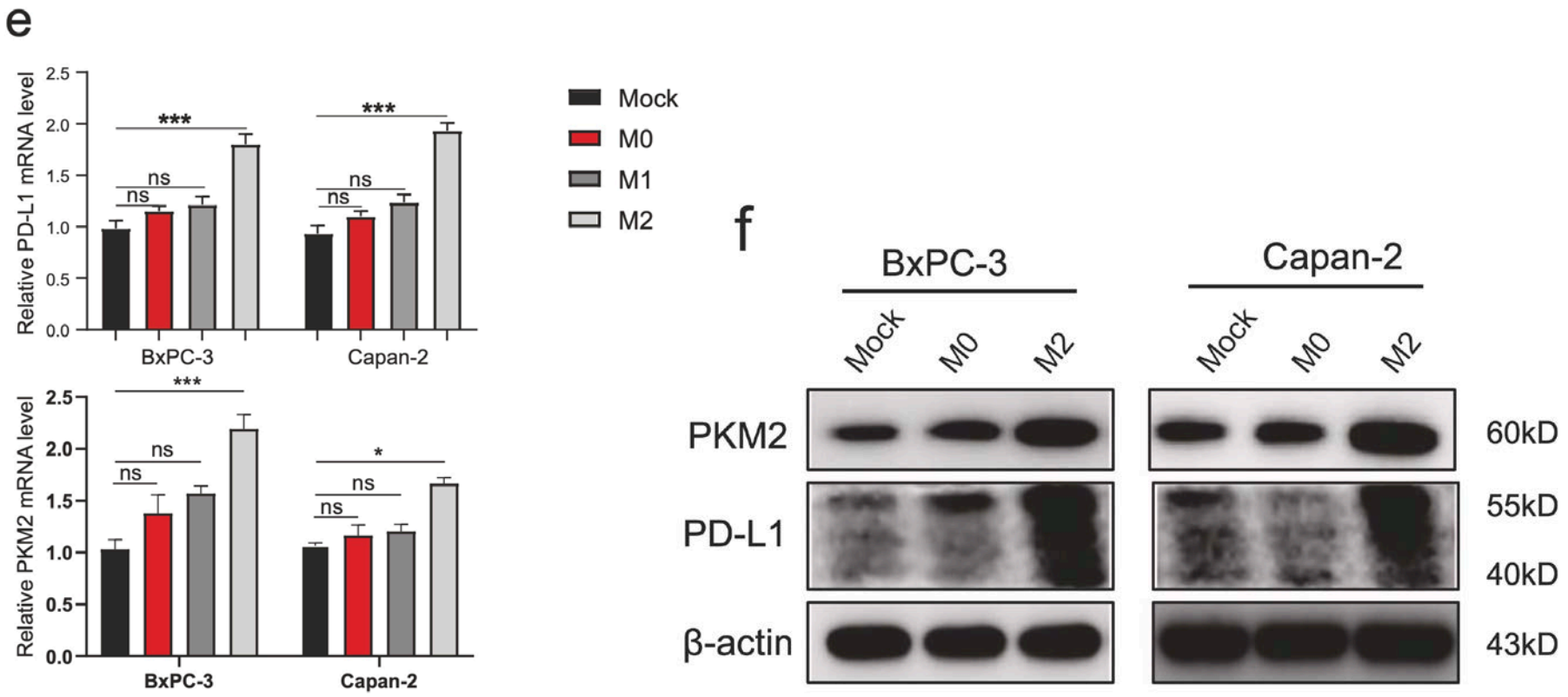
PD-L1, R = 0.38, P < 0.0001; PKM2, R = 0.26, P < 0.0001

Is there a correlation between PD-L1, PKM2 and TAMs?



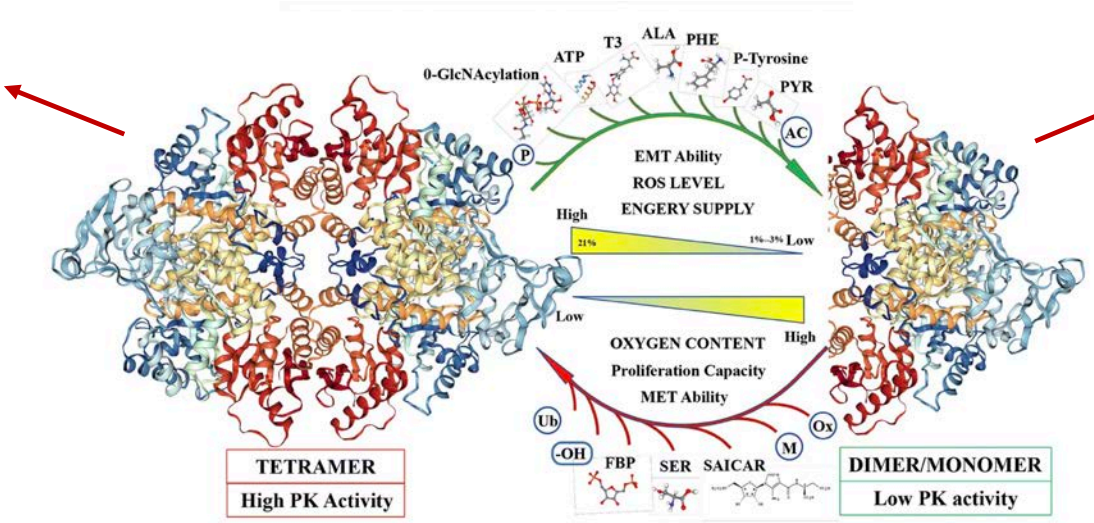


Macrophage-mediated tumor growth and PKM2-induced PD-L1 dysregulation

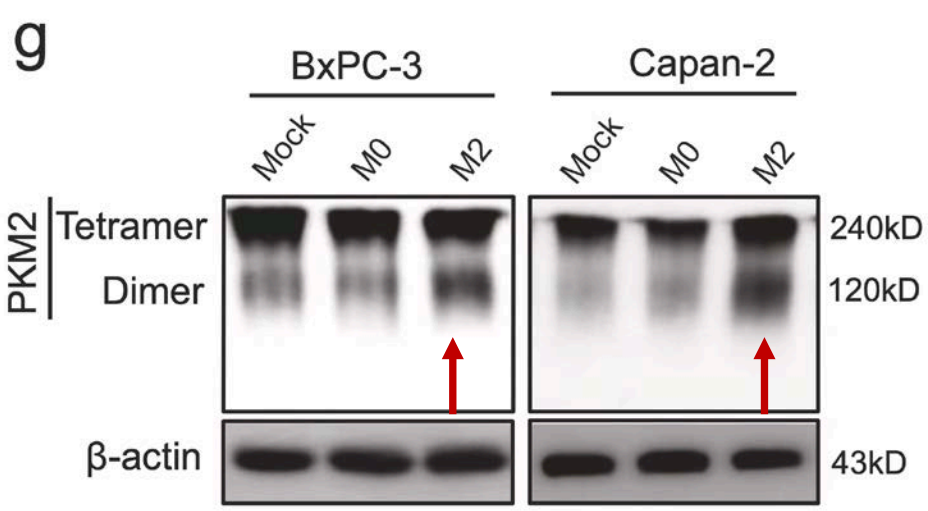


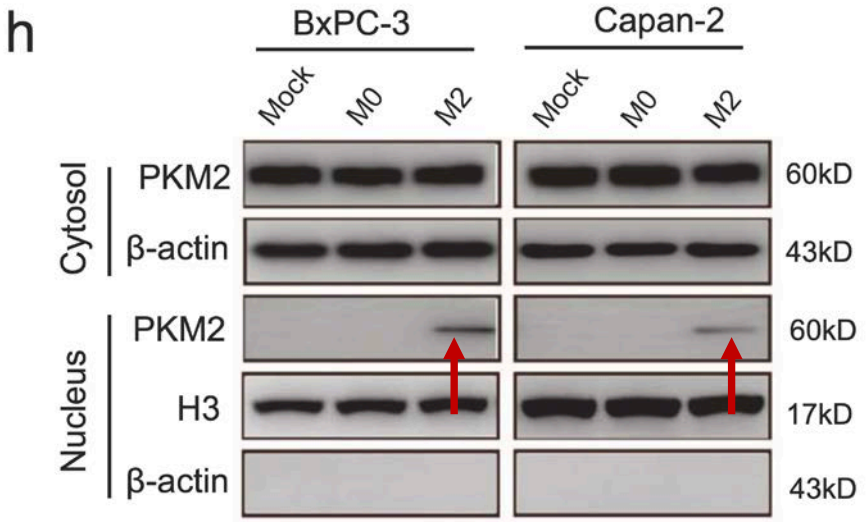
How can macrophages mediate PKM2-induced PD-L1 dysregulation?

Tetramer: high PK activity - glycolysis

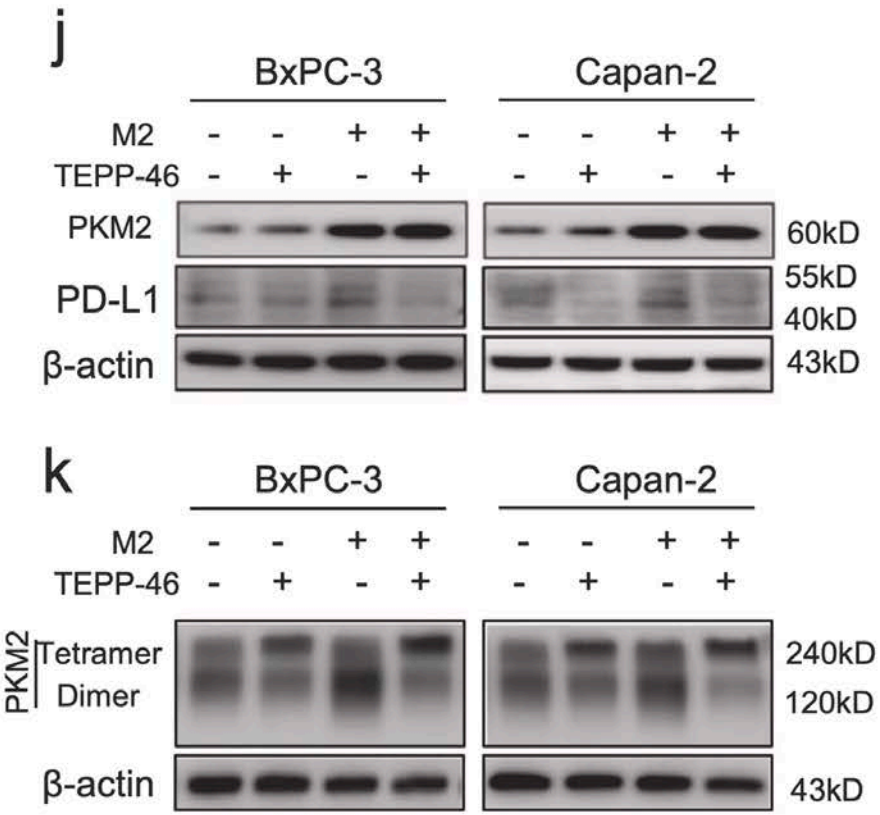


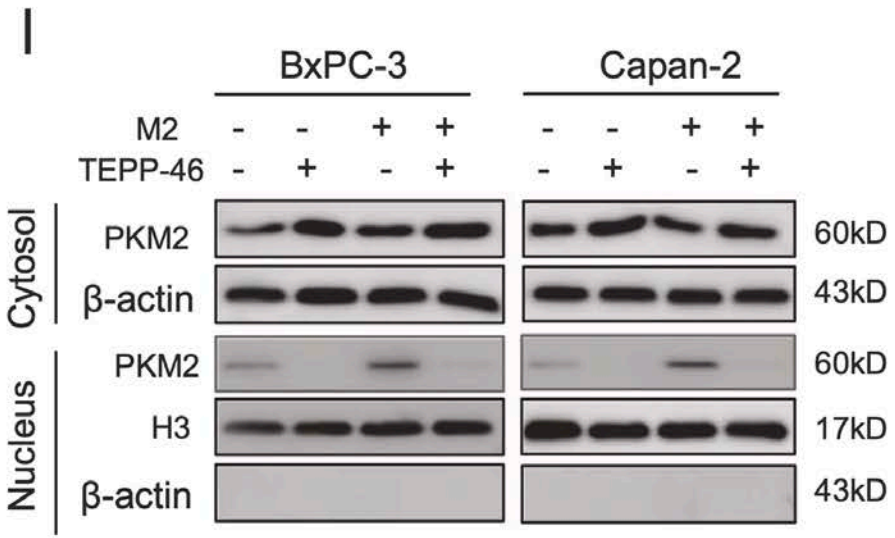
Dimer: nuclear factor invoved in PD-L1 upregulation





How can macrophages mediate PKM2-induced PD-L1 dysregulation?



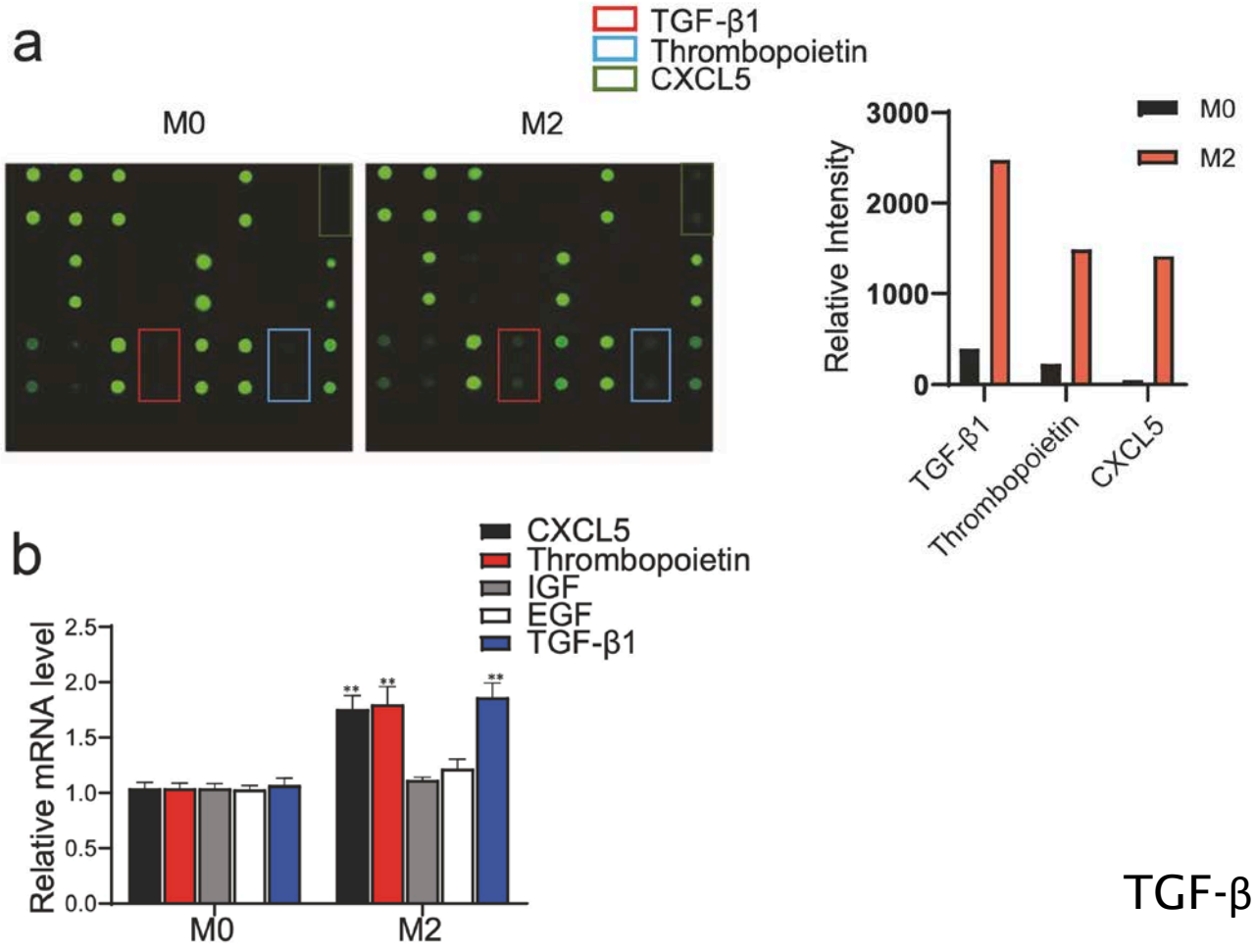


3.What is required for PKM2 mediated (and TAM- induced) PD-L1 expression in PDAC?

→TAMs may modulate PD-L1 expression by increasing PKM2 nuclear localization.

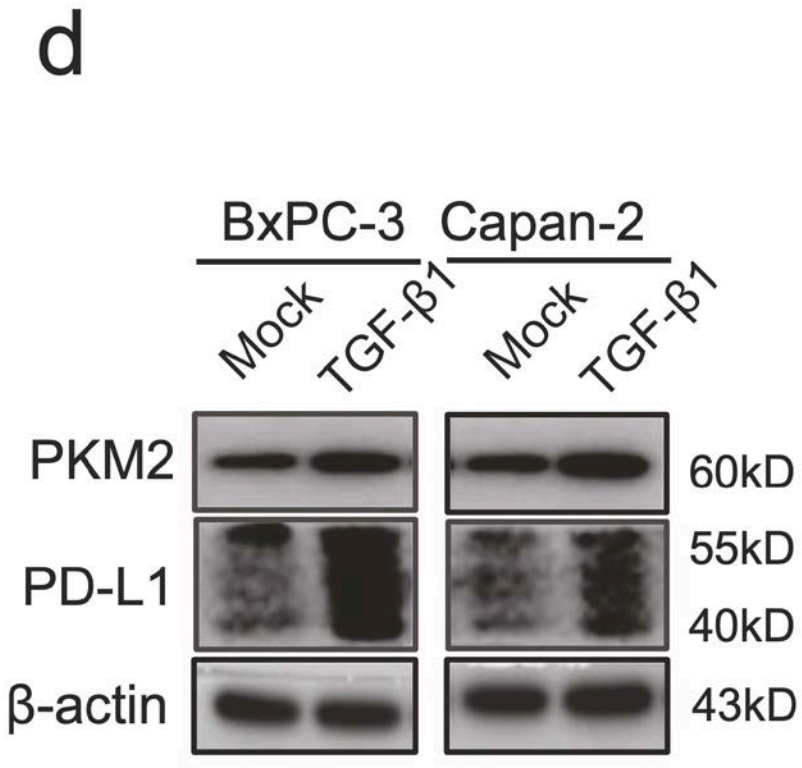
4.Which TAM-derived factor induces PD-L1 expression via PKM2 nuclear translocation in PDAC cells?

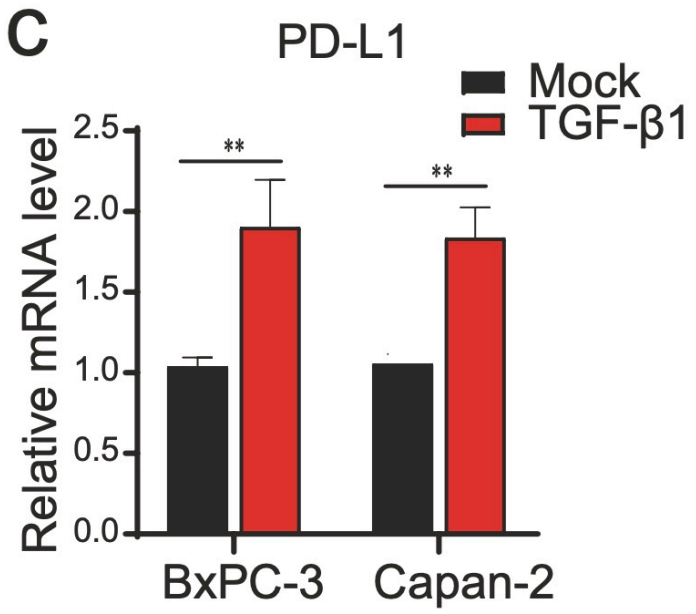
TAM-secreted factors...



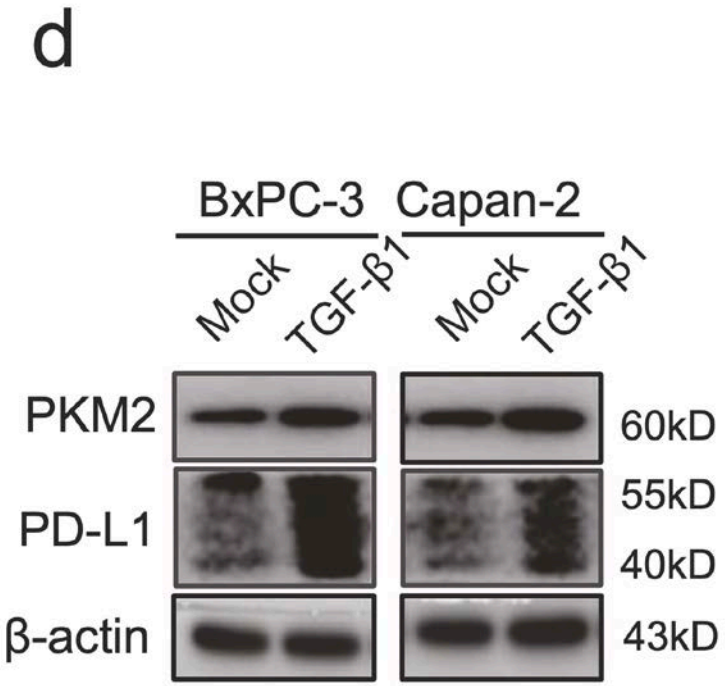
TGF-β1 → PD-L1?

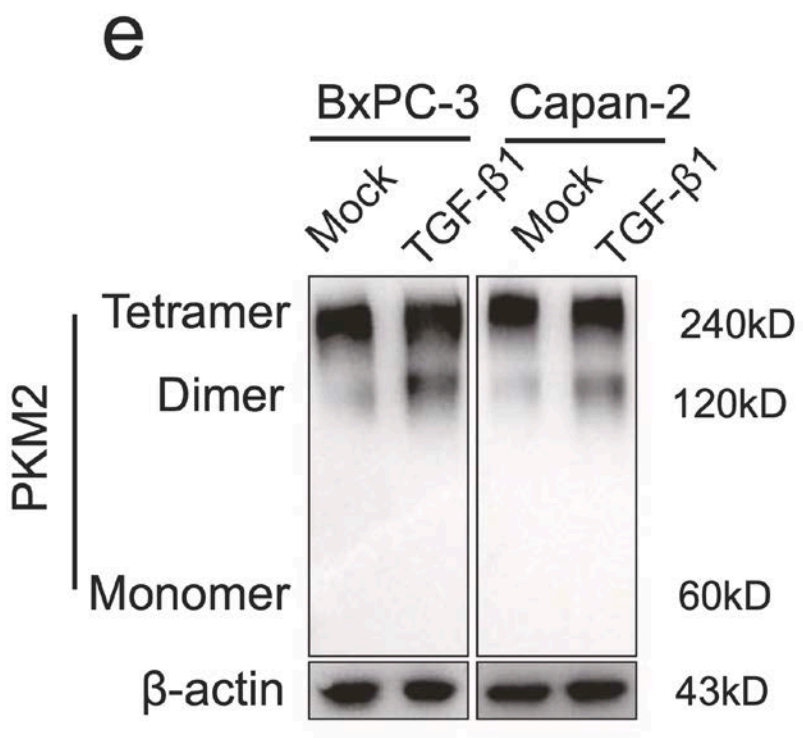
PD-L1 expression mediated by TGF-β1 ?





Does PKM2 contribute to PD-L1 upregulation via the TGF-β1 pathway?





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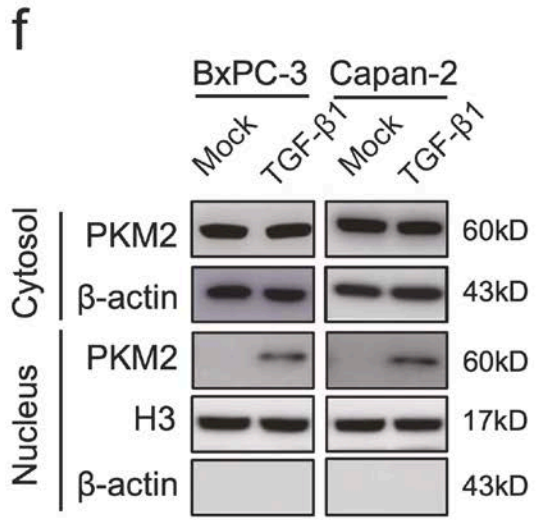
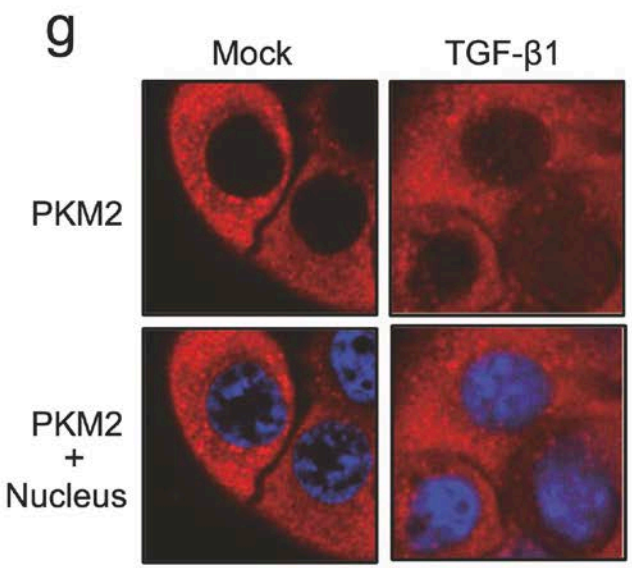
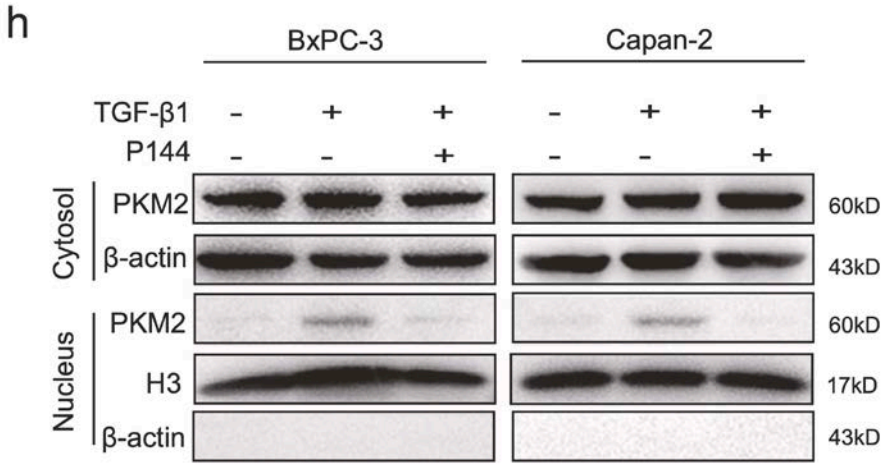






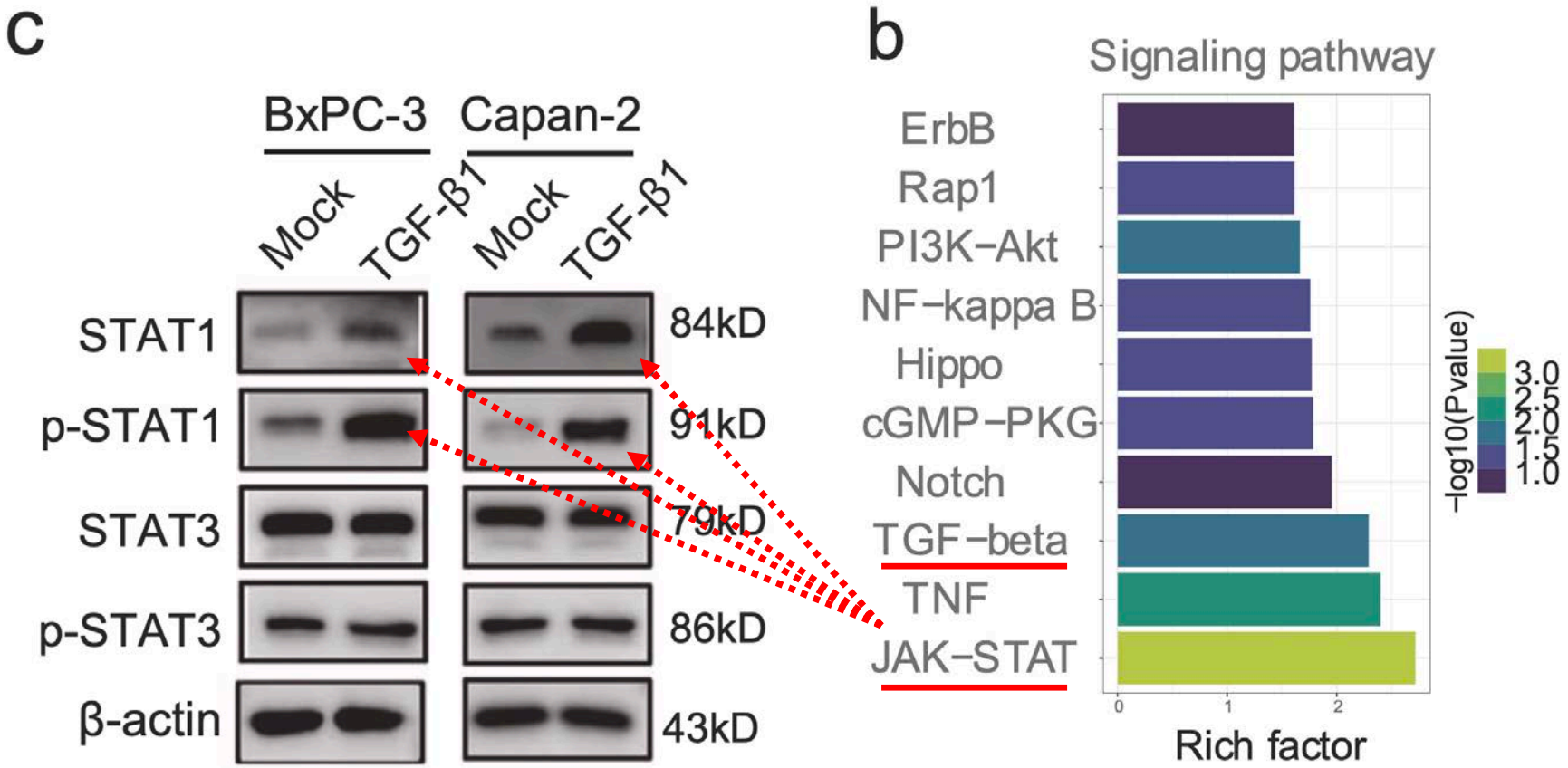
→ PKM2 expression in PDAC cells induced by M2 macrophages was eliminated when the cells were treated with TGF-β1 inhibitor P144

4.Which TAM-derived factor induces PD-L1 expression via PKM2 nuclear translocation in PDAC cells?

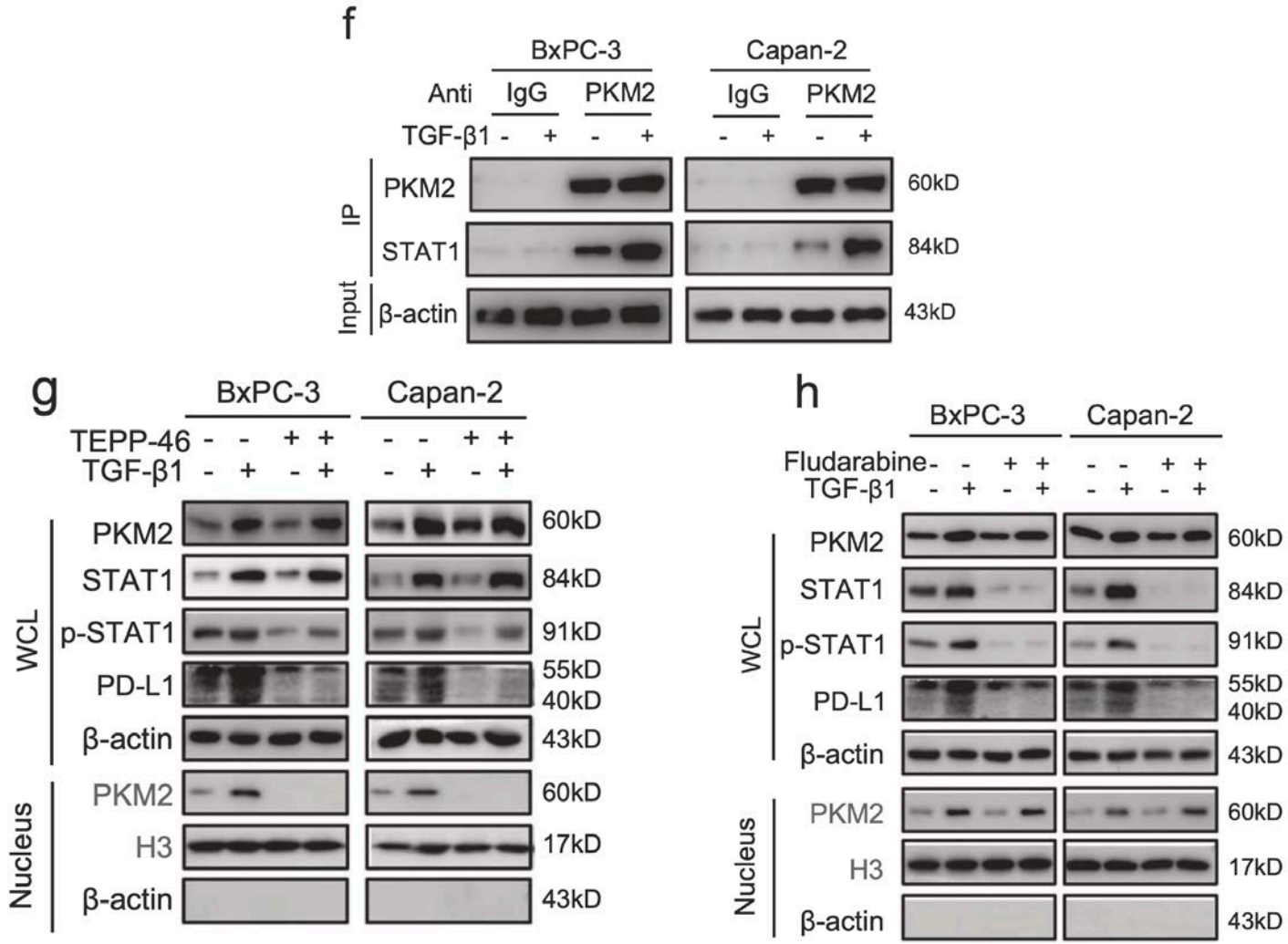
→ TGF-β1 is a major inflammatory factor secreted by M2 macrophages that upregulates PD-L1 expression by the nuclear translocation of PKM2

5.Is nuclear translocation of PKM2 and phosphorylation of STAT1 involved in TGF-β1-induced PD-L1 upregulation?

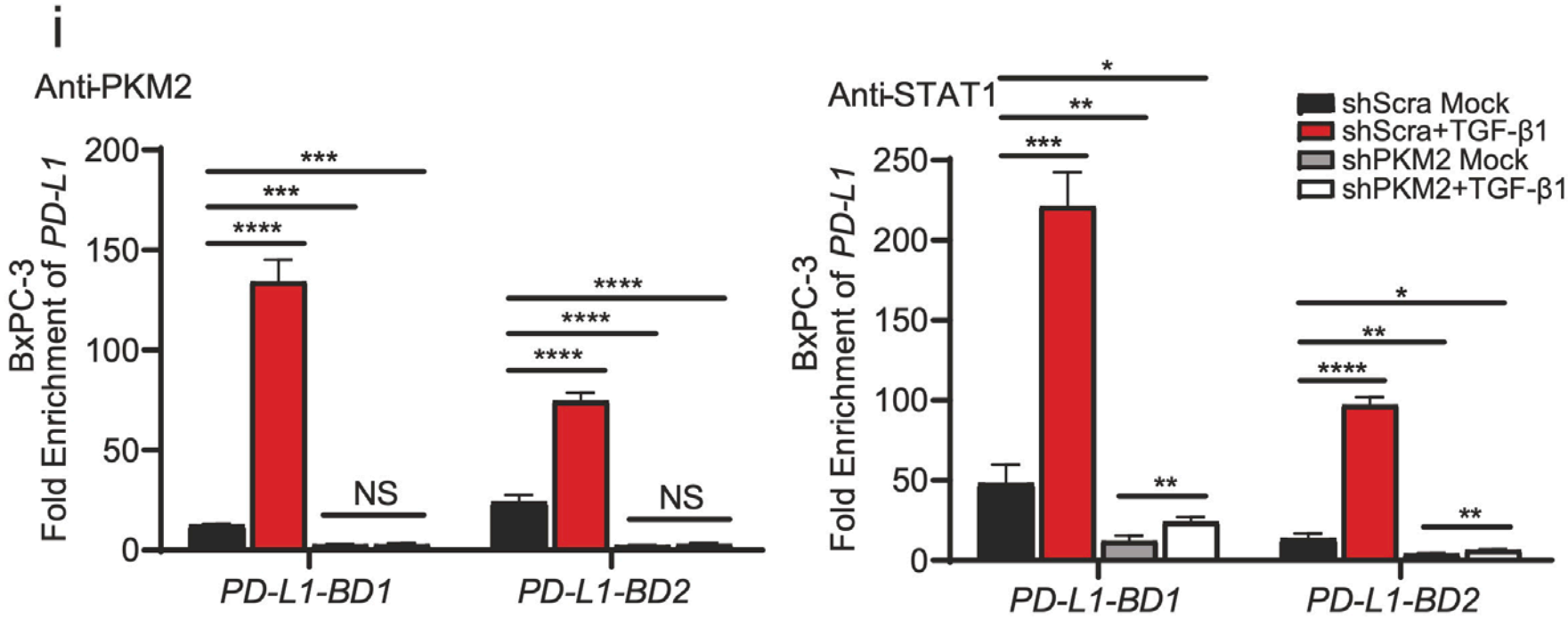
Which mechanisms are involved in the TGF-β1-dependent expression of PD-L1 in PDAC?



What is the relationship between PKM2 and STAT1 in TGF-β1-induced upregulation of PD-L1



Do PKM2 and p-STAT1 promote the transcription of PD-L1?

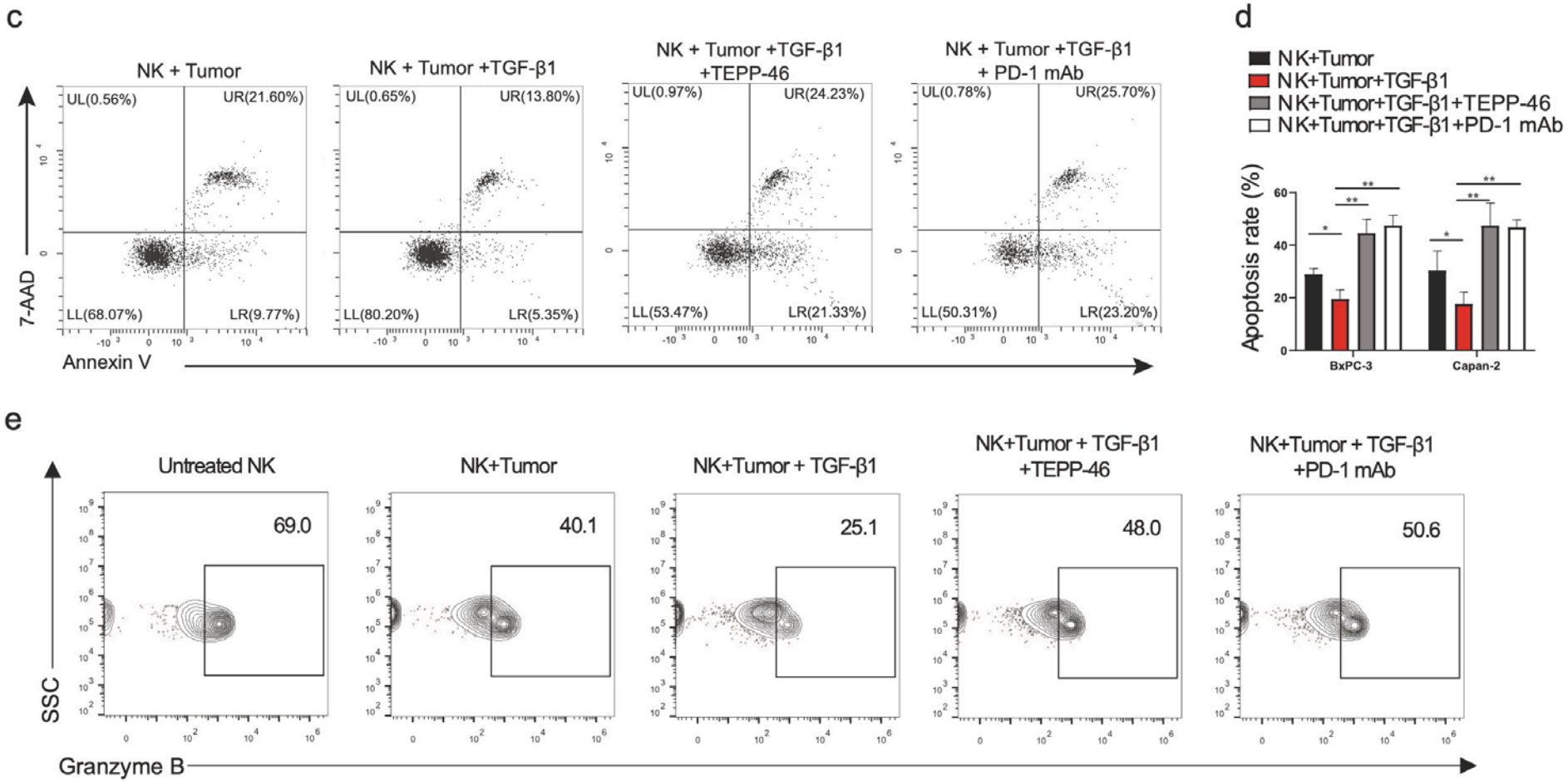


5.Is nuclear translocation of PKM2 and phosphorylation of STAT1 involved in TGF-β1-induced PD-L1 upregulation?

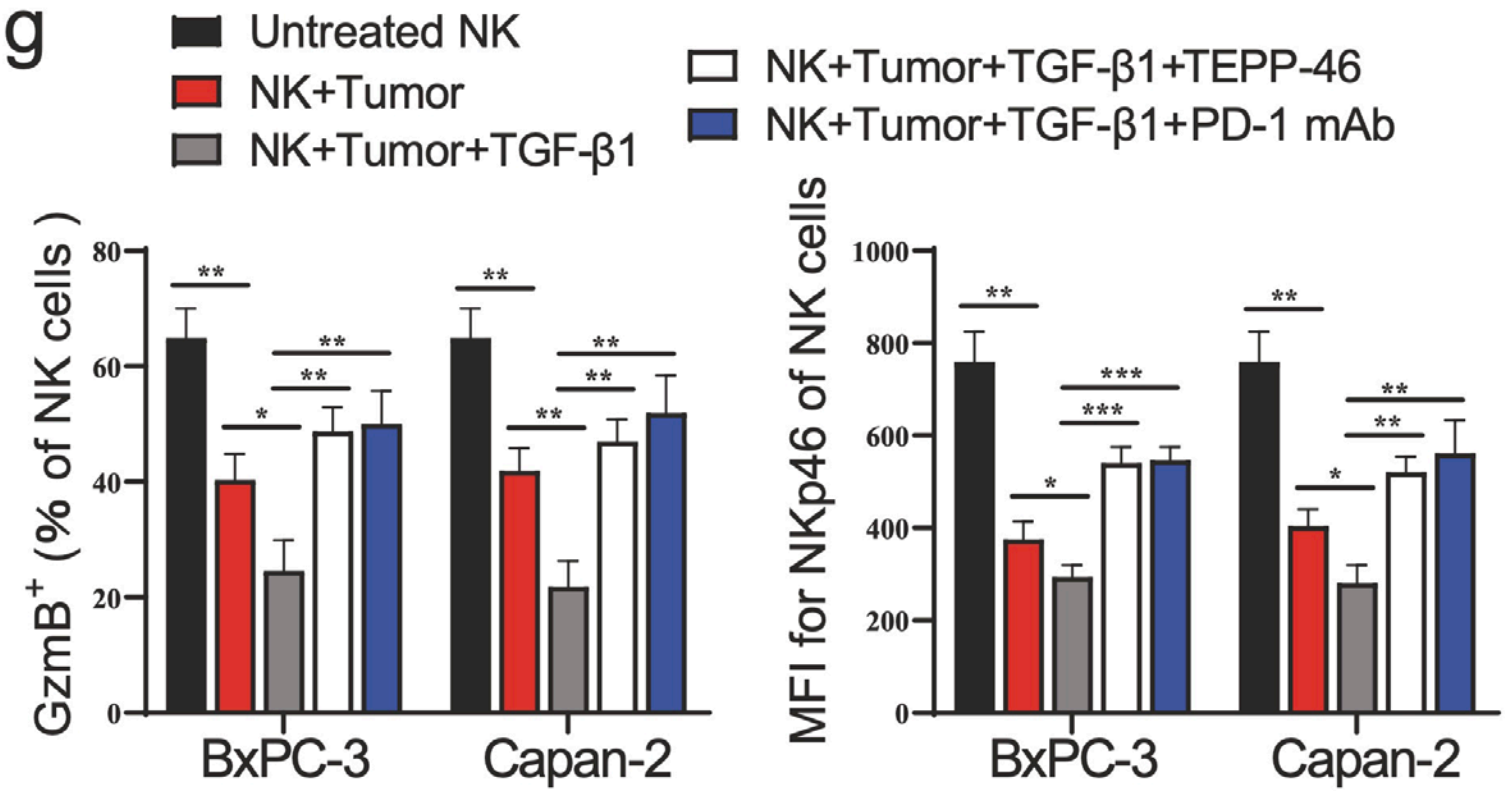
→ Nuclear translocation of PKM2 and phosphorylation of STAT1 are involved in TGF-β1-induced PD-L1 upregulation

6.How does PKM2-mediated PD-L1 upregulation effect antitumor immunity of NK cells?

Could targeting PKM2 and PD-L1 enhance the antitumor immunity of NK cells?



Could targeting PKM2 and PD-L1 enhance the antitumor immunity of NK cells?



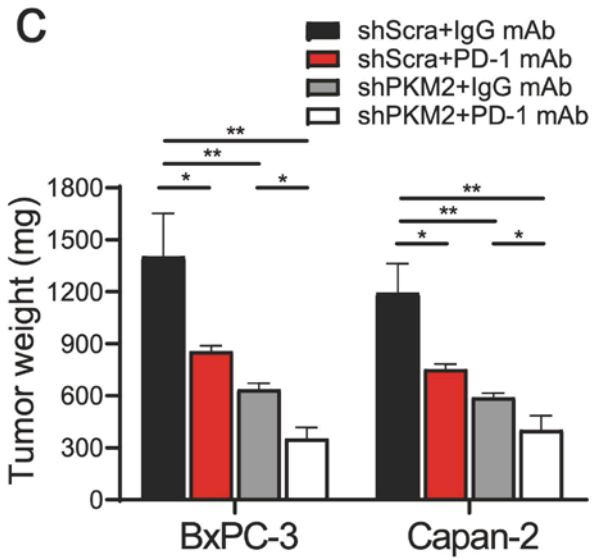
*P < 0.05,**P < 0.01,***P < 0.001

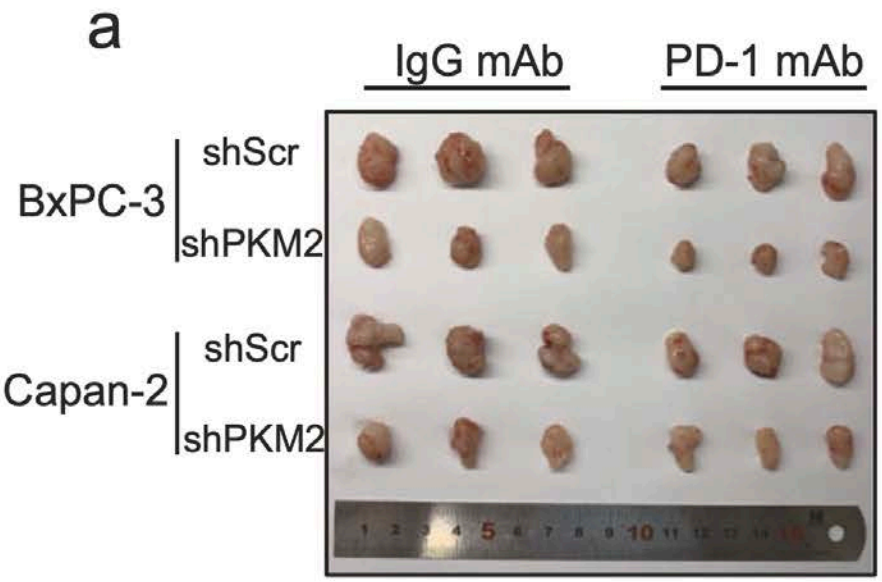
6.How does PKM2-mediated PD-L1 upregulation effect antitumor immunity of NK cells?

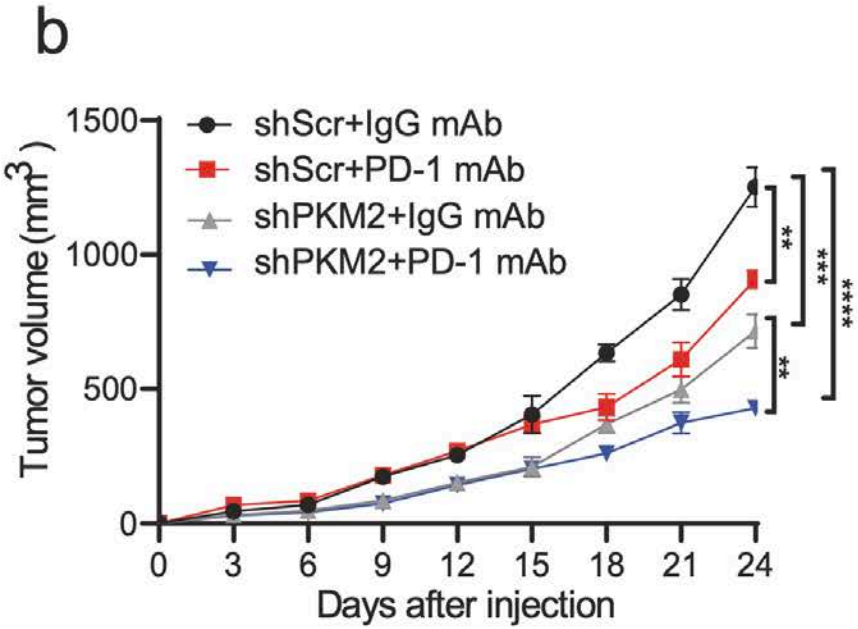
→NK cell-mediated killing of PDAC cells was enhanced following the blockade of PKM2 nuclear translocation or PD-1/PD-L1 interaction in vitro.

7.Does PKM2 deficiency enhance the antitumor effect of Anti-PD-1 blockade in PDAC (in mice with high infiltration of activated NK cells)?

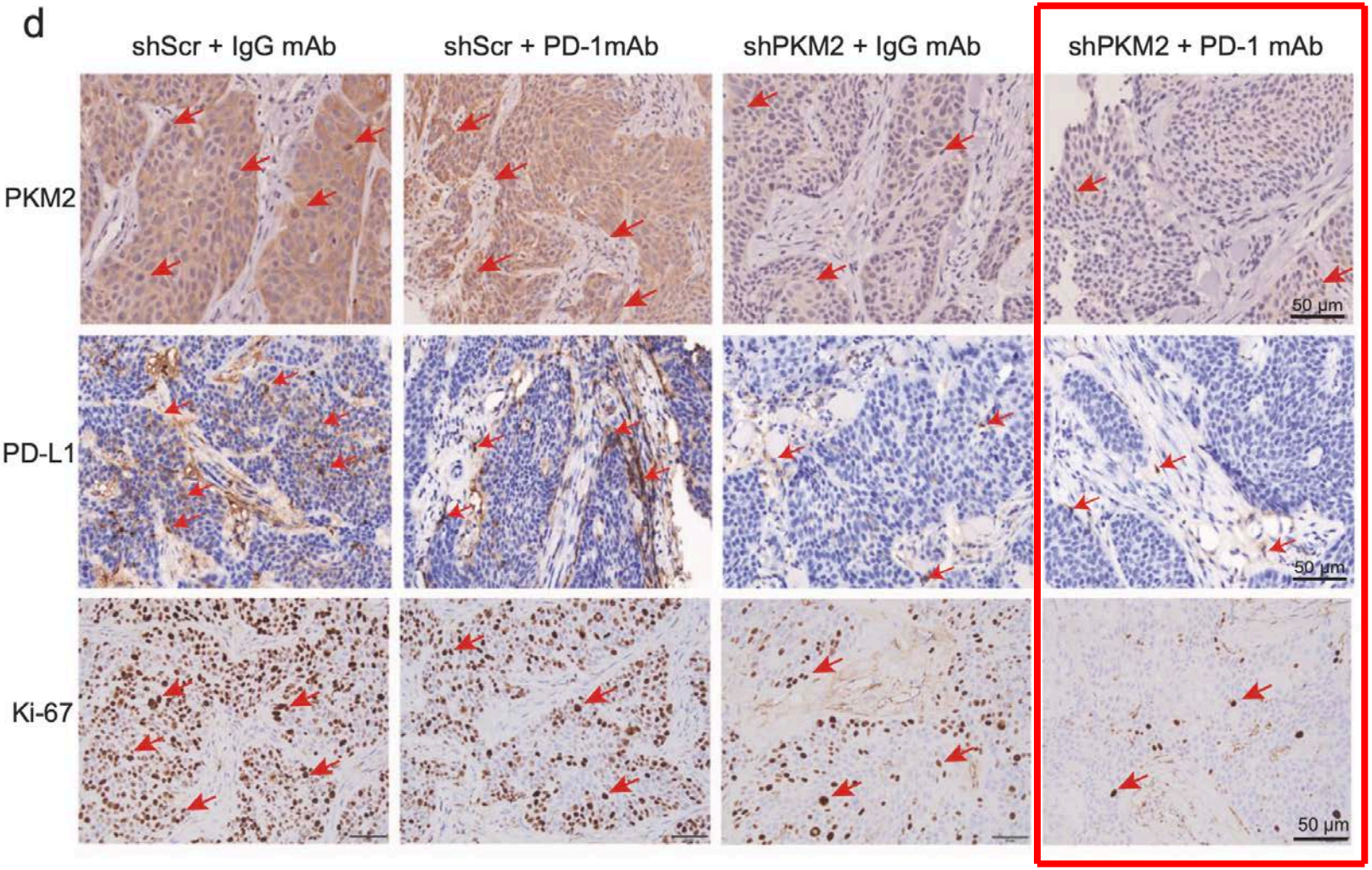
Does PKM2 deficiency enhance the antitumor effect of Anti-PD-1 blockade?

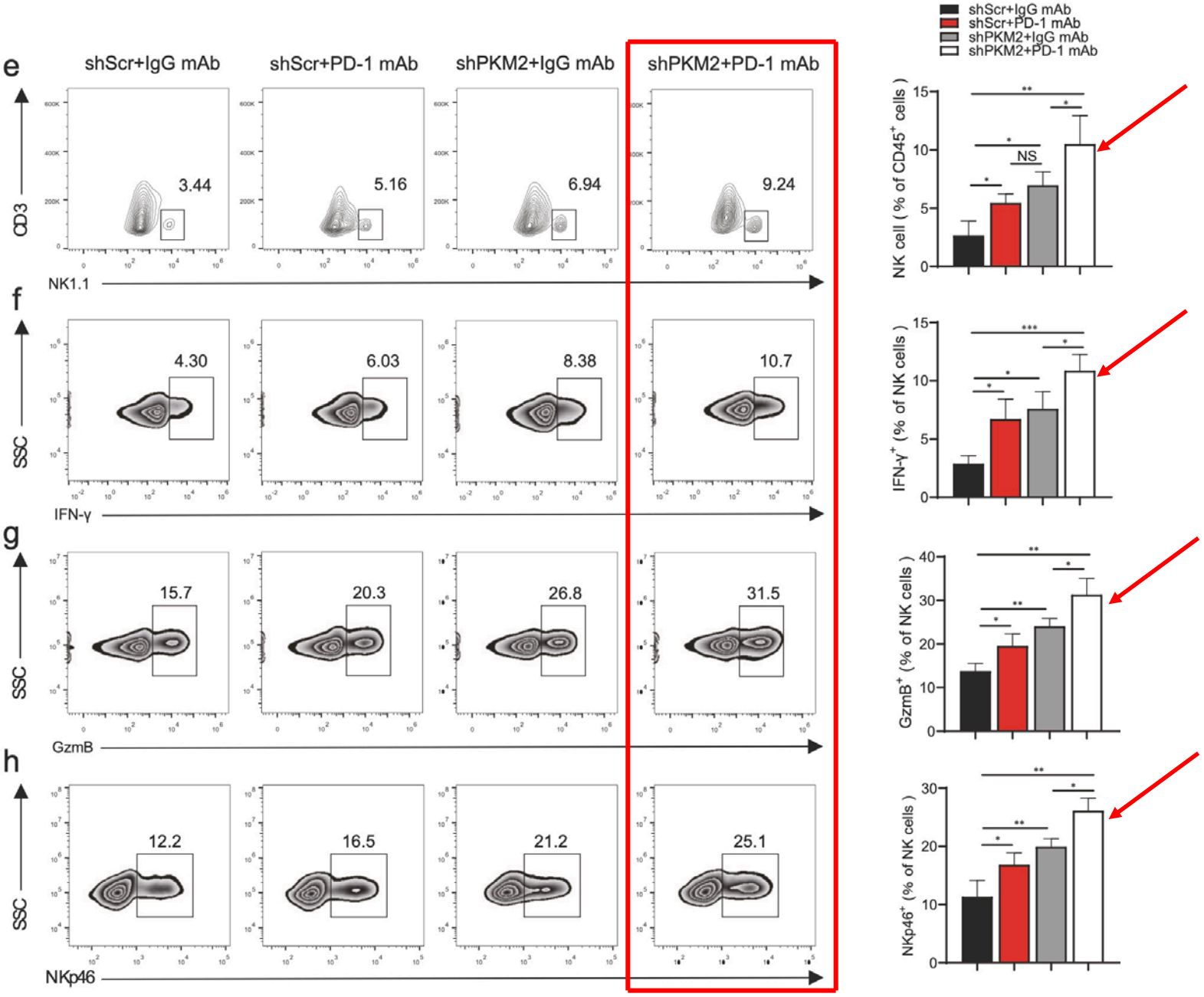






Does PKM2 deficiency enhance the antitumor effect of Anti-PD-1 blockade?




shScr+IgG mAb
shScr+PD-1 mAb
shPKM2+IgG mAb
shPKM2+PD-1 mAb
e
CD3
NK1.1
3.44
5.16
6.94
9.24
f
SSC
IFN-γ
4.30
6.03
8.38
10.7
g
SSC
GzmB
15.7
20.3
26.8
31.5
h
SSC
NKp46
12.2
16.5
21.2
25.1
NK cell (% of CD45+ cells)
IFN-γ+ (% of NK cells)
GzmB+ (% of NK cells)
NKp46+ (% of NK cells)
NS

7.Does PKM2 deficiency enhance the antitumor effect of Anti-PD-1 blockade in PDAC (in mice with high infiltration of activated NK cells)?

→Yes! Synergistic antitumor effect of combined PKM2 and PD-1/PD-L1 blockade may provide a potential therapy for treating PDAC.

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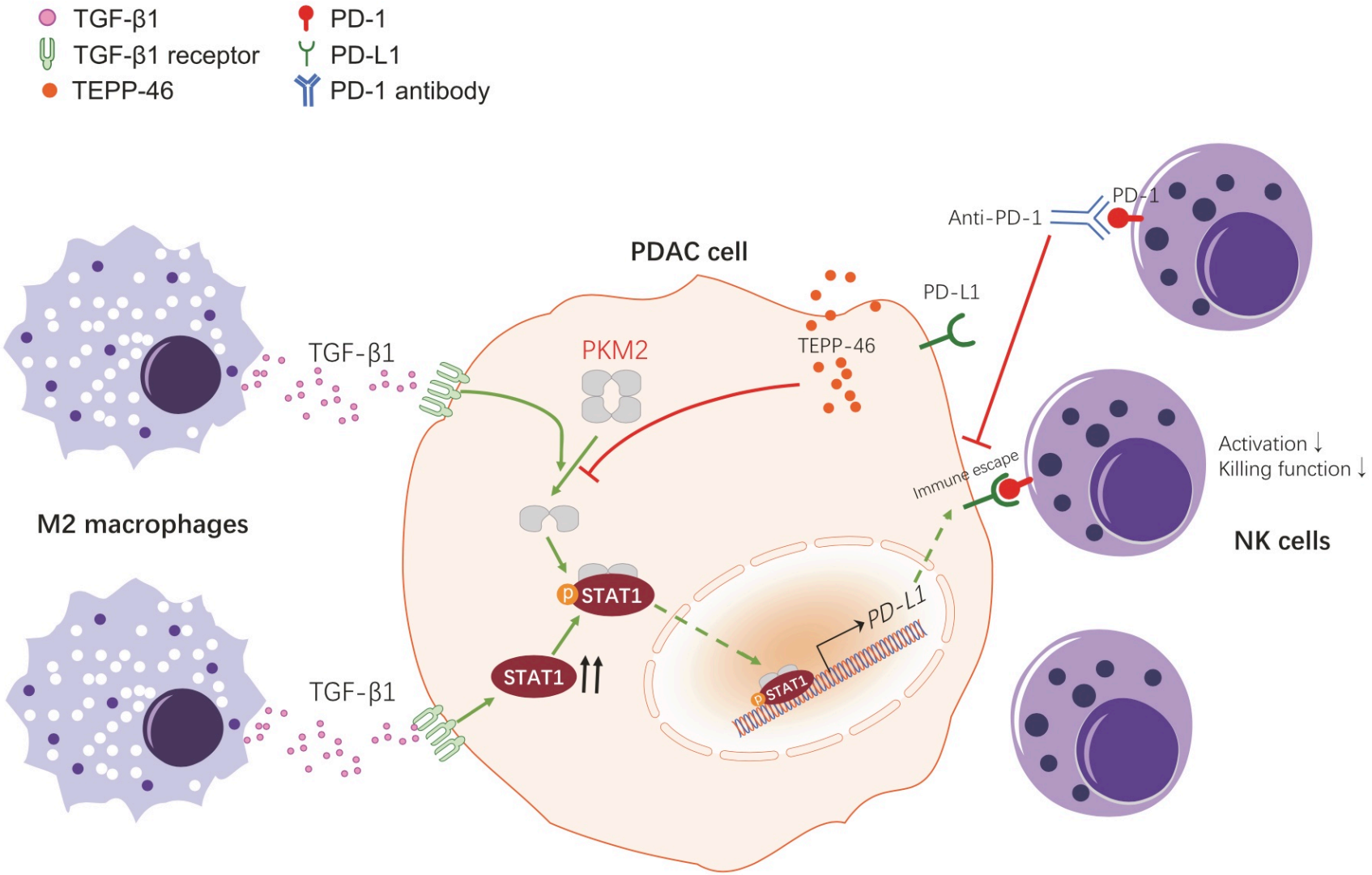
TGF-β1
TGF-β1 receptor
TEPP-46
PD-1
PD-L1
PD-1 antibody
PDAC cell
PKM2
TEPP-46
PD-L1
Anti-PD-1
PD-1
TGF-β1
M2 macrophages
TGF-β1
STAT1
STAT1
PD-L1
STAT1
Immune escape
Activation ↓
Killing function ↓
NK cells

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Take-Home Messages

1) TGF-β1 is a major inflammatory factor secreted by M2 macrophages that upregulates PD-L1 expression by the nuclear translocation of PKM2
2) Nuclear translocation of PKM2 and phosphorylation of STAT1 are involved in TGF-β1-induced PD-L1 upregulation
3) PKM2 knockdown decreases the expression of PD- L1 and elicits potent antitumor immunity by activating NK cells
4) Synergistic antitumor effect of combined PKM2 and PD-1/PD-L1 blockade may provide a potential therapy for treating PDAC.

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