Progestogen-driven B7-H4 contributes to onco-fetal immune tolerance

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Yijun Yang, August 7, 2026

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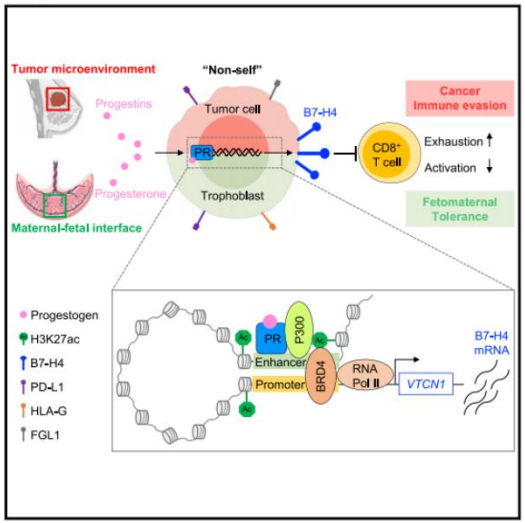
Graphical abstract



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In brief

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Highlights

- B7-H4 contributes to the onco-fetal immune tolerance
- Progesterone drives B7-H4 expression via the PR-P300-BRD4 axis
- B7-H4 expression is controlled by the −58 kb enhancer
- PR antagonist or selective BRD4 degrader sensitizes B7-H4^{+} tumors to immunotherapy

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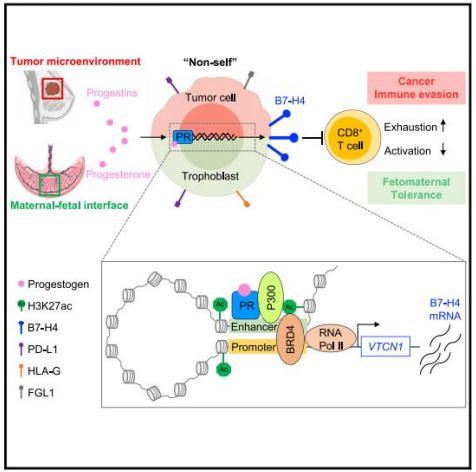

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In brief

Immune tolerance mechanisms are shared in cancer and pregnancy. B7-H4 is identified as an immune checkpoint molecule contributing to onco-fetal immune tolerance, whose expression is regulated by a sex-hormone progesterone.

Highlights

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Weiping Zou 邹伟平

University of Michigan Medical School

- Charles B de Nancrede Research Professor of Surgery, Professor of Surgery, Professor of Pathology
- Research direction: immune regulation within the tumor microenvironment and the development of novel immunotherapeutic strategies, including immune checkpoint-based cancer therapies.

1. Xiao, R., Yu, J., Yan, Y., Kryczek, I., & **Zou, W.** (2026). B7-H4 in Cancer Immune Evasion and Immunotherapy. *Clinical cancer research : an official journal of the American Association for Cancer Research*, 32(14), 2806–2813. https://doi.org/10.1158/1078-0432.CCR-25-2442

2. Pearson, A. N., Waninger, J., Huber, A. K., Holcomb, E. A., James, J. G., Kyi, J., Elaimy, A. L., Wang, Z., Lasse-Opsahl, E. L., SenGupta, S., Elliott, D. A., Choi, E., Zhang, Q., Morgan, M. A., Chang, D. T., Lawrence, T. S., Courtney, A., Shah, Y. M., Knight, J. S., Pasca Di Magliano, M., Yoo, S., Crivelli, S., Parent, C. A., Ramnath, N., Bryant, A. K., **Zou, W.** & Green, M. D. (2025). Liver Metastases License Neutrophils through IL1 to Potentiate Cancer Progression. *Cancer immunology research*, 13(12), 2023–2036. https://doi.org/10.1158/2326-6066.CIR-24-1074

3. Pitter, M. R., & **Zou, W.** (2025). Citrullination in tumor immunity and therapy. *The Journal of clinical investigation*, 135(20), e196348. https://doi.org/10.1172/JCI196348

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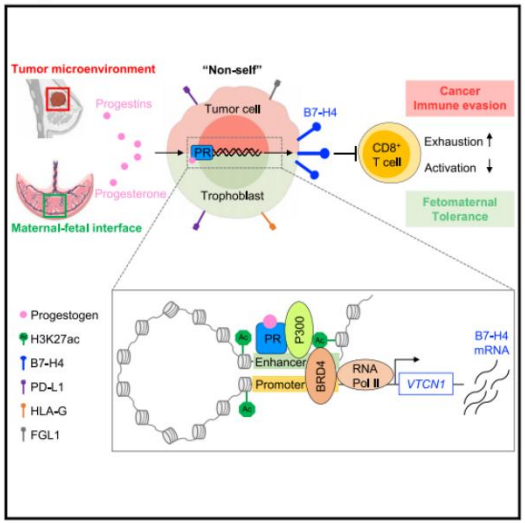

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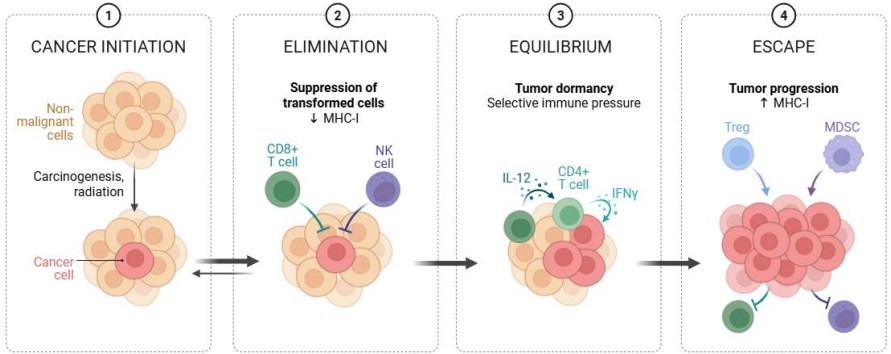
Introduction

Cancer and pregnancy appear to be very different biological processes, but both depend on **immune tolerance**.



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CD8 T cell activation
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Tumor killing

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Tumor induces immune suppression
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Immune escape
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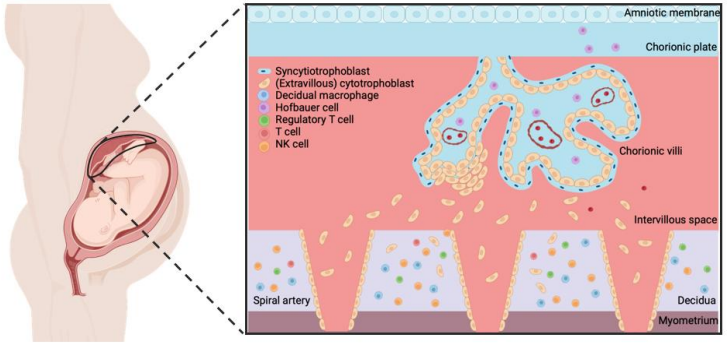
Tumor survival

Cancer immune tolerance



Fetus is a **semi-allogeneic entity carrying paternal antigens**

Normal pregnancy proceeds suceessfully

Maternal immune system would theoretically recognize and **reject the fetus**

Maternal-fetal immune tolerance

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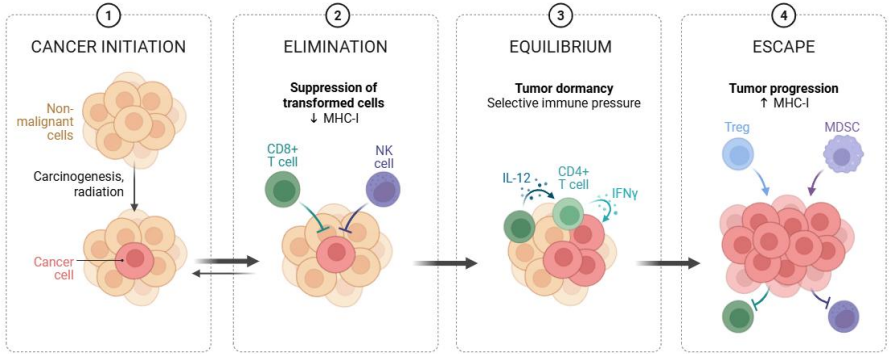

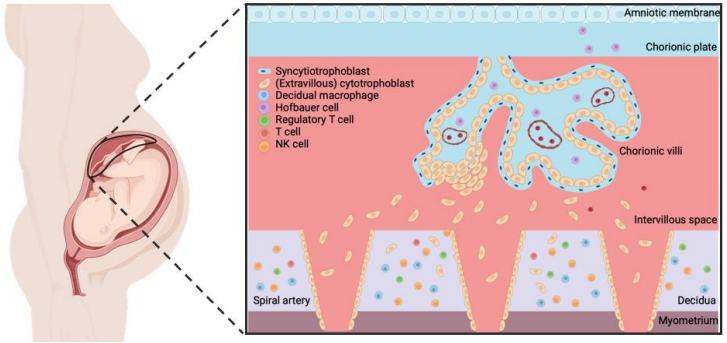

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Fetus is a **semi-allogeneic entity carrying paternal antigens**

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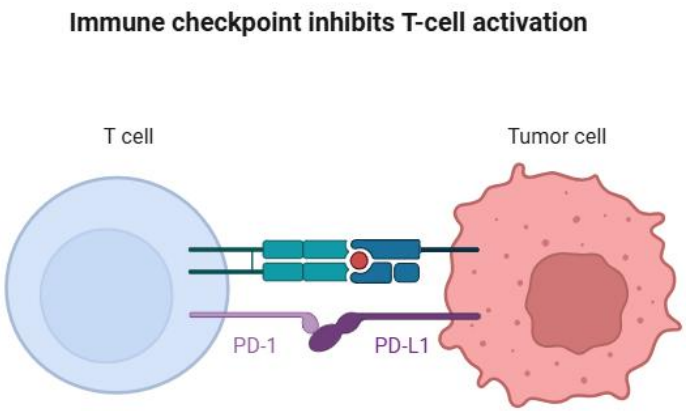
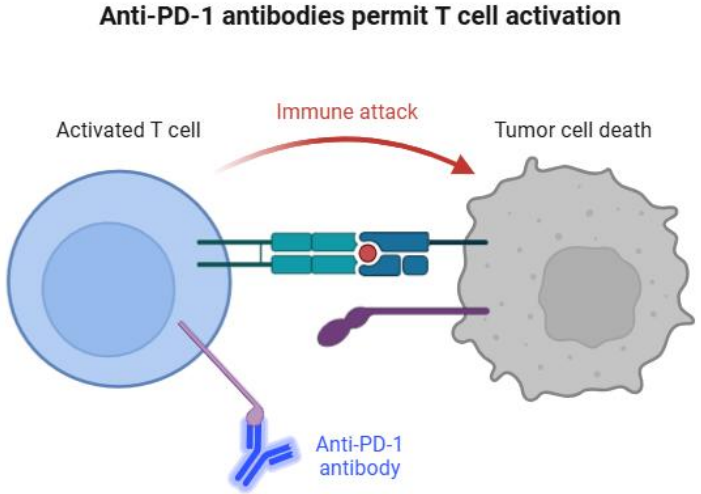
Cancer and pregnancy **share several immunosuppressive pathways**, like PD-L1 (B7-H1, CD274), HLA-G, indoleamine 2,3-dioxygenase (IDO)

Immune checkpoint

Negative regulators of immune responses, limiting excessive T cell activation and maintaining peripheral immune tolerance





Immune checkpoint blockade (ICB)

B7-H4

B7-H4 *(VTCN1)* has been identified as an inhibitory B7 family member and is thought to be an **immune checkpoint molecule in the context of tumor immunity**

Pregnancy

- Expressed in trophoblasts and decidual macrophages
- Expression is associated with pregnancy complications

Can B7-H4 function as a shared onco-fetal immune checkpoint?

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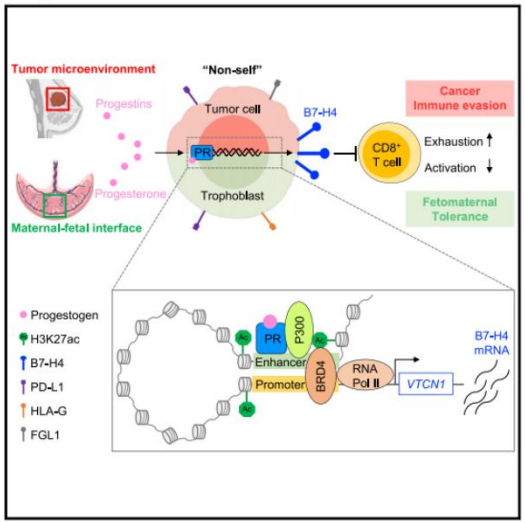

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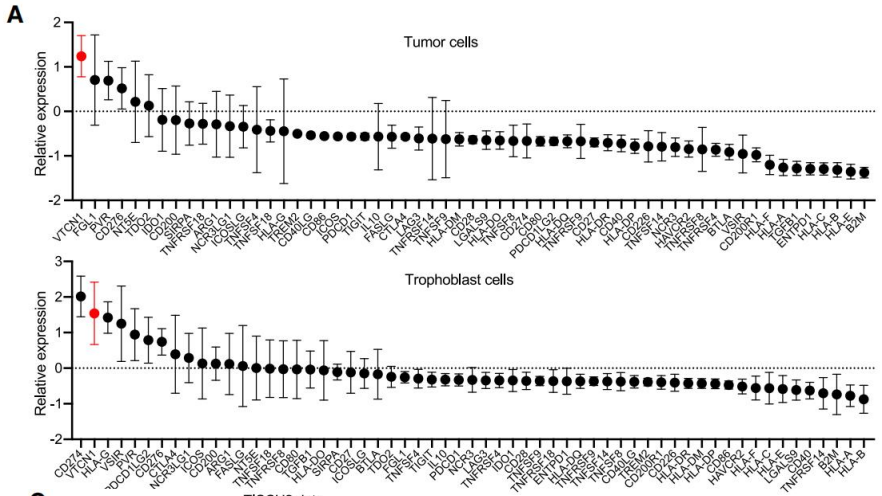
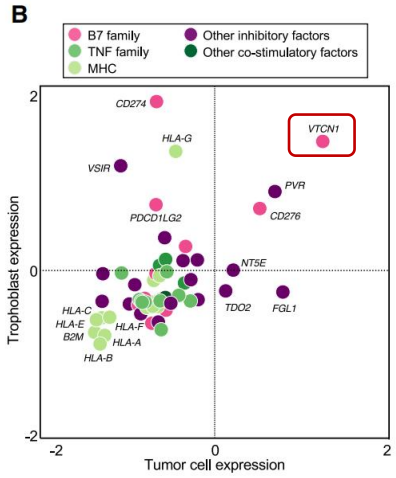
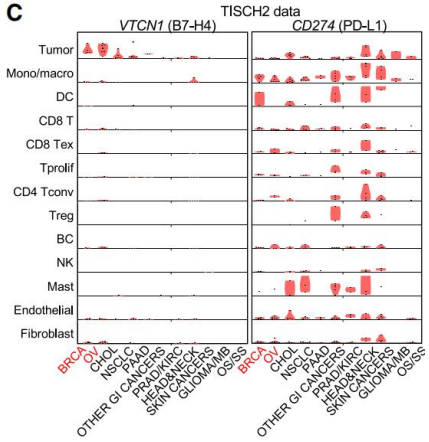
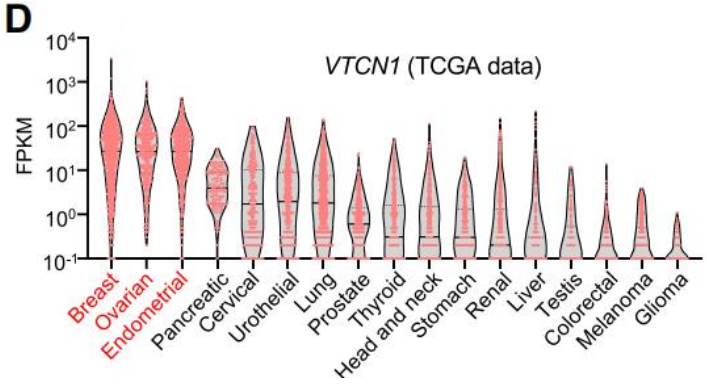
B7-H4 are expressed in the major cellular components of both TME and placenta and highly expressed in pan-gynecological cancers









Cross-analyzation of 14 scRNA-seq datasets from TME and placenta

- B7-H4 highly expressed **in both tumor cells** in the TME **and trophoblast cells** in the placenta

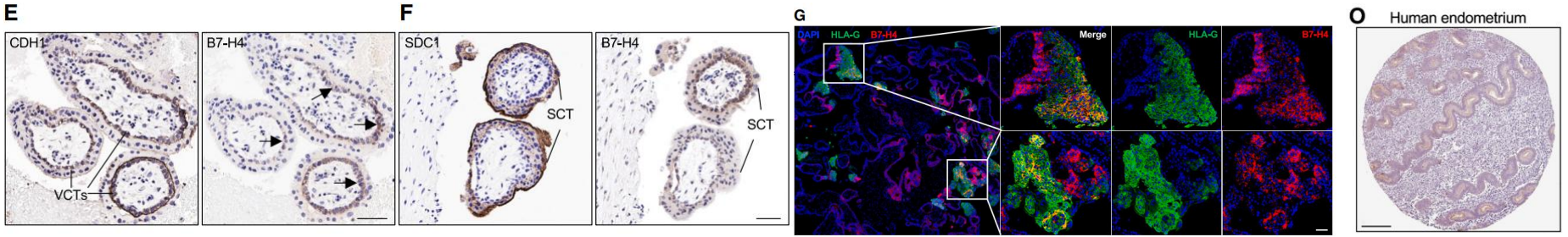
Analysis of **tumor** datasets

- B7-H4 was **mainly expressed by tumor cells**
- Highest levels of B7-H4 transcripts were in cancers originating from **female reproductive organs**

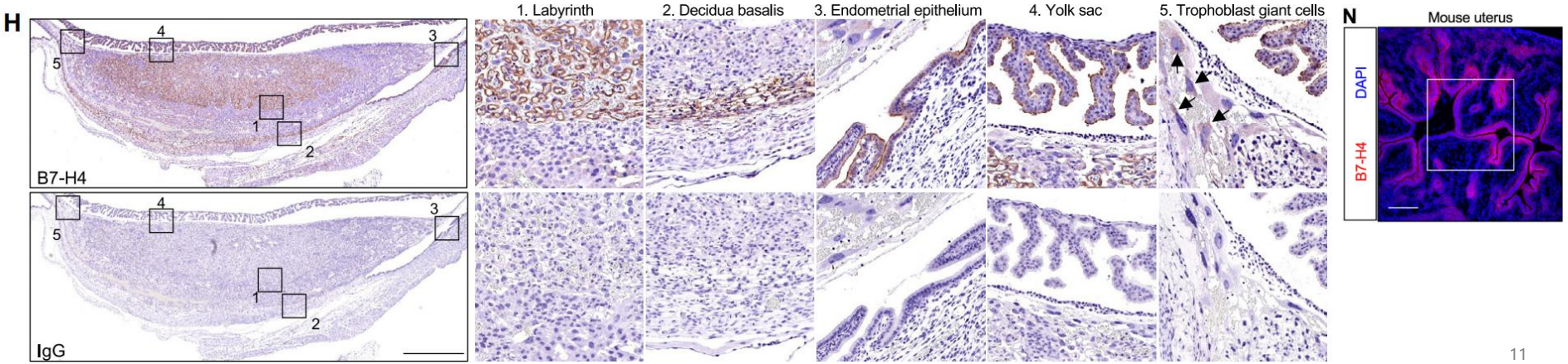
B7-H4 is expressed by cells and tissues of both maternal and fetal origin, and its expression pattern is conserved in human and mouse placentas

Immunohistochemistry (IHC) of **placental** tissues

Human placenta:



Mouse placenta:



Summary 1

Result: B7-H4 are expressed in the major cellular components of **both tumor and placenta**

- Cancer: highly expressed in pan-gynecological cancers
- Placenta: expressed by cells and tissues of both maternal and fetal origin, and its expression pattern is conserved in human and mice

Hypothesis 1

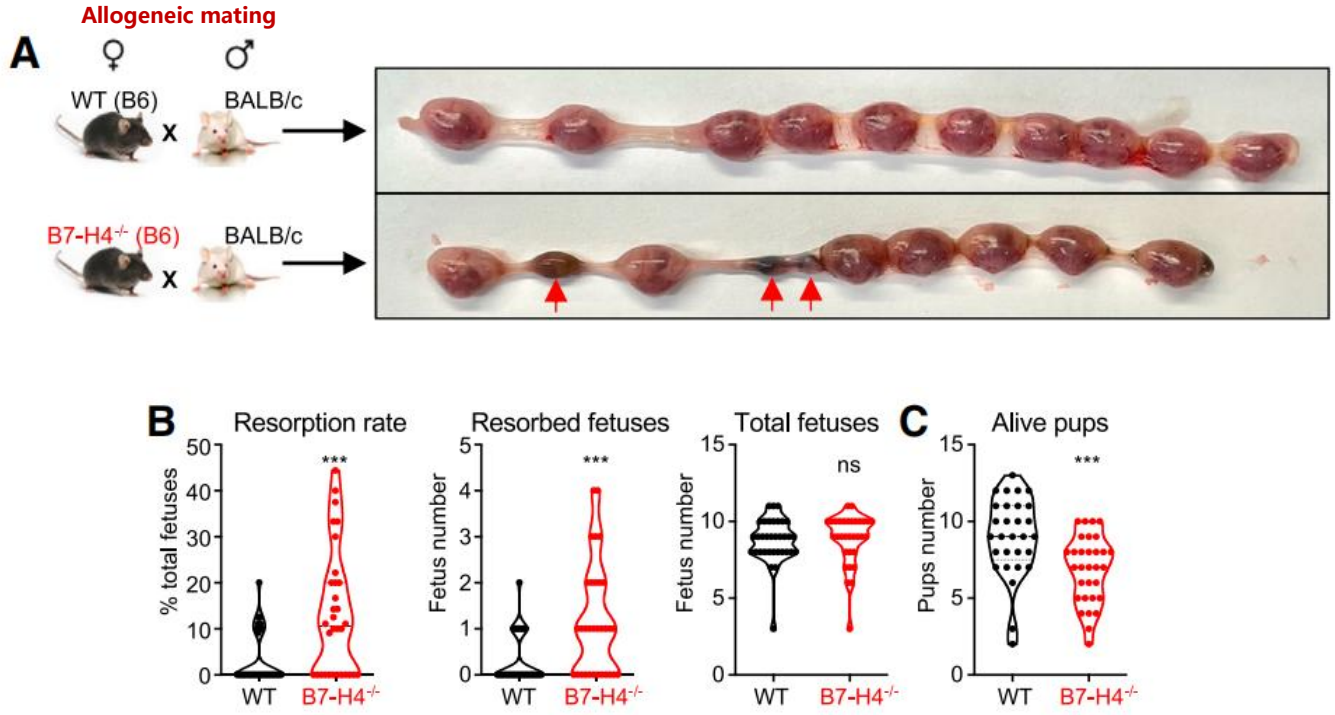
B7-H4 is a potential onco-fetal immune tolerance checkpoint

Question 1.1

Whether B7-H4 plays an active immunological role in maternal-fetal immune tolerance?

B7-H4 regulates allogeneic mating-associated immune activation

- Despite similar fetus numbers, there were more resorbed fetuses in pregnant B7-H4$^{-/-}$ mice than in pregnant WT mice



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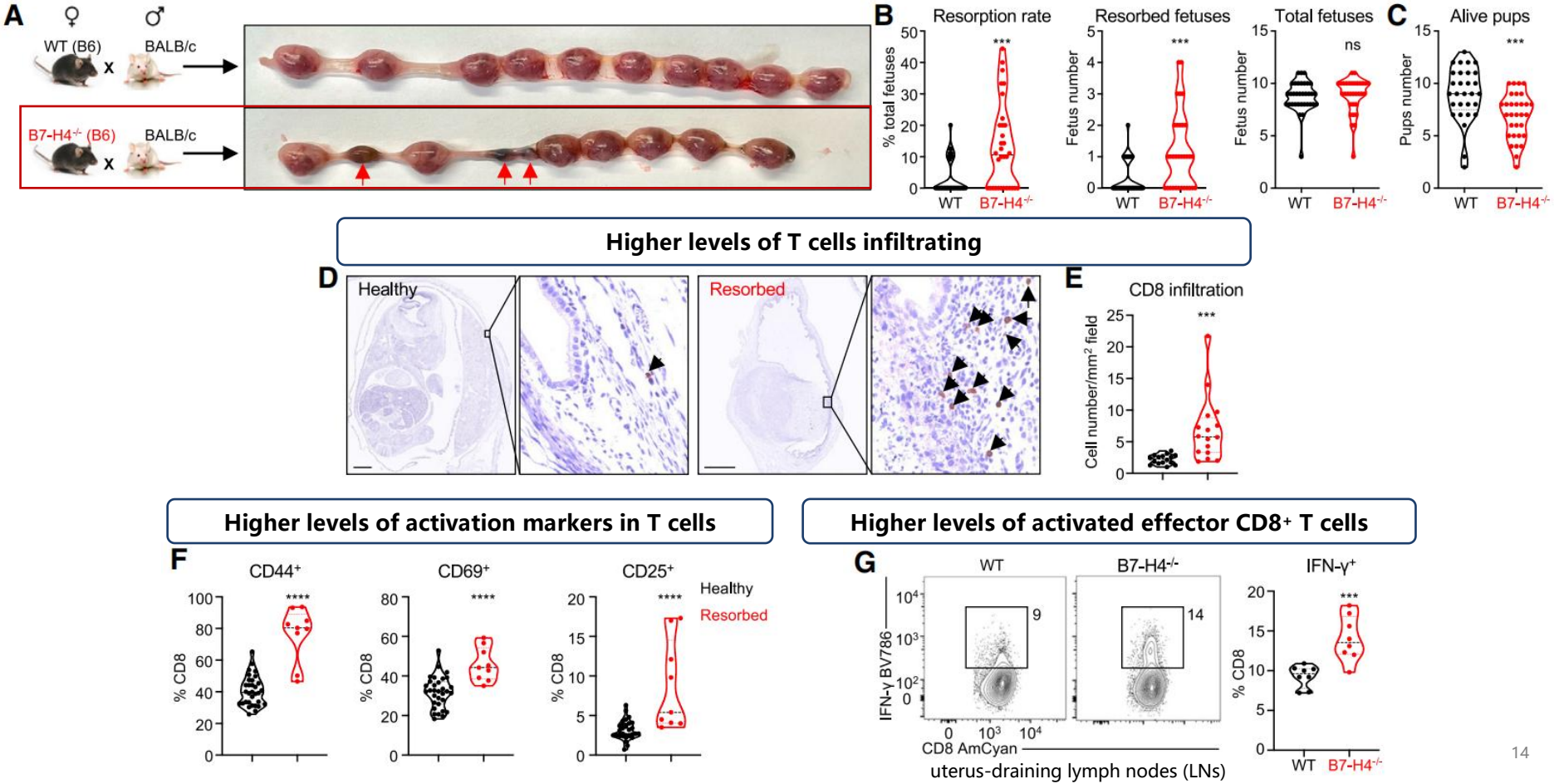
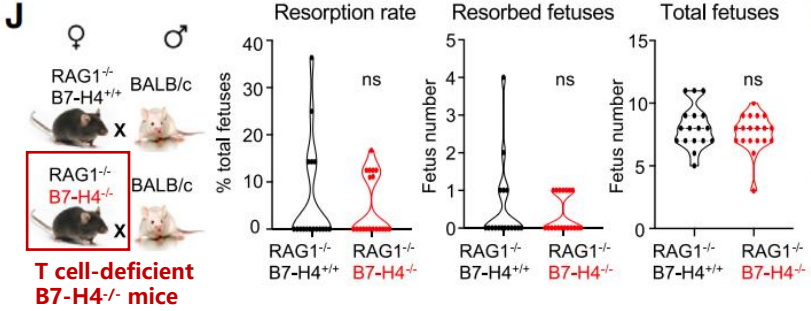


Question 1.2

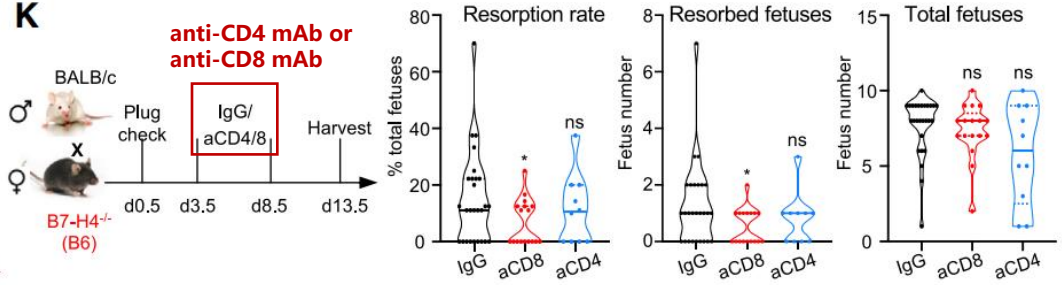
Whether fetus resorption was related to the changes of T cells ?

Activated CD8+ T cells contribute to fetus resorption in B7-H4$^{-/-}$ mice

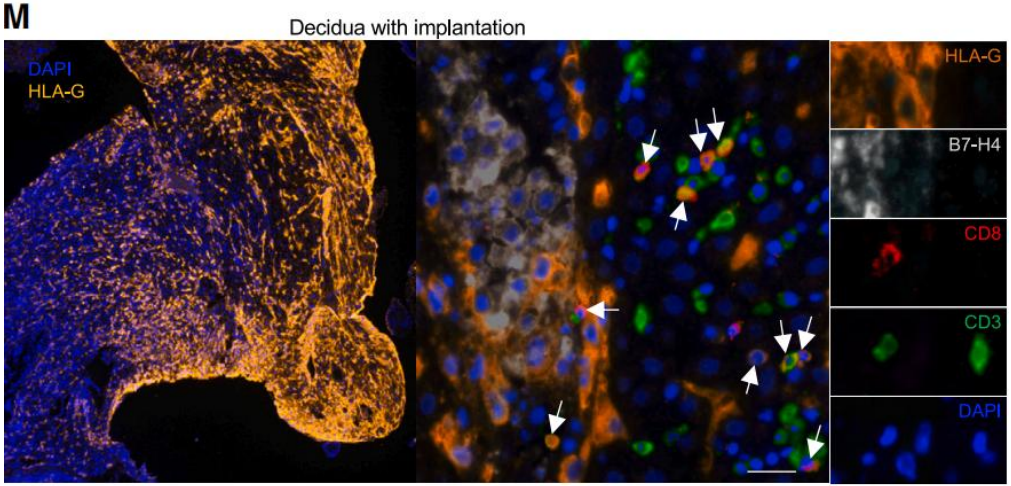
T cell deficiency



CD8 or CD4 deficiency



Close contact between CD8⁺ T cell and B7-H4⁺ EVTs



Human first trimester POC samples

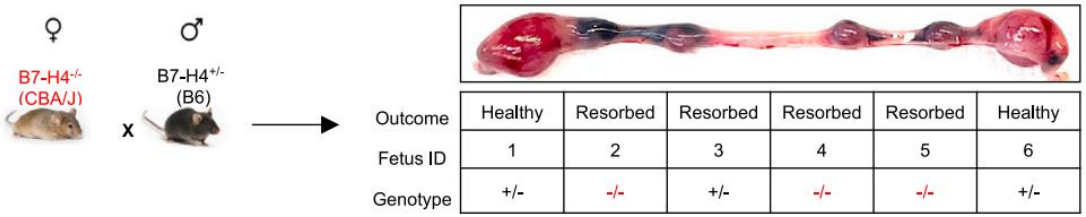
Speculation

CD8⁺ T cells may interact with B7-H4⁺ EVTs during the first trimester of human pregnancy

Question 1.3

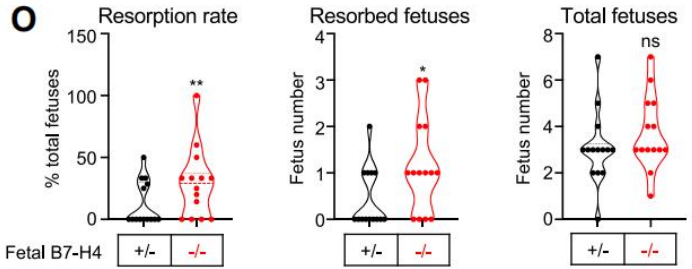
What is the role of fetal B7-H4 in fetus resorption?

N



Outcome	Healthy	Resorbed	Resorbed	Resorbed	Resorbed	Healthy
Fetus ID	1	2	3	4	5	6
Genotype	+/-	-/-	+/-	-/-	-/-	+/-

O



There is a protective role of fetal B7-H4 during the pregnancy

N

Outcome	Healthy	Resorbed	Resorbed	Resorbed	Resorbed	Healthy
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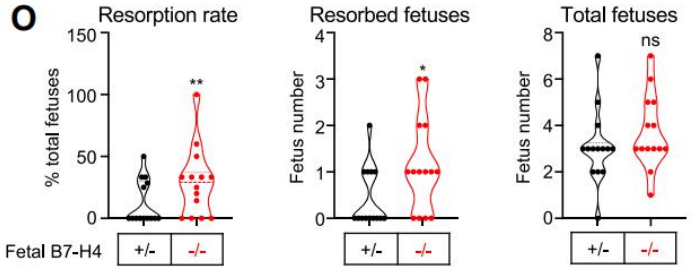


Summary 2

Result: B7-H4 expression **supports the maternal-fetal immune tolerance** via **keeping CD8⁺ T cells in check**

Background: B7-H4 *(VTCN1)* has been identified as an inhibitory B7 family member and is thought to be an immune checkpoint molecule **in the context of tumor immunity**

B7-H4 is a onco-fetal immune tolerance checkpoint

Summary 1

Result: B7-H4 are expressed in the major cellular components of **both tumor and placenta**

- Cancer: highly expressed in **pan-gynecological cancers**
- Placenta: expressed by cells and tissues of both maternal and fetal origin, and its expression pattern is conserved in human and mice

Background: Recent studies on the intersection of endocrine and immune systems have shed light on a role of androgen, a male sex hormone, in regulating T cell function in cancers, including prostate cancer

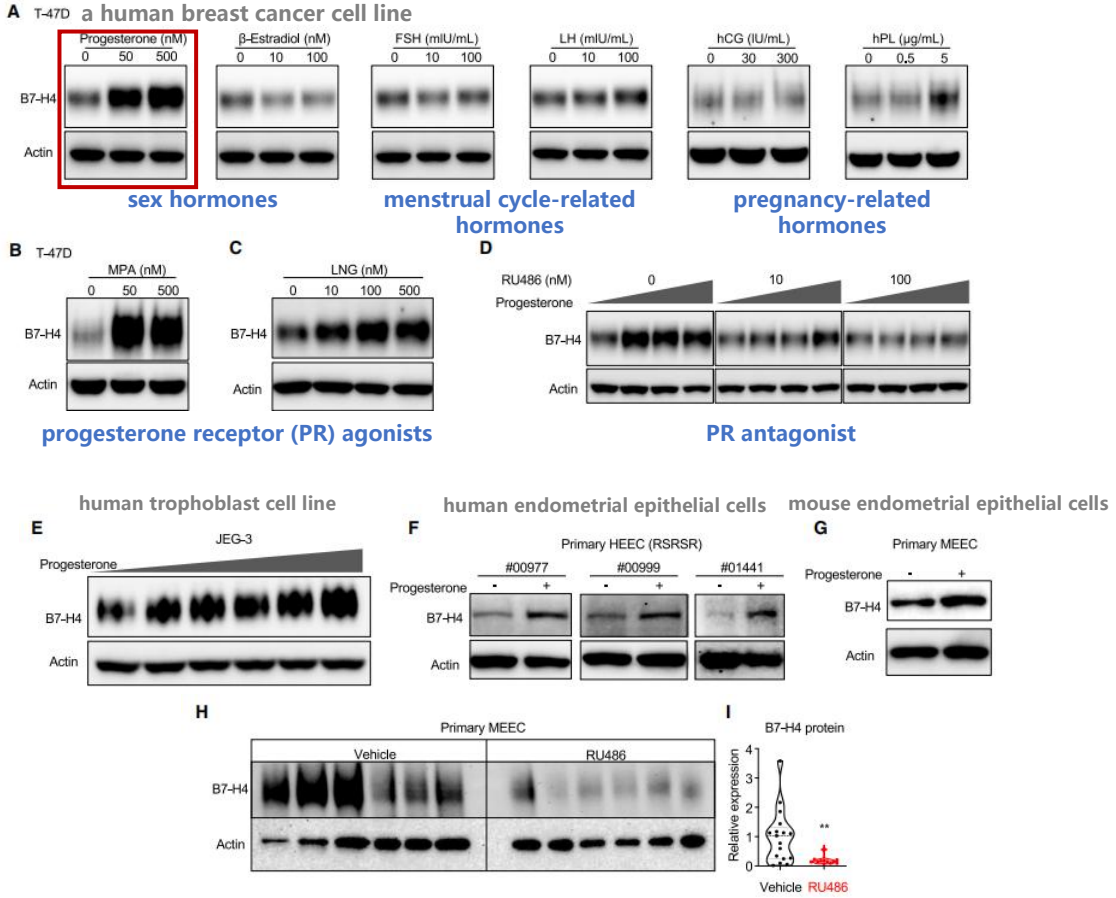
Hypothesis 2

Female hormones may influence the immune tolerance of pregnancy and cancer by regulating B7-H4 expression

Question 2

Which female hormones can influence B7-H4 expression?

Progesterone promotes B7-H4 expression in human breast cancer cells and cells at the maternal-fetal interface



- Progesterone promotes B7-H4 expression **in a PR-dependent manner** in the **breast cancer**
- Similar situtaions were also found in **placental cells**

Summary 3

Result: B7-H4 expression **supports the maternal-fetal immune tolerance** via **keeping CD8⁺ T cells in check**

Result: Progesterone promotes B7-H4 expression in human breast cancer cells and cells at the maternal-fetal interface

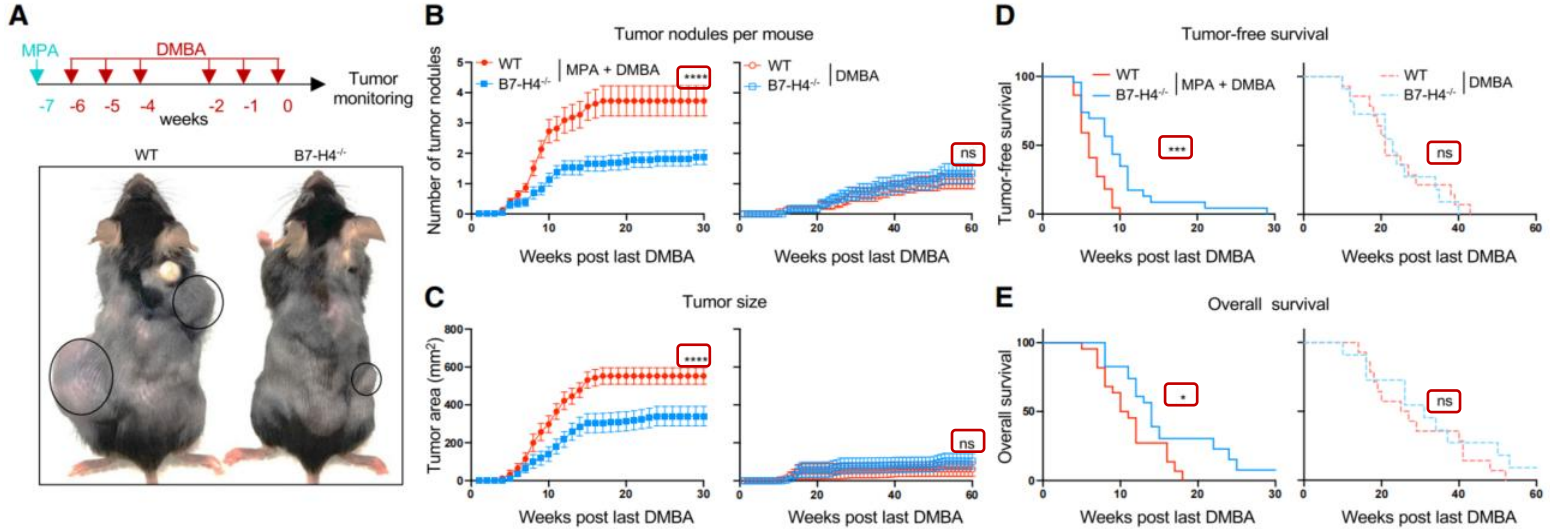
Hypothesis 3

Progesterone promotes cancer immune evasion by controlling B7-H4 expression

Question 3.1

What is the immunological role of progesterone signaling in breast cancer progression?

Progesterone stimulates tumor B7-H4 expression, thereby contributing to breast cancer progression



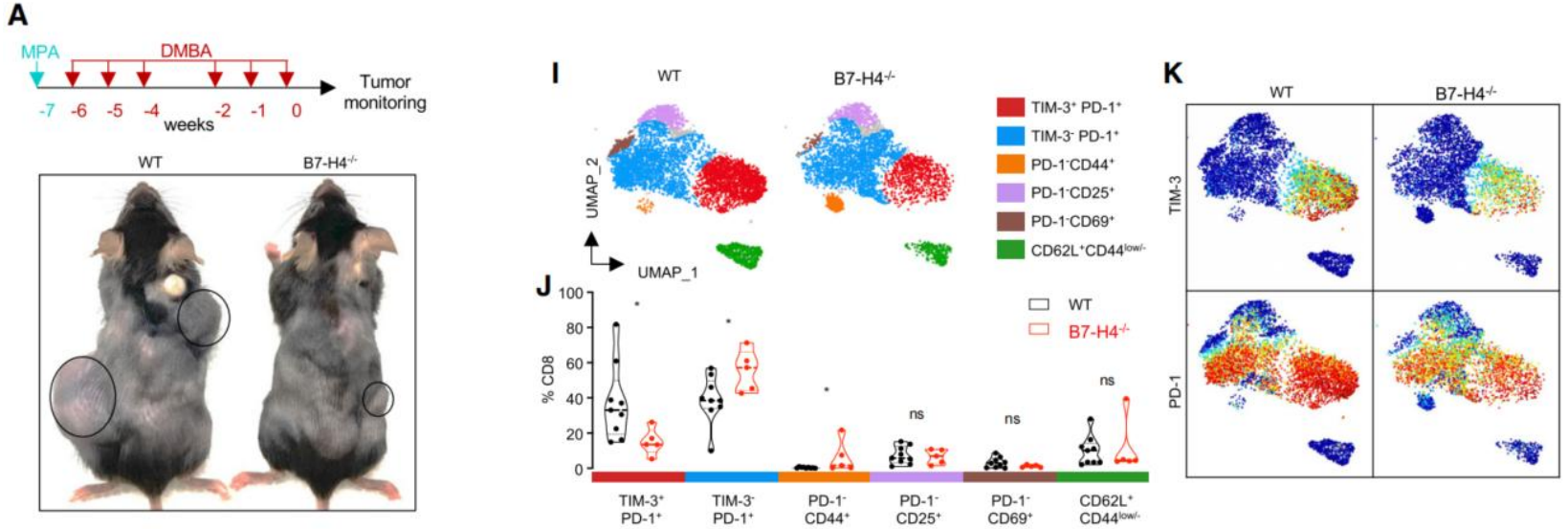
- An increase in breast cancer rate and progression with MPA
- Slower tumor progression and longer survival in B7-H4$^{-/-}$ mice

Progesterone stimulates tumor B7-H4 expression, thereby contributing to breast cancer progression

B7-H4 enhances breast cancer progression via inhibiting T cell activation and promoting T cell exhaustion

B7-H4$^{-/-}$: B7-H4 deficiency shifts CD8^{+} T cells **from** a TIM-3^{+} PD-1^{+} **exhausted phenotype** toward a TIM-3^{-} PD-1^{+} **less-exhausted phenotype**

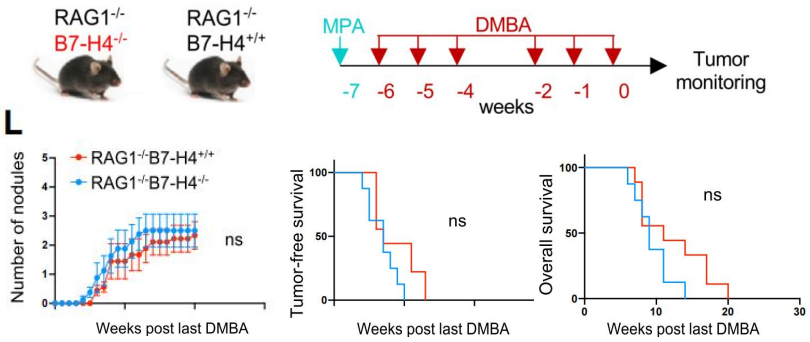
Mass cytometry (CyTOF)



B7-H4 enhances breast cancer progression via inhibiting T cell activation and promoting T cell exhaustion

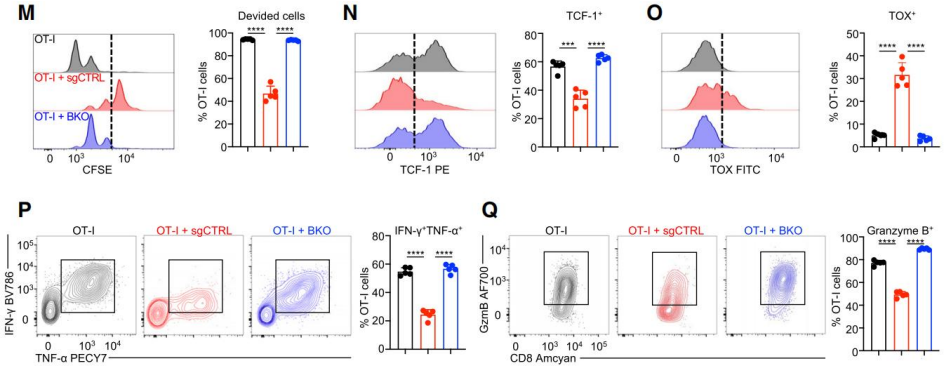
T cell deficiency

- Tumor-promoting effect was abolished in the absence of T cells



Co-culturation of OT-I cells and B7-H4$^{+/+}$ (sgCTRL) or B7-H4$^{-/-}$ (BKO) tumor cells

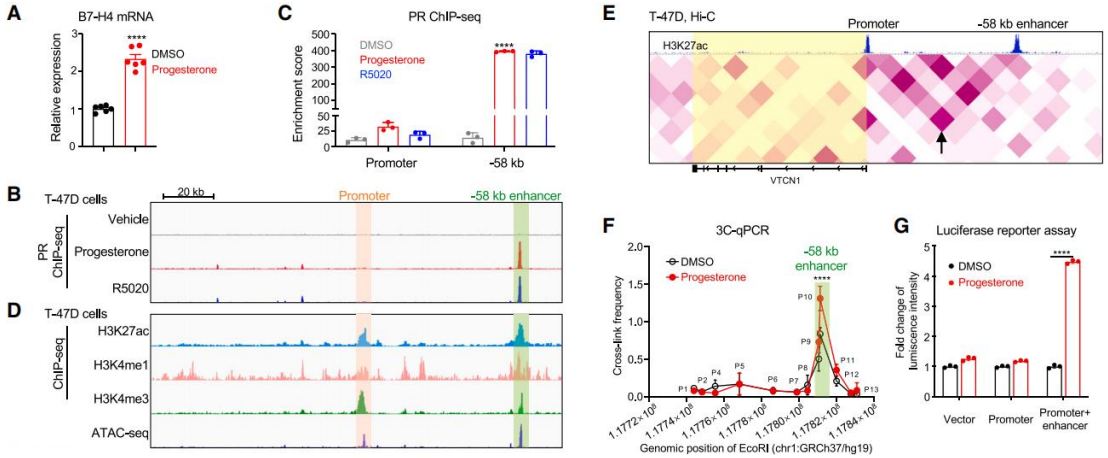
- Decreased cell proliferation
- ↓ TCF-1, ↑ TOX, ↓IFN-γ, ↓ Granzyme B
  -> increasing terminal exhausted CD8^{+} T cells



-58 kb region is the specific enhancer for B7-H4 and contributes to progesterone-mediated B7-H4 transcriptional regulation

Question 3.2

What is the potential mechanism linking progesterone to B7-H4 expression?

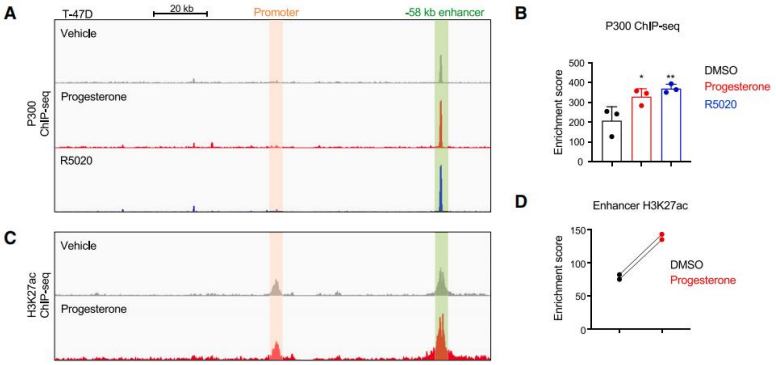


- A strong PR-binding peak at the **-58 kb region**, which might be a **enhancer** with histone modification marks H3K27ac and H3K4me1
- Progesterone treatment enhanced the B7-H4 promoter activity **in the presence of the -58 kb enhancer**

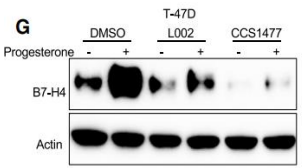
B7-H4 expression is regulated by the PR-P300-BRD4 axis

Histone acetyltransferase **P300**

- Activation of PR:
  - Enhanced binding of P300
  - Enhanced H3K27ac signal
- Abolished effect of progesterone by P300 inhibitor

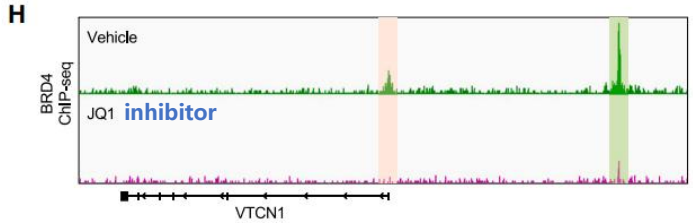


P300 inhibitors dealing

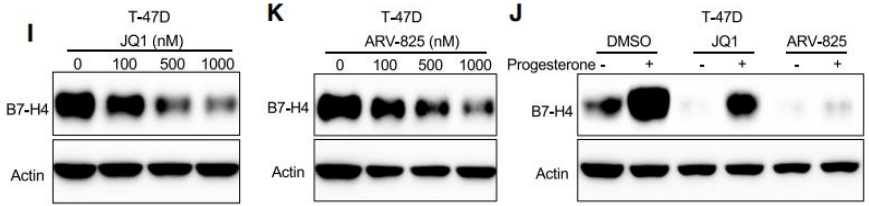


Epigenetic reader **BRD4** for H3K27ac

- Decreased binding of BRD4 with JQ1
- Abolished effect of progesterone by BRD4 inhibitor and degrader



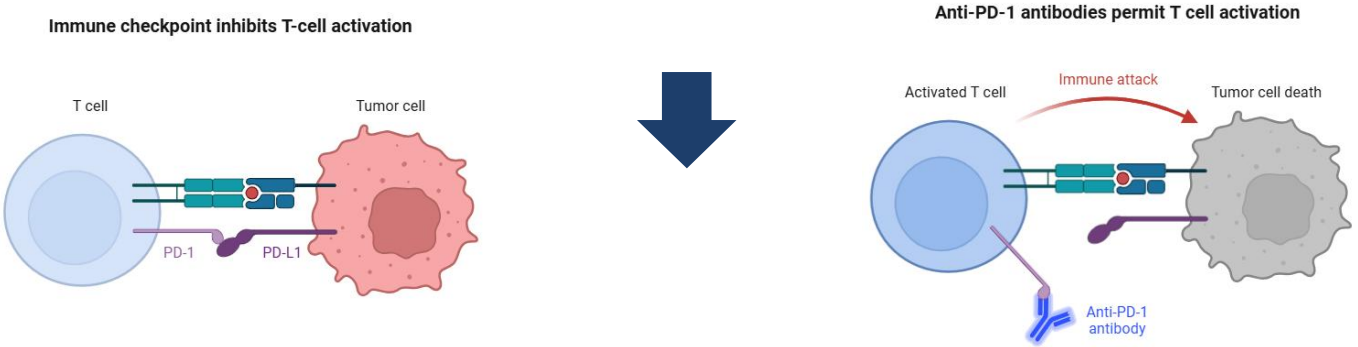
inhibitor **degrader**



Summary 3

Result:

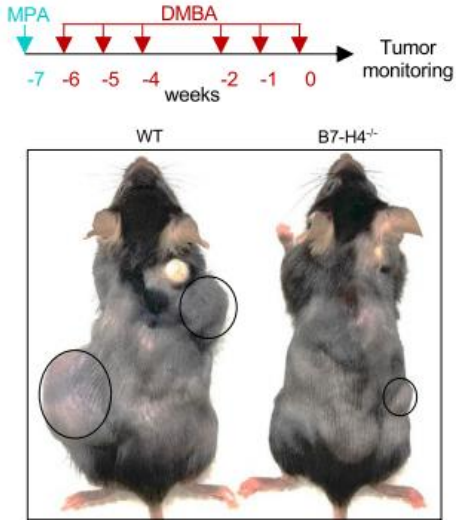
- B7-H4 enhances breast cancer progression via inhibiting T cell activation and promoting T cell exhaustion
- B7-H4 expression is regulated by the PR-P300-BRD4 axis via the -58kb enhancer



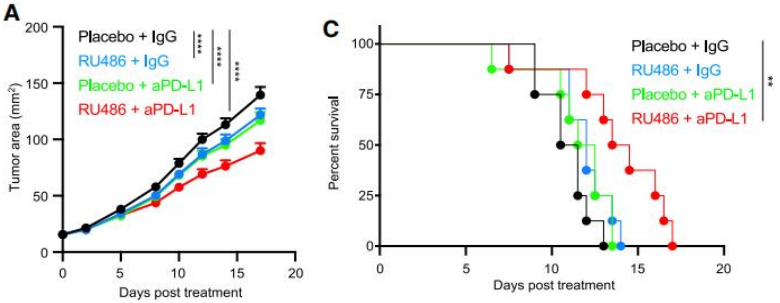
Question 4

Can we target B7-H4 for treatment or to improve ICB efficacy in pan-gynecological cancers?

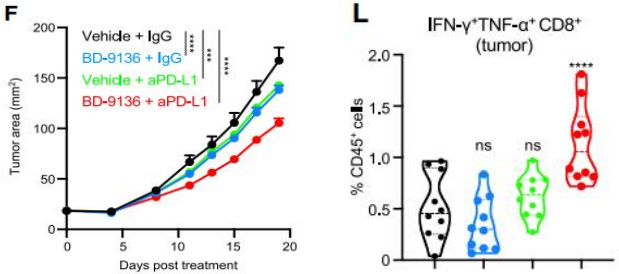
Targeting the regulatory axis of B7-H4 with PR antagonist or BRD4 degrader can potentiate the therapeutic efficacy of ICB in B7-H4^{+} breast cancer model



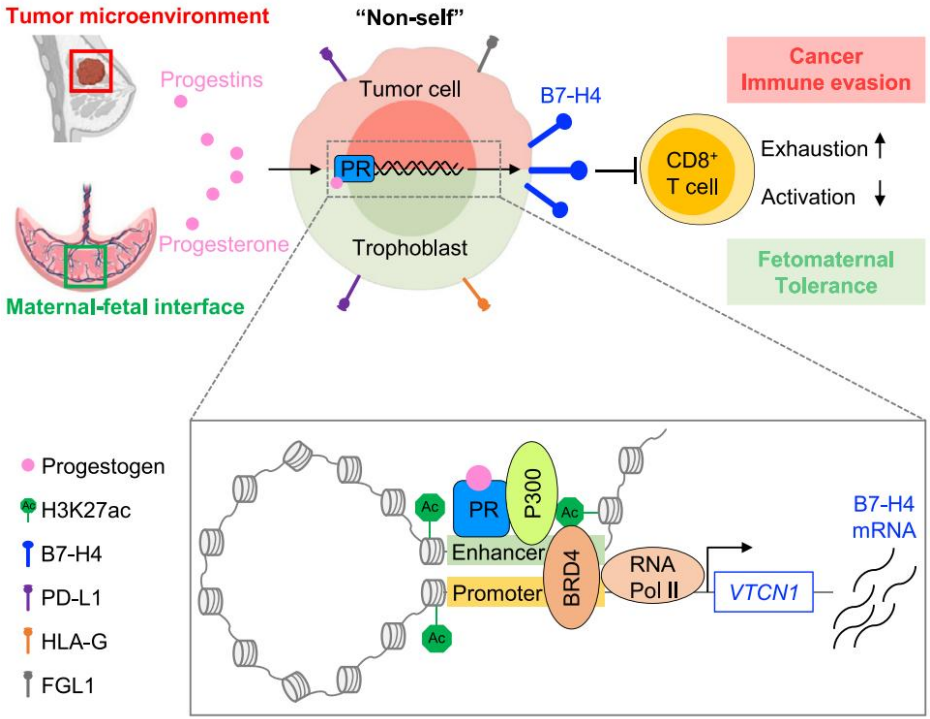
RU486: PR antagonist



BD-9136: BRD4 degrader



Summary



B7-H4 supports the **maternal-fetal immune tolerance**

B7-H4 is an **onco-fetal immune tolerance checkpoint**

Progesterone promotes B7-H4 expression in cancer and placenta

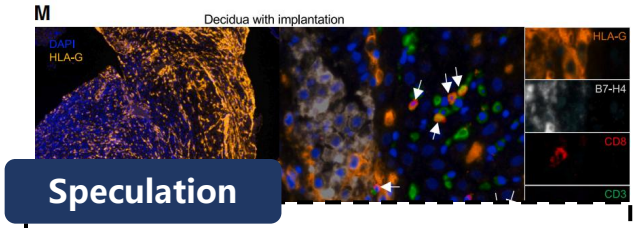
B7-H4 promotes breast cancer progression by **inhibiting CD8⁺ T cells**

PR signaling promotes B7-H4 transcription via binding to the **-58 kb enhancer**

Progesterone promotes B7-H4 expression via the **PR-P300-BRD4 axis**

Targeting the regulatory axis of B7-H4 **potentiates ICB efficacy**

Limitation and future direction

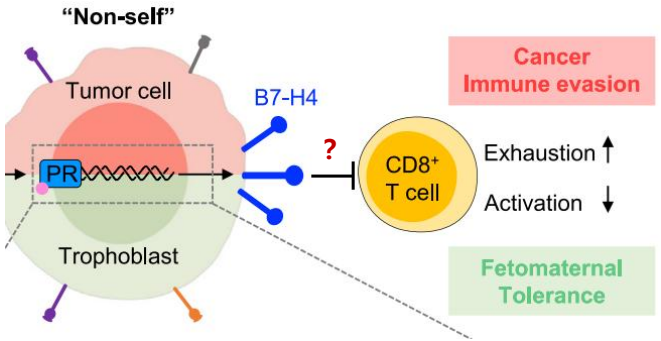


Speculation

CD8⁺ T cells may interact with B7-H4⁺ EVTs during the first trimester of human pregnancy

- Spatial proximity supports potential interaction but **does not demonstrate antigen-specific cytotoxicity**

- The upstream regulation of B7-H4 is well characterized whereas its **downstream receptor and signaling pathway remain unresolved**



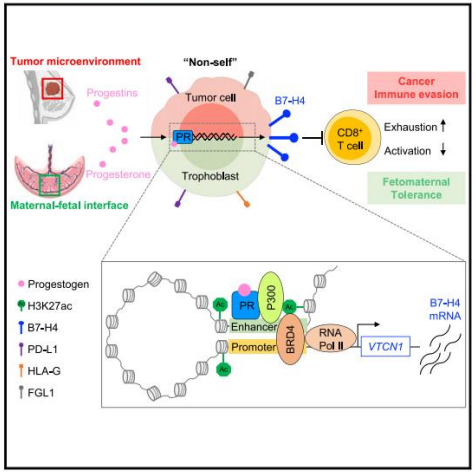
Why is this study impactful?

Cell

Article

Progestogen-driven B7-H4 contributes to onco-fetal immune tolerance

Graphical abstract



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In brief

Immune tolerance mechanisms are shared in cancer and pregnancy. B7-H4 is identified as an immune checkpoint molecule contributing to onco-fetal immune tolerance, whose expression is regulated by a sex-hormone progesterone.

Highlights

- B7-H4 contributes to the onco-fetal immune tolerance
- Progesterone drives B7-H4 expression via the PR-P300-BRD4 axis
- B7-H4 expression is controlled by the −58 kb enhancer
- PR antagonist or selective BRD4 degrader sensitizes B7-H4^{+} tumors to immunotherapy

- **Conceptual advance:** Establishes B7-H4 as a shared onco-fetal immune checkpoint connecting pregnancy and cancer
- **Biological significance:** Demonstrates its functional roles in both fetal protection and tumor immune evasion
- **Mechanistic depth:** Defines the progesterone–PR–P300–BRD4–B7-H4 regulatory axis
- **Evidence breadth:** Integrates human datasets, clinical samples, genetic models, multi-omics and functional experiments
- **Translational potential:** Identifies actionable strategies to sensitize B7-H4^{+} tumors to immunotherapy

Thanks for your attention!