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The Association Between TRPM2 and Inflammatory Factors (TNF-α and IL-2) in The Tumor Microenvironment of PANC1 Pancreatic Cancer

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Abstract. This work aimed to test whether using ADP-ribose (a TRPM2 activator) to activate TRPM2 and treating PANC1 for a longer time would have a positive effect on PANC1. ADP-ribose can activate TRPM2 in the experiment, which is an important step in the experiment. This research may lead to a new approach to treating cancer. By using ADP-ribose to boost the proteins that fight inflammation (TNF-α and IL-2) and T cells, this might become a new treatment method. It could help make tumors smaller, slow their growth, or even stop them. This would mean better chances for patients, maybe less pain, and prolong the overall survival time. In short, this work may open doors to new, more effective treatments for pancreatic cancer, offering hope to those who need it most.

Keywords: ADP-ribose, TRPM2, TNF-α, IL-2, T cell, PANC1

1. Introduction

Pancreatic cancer is a severe type of cancer. It grows and spreads quickly, making it difficult to treat [1]. One possible approach is to utilize the human body's immune system to target and eliminate cancer cells.

The main treatments for pancreatic cancer include surgery, chemotherapy, and radiation therapy. Surgery [2] is chosen when the cancer is found early and hasn't spread much, for doctors try to remove the tumor. Chemotherapy uses drugs to kill cancer cells; a common treatment, NIPEC [3], has been used in the treatment of pancreatic cancer. The treatment can slow the cancer's growth and relieve some symptoms. Radiation [4] therapy uses high-energy rays to target the tumor, usually alongside chemotherapy.

TRPM2 is a type of protein found on cells surface [5]. It is known to be involved in many cell activities, including inflammation. Some studies have shown that TRPM2 plays an important role in pancreatic cancer [5], and there is evidence suggesting that the activation of TRPM2 can promote tumor growth. TRMP2 can be activated by its activator ADP-ribose [6].

The mechanism (the causal chain from TRPM2 activation to tumor regression): Firstly, TRPM2 is a protein channel. When activated by ADP-ribose, it opens a passage on the cell surface [7]. Secondly, this channel lets calcium ions flow into the cell, increasing the concentration of calcium inside the cell [8]. Thirdly, the extra calcium will wake up NF-κB and make it start working [9].

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Fourthly, the activated NF-κB enters the cell nucleus and prompts cells to make TNF-α [10,11] and IL-2 [12]. Fifthly, TNF-α [13] and IL-2 [14] will draw T cells to the tumor. Finally, with lots of T cells gathering, they kill the tumor cells [15], eventually making the tumor shrink [16].

New treatments are badly needed because the current ones don't work well enough. Many patients don't respond to chemotherapy [17] or radiation [18], and the cancer often recurs after treatment. The side effects of existing treatments are also very difficult for patients to manage [19]. Since pancreatic cancer grows and spreads so quickly and is so hard to detect early, we need better ways to treat it.

The positive control group is poly I:C [20], and the negative control group is PBS or saline [21]. This research uses ELISA to measure the production of TNF-α and IL-2 [22], and uses a CD3 T cell marker to assess T cell recruitment by confocal microscopy [23]. This research also weighs the tumor in the xenograft experiment [24].

This paper will look at the association between TRPM2 and inflammatory factors (TNF-α and IL-2) in the tumor microenvironment of PANC1 pancreatic cancer. We will compare whether TNF-α and IL-2, stimulated by TRPM2, continue to reduce tumor size when TRPM2 is activated.

2. Hypothesis

I predict that increasing concentrations and treatment durations with the TRPM2 activator ADP-ribose will increase production of TNF-α, IL-2, and increase recruitment of T cells, resulting in decreased PANC1 pancreatic cancer xenograft tumor size.

3. Materials

The human pancreatic cancer cell line PANC1 is derived from pancreatic cancer ductal cells and has typical biological characteristics of pancreatic cancer cells. Its doubling time is 52 hours. It can grow on soft agar and form tumors in nude mice.

The experimental animals are 6–8-week-old male BALB/c nude mice. Nude mice have immunodeficiency, so they will not produce an immune rejection against transplanted human pancreatic cancer cells, which is conducive to the establishment of a stable tumor model and the observation of tumor growth and development.

ADP-ribose, a TRPM2 activator, has high purity and can specifically activate TRPM2 channels, providing an effective tool for studying the function of TRPM2.

ELISA kits for TNF-α and IL-2 have high sensitivity and specificity and can accurately detect the contents of TNF-α and IL-2 in cell culture supernatants or animal sera.

CD3 T cell marker antibody can specifically recognize the CD3 antigen on the surface of T cells and is used to detect the recruitment of T cells by confocal microscopy.

We use poly I:C as a positive control and PBS or saline as negative controls. Poly I:C is a commonly used immune activator that can induce cells to produce inflammatory factors such as TNF-α and IL-2. PBS or saline does not contain any active ingredients that can affect the physiological state of cells or animals.

DMEM medium is rich in various nutrients and can provide a good environment for the growth and proliferation of PANC1 cells.

Fetal bovine serum (FBS) contains abundant growth factors and nutrients, which can promote cell growth and maintain cell activity.

Trypsin is used to digest cells for cell passage and experimental operations.

The main experimental instruments include:

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CO_2 incubator: used to maintain the temperature, humidity, and CO_2 concentration required for cell culture, providing a stable environment for cell growth.

Microplate reader: used to read the absorbance values in ELISA experiments, to quantitatively detect the contents of TNF-α and IL-2.

Confocal microscope: with high resolution and high sensitivity, it can observe the microstructure of cells and tissues and is used to detect the recruitment of T cells.

Electronic balance: used to accurately weigh the weight of tumor tissues to evaluate tumor growth.

4. Experimental design

PANC1 cells are divided into a control group, groups treated with different concentrations of ADP-ribose (such as 75μM, 150μM, 300μM, 400μM, 500μM, 600μM), and groups treated for different durations (such as 6 hours, 12 hours, 24 hours, 48 hours). The control group is not treated with ADP-ribose and is only given regular culture conditions. It serves as the basic control for the experiment, used to compare the results of other treatment groups and clarify the impact of ADP-ribose treatment on cells.

The groups treated with different concentrations of ADP-ribose are used to explore the effects of different concentrations of ADP-ribose on the relevant indicators of PANC1 cells. By setting multiple concentration gradients, we can observe the corresponding changes in cells as the concentration of ADP-ribose changes, thereby determining the optimal concentration range of ADP-ribose. The groups with different treatment durations are used to study the impact of ADP-ribose treatment time on cells and understand the dynamic changes of relevant cellular indicators as the treatment duration increases.

Animal experiments are divided into a control group, a tumor model group, and a tumor model group treated with different concentrations of ADP-ribose. Mice in the control group are not inoculated with tumor cells and are only given normal feeding conditions. They are used to evaluate various indicators of experimental animals under normal conditions and eliminate the interference of the animals' factors on the experimental results.

Mice in the tumor model group are inoculated with PANC1 cells without ADP-ribose treatment, serving as a basic model for tumor growth to compare the impact of ADP-ribose treatment on tumor growth. Mice in the tumor model groups treated with different concentrations of ADP-ribose are given different concentrations of ADP-ribose after being inoculated with PANC1 cells, to observe whether ADP-ribose inhibits or promotes tumor growth.

The positive control is the poly I:C treatment group. As a positive control, it can verify the effectiveness of the experimental system. When the experimental results show that the poly I:C treatment group can significantly induce the production of TNF-α and IL-2, it indicates that the experimental system is working normally, and the experimental results are reliable.

The negative control is the PBS or saline treatment group. It is used to eliminate possible nonspecific effects during the experimental operation and ensure the accuracy of the experimental results.

5. Experimental procedure

PANC1 cell culture: After thawing PANC1 cells, they are seeded in DMEM medium containing 10% fetal bovine serum and 1% double antibiotics (penicillin-streptomycin), and cultured in a 37°C, 5% CO_2 incubator. The growth state of the cells is observed regularly. When the cell confluency

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reaches 80%-90%, subculture is performed. During subculture, first rinse the cells 2-3 times with PBS to remove serum and impurities in the medium, then add an appropriate amount of 0.25% trypsin to digest the cells. When the cells become round and start to detach, add serum-containing medium to stop digestion, gently blow the cells to make them into a single-cell suspension, and then seed the cells into new culture flasks at a ratio of 1:2 or 1:3 for continued culture.

Establishment of animal models: PANC1 cells in the logarithmic growth phase are digested with trypsin to prepare a single-cell suspension, and the cell concentration is adjusted to 1×10^7 cells per milliliter. Under sterile conditions, 0.1 milliliter of the cell suspension is inoculated subcutaneously into the right axilla of nude mice to establish a pancreatic cancer xenograft model. After inoculation, the general state and tumor growth of nude mice are observed regularly, including changes in body weight, mental state, and diet. A vernier caliper is used to measure the long diameter (a) and short diameter (b) of the tumor, and the tumor volume is calculated according to the formula $V = 1/2 \times a \times b^2$, and the tumor growth curve is drawn.

ADP-ribose treatment: When the tumor volume reaches about $100mm^3$, the tumor-bearing nude mice are randomly divided into different treatment groups. The groups treated with different concentrations of ADP-ribose are given intraperitoneal injections of ADP-ribose solutions of different concentrations (such as 75μM, 150μM, 300μM, 400μM, 500μM, 600μM), respectively, while the negative control group and the tumor model group are given an equal volume of PBS or normal saline, and positive control group is given an equal volume of poly I:C. Injections are given every 2 days for 2 consecutive weeks. During the injection process, strict adherence to aseptic operation principles is required to ensure the accuracy of the injection dose, and at the same time, the reaction of nude mice is closely observed, such as abnormal behavior, sharp weight loss, etc.

6. Data collection and analysis

ELISA detection of TNF-α and IL-2: Collect cell culture supernatants or mouse sera and operate according to the ELISA kit instructions. First, coat the capture antibody on the microplate and leave it at 4°C overnight to allow the antibody to firmly bind to the plate. Then, wash the microplate 3-5 times with PBST to remove unbound antibodies, add blocking solution, and incubate at room temperature for 1-2 hours to block non-specific binding sites. Next, add the test samples and standards, incubate at 37°C for 1-2 hours to allow TNF-α or IL-2 in the samples to bind to the capture antibody. Wash the microplate again with PBST, add the detection antibody, and incubate at 37°C for 1-2 hours so that the detection antibody binds to the bound TNF-α or IL-2. After washing, add the substrate solution and react at room temperature in the dark for 15-30 minutes to make the substrate undergo a color reaction under the catalysis of the enzyme. Finally, add the stop solution to terminate the reaction, measure the absorbance at 450nm with a microplate reader, and calculate the concentrations of TNF-α and IL-2 in the samples according to the standard curve.

Detection of T cell recruitment: Take tumor tissues, prepare frozen sections, and perform immunofluorescence staining with CD3 T cell marker antibodies. Take the sections out of the refrigerator, rewarm at room temperature for 30 minutes, then wash with PBS 3 times, 5 minutes each time. Add an appropriate amount of fixative and fix for 15-20 minutes to fix the cell structure. After washing with PBS again, add blocking solution and incubate at room temperature for 30-60 minutes to block non-specific binding sites. Add CD3 T cell marker antibody and incubate at 4°C overnight to allow the antibody to bind to the CD3 antigen on the surface of T cells. The next day, wash the sections 3 times with PBS, add fluorescent secondary antibody, and incubate at room temperature in the dark for 1-2 hours to allow the fluorescent secondary antibody to bind to the primary antibody. After washing, stain the nuclei with DAPI and incubate at room temperature for 5-

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10 minutes to stain the cell nuclei. Finally, mount the sections with anti-fluorescence quenching mounting medium, observe and take photos under a confocal microscope, and evaluate the recruitment of T cells by analyzing the fluorescence intensity and the number of positive cells.

Detection of tumor weight: After the experiment, euthanize the nude mice, take out the tumor tissues completely, rinse them with normal saline to remove surface blood and impurities, blot dry with filter paper, then weigh the tumor weight with an electronic balance, and compare the differences in tumor weight among different treatment groups. During the weighing process, ensure the accuracy and stability of the balance to avoid the influence of external factors on the weighing results.

I will repeat the experiments three times, and use normal distribution, t-test and one-way Anova to analyze the experimental data.

7. Results

Table 1. The combination results

Combination Result # (CR#)	Increasing ADP-ribose increases TNF-α	Increasing ADP-ribose increases IL-2	Increasing ADP-ribose increases T cell recruitment	Increasing ADP-ribose decreases tumor size	Support of hypothesis
1	+	+	+	+	Full
2	+	-	+	+	Partial
3	-	+	+	+	Partial
4	+	+	-	+	Partial
5	+	-	-	+	Partial
6	-	+	-	+	Partial
7	-	-	+	+	Partial
8	-	-	-	+	Partial
9	+	-	+	-	Partial
10	-	+	+	-	Partial
11	-	-	+	-	Partial
12	+	-	-	-	Partial
13	-	+	-	-	Partial
14	+	+	-	-	Partial
15	+	+	+	-	Partial
16	-	-	-	-	Fully Contradicts

Table legend: The "+" indicates that the heading phenomenon is observed similarly to the poly I:C (positive control group) and opposite to the PBS (negative control group) in the experiments and is statistically significant. The "-" indicates that the phenomenon observed is neither like the poly I:C (positive control group) nor opposite to the PBS (negative control group), nor is not statistically significant.

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In the positive control group (treated with poly I:C), the concentrations of TNF-α and IL-2 and the number of CD3-positive T cells were significantly higher than those in the control group, and the tumor weight was significantly lower than that in the tumor model group, verifying the effectiveness of the experimental system. In the negative control group (treated with PBS or normal saline), there was no significant difference in the above - mentioned indicators compared with the control group or the tumor model group, ruling out the non - specific effects of experimental operations, and thus confirming that the inhibitory effect of ADP - ribose on tumor growth is a specific result of TRPM2 activation.

CR1: After the concentration of ADP-ribose and the treatment duration increase, the concentrations of TNF-α and IL-2 increase compared with the negative control group, measured by ELISA; the T cell recruitment increases compared with the negative control group, measured with confocal microscopy using the CD3 T cell marker; the tumor size decreases compared with the negative control group, measured by xenograft experiment.

CR2: After the concentration of ADP-ribose and the treatment duration increase, the concentration of TNF-α increase compared with the negative control group, measured by ELISA; the concentration of IL-2 decrease compared with the negative control group, measured by ELISA; the T cell recruitment increases compared with the negative control group, measured with confocal microscopy using the CD3 T cell marker; the tumor size decreases compared with the negative control group, measured by xenograft experiment.

CR3: After the concentration of ADP-ribose and the treatment duration increase, the concentration of IL-2 increase compared with the negative control group, measured by ELISA; the concentration of TNF-α decrease compared with the negative control group, measured by ELISA; the T cell recruitment increases compared with the negative control group, measured with confocal microscopy using the CD3 T cell marker; the tumor size decreases compared with the negative control group, measured by xenograft experiment.

CR4: After the concentration of ADP-ribose and the treatment duration increase, the concentrations of TNF-α and IL-2 increase compared with the negative control group, measured by ELISA; the T cell recruitment decreases compared with the negative control group, measured with confocal microscopy using the CD3 T cell marker; the tumor size decreases compared with the negative control group, measured by xenograft experiment.

CR5: After the concentration of ADP-ribose and the treatment duration increase, the concentration of TNF-α increase compared with the negative control group, measured by ELISA; the concentration of IL-2 decrease compared with the negative control group, measured by ELISA; the T cell recruitment decreases compared with the negative control group, measured with confocal microscopy using the CD3 T cell marker; the tumor size decreases compared with the negative control group, measured by xenograft experiment.

CR6: After the concentration of ADP-ribose and the treatment duration increase, the concentration of IL-2 increase compared with the negative control group, measured by ELISA; the concentration of TNF-α decrease compared with the negative control group, measured by ELISA; the T cell recruitment decreases compared with the negative control group, measured with confocal microscopy using the CD3 T cell marker; the tumor size decreases compared with the negative control group, measured by xenograft experiment.

CR7: After the concentration of ADP-ribose and the treatment duration increase, the concentrations of TNF-α and IL-2 decrease compared with the negative control group, measured by ELISA; the T cell recruitment increases compared with the negative control group, measured with

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confocal microscopy using the CD3 T cell marker; the tumor size decreases compared with the negative control group, measured by xenograft experiment.

CR8: After the concentration of ADP-ribose and the treatment duration increase, the concentrations of TNF-α and IL-2 decrease compared with the negative control group, measured by ELISA; the T cell recruitment decreases compared with the negative control group, measured with confocal microscopy using the CD3 T cell marker; the tumor size decreases compared with the negative control group, measured by xenograft experiment.

CR9: After the concentration of ADP-ribose and the treatment duration increase, the concentration of TNF-α increase compared with the negative control group, measured by ELISA; the concentration of IL-2 decrease compared with the negative control group, measured by ELISA; the T cell recruitment increases compared with the negative control group, measured with confocal microscopy using the CD3 T cell marker; the tumor size increases compared with the negative control group, measured by xenograft experiment.

CR10: After the concentration of ADP-ribose and the treatment duration increase, the concentration of IL-2 increase compared with the negative control group, measured by ELISA; the concentration of TNF-α decrease compared with the negative control group, measured by ELISA; the T cell recruitment increases compared with the negative control group, measured with confocal microscopy using the CD3 T cell marker; the tumor size increases compared with the negative control group, measured by xenograft experiment.

CR11: After the concentration of ADP-ribose and the treatment duration increase, the concentrations of TNF-α and IL-2 decrease compared with the negative control group, measured by ELISA; the T cell recruitment increases compared with the negative control group, measured with confocal microscopy using the CD3 T cell marker; the tumor size increases compared with the negative control group, measured by xenograft experiment.

CR12: After the concentration of ADP-ribose and the treatment duration increase, the concentration of TNF-α increase compared with the negative control group, measured by ELISA; the concentration of IL-2 decrease compared with the negative control group, measured by ELISA; the T cell recruitment decreases compared with the negative control group, measured with confocal microscopy using the CD3 T cell marker; the tumor size increases compared with the negative control group, measured by xenograft experiment.

CR13: After the concentration of ADP-ribose and the treatment duration increase, the concentration of IL-2 increase compared with the negative control group, measured by ELISA; the concentration of TNF-α decrease compared with the negative control group, measured by ELISA; the T cell recruitment decreases compared with the negative control group, measured with confocal microscopy using the CD3 T cell marker; the tumor size increases compared with the negative control group, measured by xenograft experiment.

CR14: After the concentration of ADP-ribose and the treatment duration increase, the concentrations of TNF-α and IL-2 increase compared with the negative control group, measured by ELISA; the T cell recruitment decreases compared with the negative control group, measured with confocal microscopy using the CD3 T cell marker; the tumor size increases compared with the negative control group, measured by xenograft experiment.

CR15: After the concentration of ADP-ribose and the treatment duration increase, the concentrations of TNF-α and IL-2 increase compared with the negative control group, measured by ELISA; the T cell recruitment increases compared with the negative control group, measured with confocal microscopy using the CD3 T cell marker; the tumor size increases compared with the negative control group, measured by xenograft experiment.

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CR16: After the concentration of ADP-ribose and the treatment duration increase, the concentrations of TNF-α and IL-2 decrease compared with the negative control group, measured by ELISA; the T cell recruitment decreases compared with the negative control group, measured with confocal microscopy using the CD3 T cell marker; the tumor size increases compared with the negative control group, measured by xenograft experiment.

8. Discussion

CR1: I think this combination result can prove that the hypothesis is fully correct. The possible reasons for this outcome are as follows. First, TNF-α may directly trigger the death of tumor cells or help T cells better recognize and target tumor cells. Second, IL-2 likely plays a key role in boosting the growth and activity of CTLs, making these cells more effective at killing tumor cells. Meanwhile, the increasing recruitment of T cells—possibly stimulated by both TNF-α and IL-2—creates a stronger immune response against the tumor, leading to reduced tumor weight. Additionally, longer treatment with higher concentrations of ADP-ribose may keep TRPM2 channels more active, which in turn promotes the continuous release of TNF-α and IL-2, creating a "chain reaction" that strengthens the anti-tumor effect over time. The next experiments could include several steps. First, to dig deeper into TRPM2's role, we can block the TRPM2 channel (using inhibitors) and check if TNF-α, IL-2 levels, and T cell recruitment drop, while tumor weight increases—this would confirm that TRPM2 is the main driver. Second, to study the downstream pathways, we can test if proteins like NF-κB are more active when ADP-ribose concentrations are high, as this would show how TRPM2 signals to produce TNF-α and IL-2. Third, to verify TNF-α's direct effect, we can add TNF-α alone to tumor cells and see if they die faster. Similarly, we can add IL-2 alone to T cells and check if they become better at killing tumor cells. Fourth, we can use antibodies to block TNF-α or IL-2 in the system; if the tumor stops shrinking, it will prove that these factors are necessary for the anti-tumor effect. Finally, we can look at the interaction between T cells and tumor cells under a microscope to see if more T cells attach to and attack tumor cells when TNF-α and IL-2 levels are high.

CR2: I think this combination of results can suggest that the hypothesis is partly correct. The possible reason for this result is the consumption of IL-2. For example, the increased recruitment of T cells might rapidly use up IL-2, leaving little in the detected samples, which could explain why its concentration does not rise or even decreases. Another possibility is that the anti-tumor effect here relies more on TNF-α and T cells, while IL-2 is not the main driver. TNF-α itself might directly kill tumor cells or inhibit their growth, and the recruited T cells could attack tumors through other ways that do not depend on IL-2, such as releasing cytotoxic substances. Additionally, TRPM2 activation by ADP-ribose might trigger pathways that suppress IL-2 production, while still promoting TNF-α and T cell recruitment to fight tumors. The next experiments could include several steps. First, to check if IL-2 is being consumed, we can measure the expression of IL-2 receptors on T cells—higher receptor levels might mean more IL-2 is being taken up. Second, we can add extra IL-2 to the system and see if it changes the results, such as making IL-2 concentrations rise or affecting tumor weight, which would show if IL-2 is involved indirectly. Third, to explore TNF-α's role, we can block TNF-α activity (using antibodies) and observe if the tumor stops shrinking or if T cell recruitment drops, proving its importance. Fourth, we can test the cytotoxic substances released by T cells to see if they increase when IL-2 is low, indicating alternative killing ways. Finally, we can study whether TRPM2 activation directly affects IL-2 production by checking related genes or proteins in the pathway, to find out why IL-2 levels do not rise.

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CR3: I think this combination of results can suggest that the hypothesis is partly correct. The possible reasons for this result are as follows. One reason could be the consumption of TNF-α: as T cell recruitment increases, TNF-α might be used up quickly in processes like activating T cells, leaving less to detect in samples, which explains why its concentration doesn't rise or even drops. Another possibility is that the anti-tumor effect here mainly relies on IL-2 and T cells, while TNF-α isn't a key player. IL-2 could directly boost T cell growth and activity, making these T cells strong enough to attack tumors on their own, without needing TNF-α. Additionally, TRPM2 activation by ADP-ribose might mainly trigger pathways that promote IL-2 and T cell recruitment, while either suppressing TNF-α production or having no effect on it. The next experiments could include several steps. First, to check if TNF-α is being consumed, we can measure the levels of TNF-α receptors on T cells—higher receptor levels might mean more TNF-α is being taken up and used. Second, we can add extra TNF-α to the system and see if it changes the results, such as affecting tumor weight or T cell recruitment, which would show if TNF-α has any indirect role. Third, to confirm IL-2's main role, we can block IL-2 activity (using antibodies) and observe if T cell recruitment drops and tumors grow larger, proving IL-2 is necessary. Fourth, we can test the killing ability of T cells when TNF-α is low, for example, checking if they release more cytotoxic substances to see if they use alternative ways to fight tumors. Finally, we can study whether TRPM2 activation directly affects TNF-α production by looking at related genes or proteins, to find out why TNF-α levels don't rise.

CR4: I think this combination of results can suggest that the hypothesis is partly correct. The possible reasons for this result are as follows. One reason could be the consumption of T cells: the recruited T cells might be quickly used up when attacking tumor cells (e.g., dying after killing tumors), so their numbers detected in samples don't rise or even drop. Another possibility is that TNF-α and IL-2 themselves can kill tumor cells through pathways that don't need T cells. For example, TNF-α might directly trigger tumor cell death or stop tumor blood vessel growth, while IL-2 could activate other immune cells (like NK cells) to fight tumors, bypassing T cells. Additionally, ADP-ribose activating TRPM2 might mainly boost TNF-α and IL-2 production but also trigger signals that reduce T cell recruitment, such as releasing substances that stop T cells from moving into the tumor. The next experiments could include several steps. First, to check if T cells are being consumed, we can test for T cell death markers (like certain proteins) in tumor tissues—higher levels would mean more T cells are dying after action. Second, we can test TNF-α and IL-2 alone on tumor cells in a dish, without any T cells, to see if the tumor cells die faster—this would show they can act directly. Third, we can look for other immune cells (like NK cells) in the tumor: if their numbers rise when T cells don't, they might be helping TNF-α and IL-2 fight tumors. Fourth, we can block TNF-α or IL-2 (using antibodies) and see if the tumor stops shrinking, which would prove they're key to the anti-tumor effect. Finally, we can check if TRPM2 activation reduces substances that attract T cells (like chemokines)—lower levels of these would explain why T cell recruitment doesn't increase.

CR5: I think this combination of results can suggest that the hypothesis is partly correct. The possible reasons for this result are as follows. One reason could be the consumption of T cells and IL-2: T cells might be used up quickly in attacking tumors (e.g., dying after killing tumor cells), and IL-2 could be rapidly consumed to support any remaining T cell activity, leading to their decreased levels. Another possibility is that TNF-α alone is strong enough to kill tumor cells without needing T cells or IL-2. For example, TNF-α might directly trigger tumor cell death, stop tumor blood vessel growth, or damage tumor cell structures on its own. Additionally, TRPM2 activation by ADP-ribose might mainly promote TNF-α production while suppressing pathways that make IL-2 or recruit T cells, shifting the anti-tumor effect to rely solely on TNF-α. The next experiments could include

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several steps. First, to check if IL-2 is being consumed, we can measure IL-2 receptors on T cells—more receptors might mean IL-2 is being taken up and used, even if levels seem low. Second, to test TNF-α's direct role, we can block TNF-α (using antibodies) and see if the tumor stops shrinking, which would prove that it's the main driver. Third, to find out why IL-2 is low, we can check genes or proteins that make IL-2; if they're less active, it might mean TRPM2 activation suppresses them. Fourth, we can look at T cell function even if their numbers are low—do they release cytotoxic substances (like perforin)? This would show if they're still working, just in smaller numbers. Finally, we can test if adding IL-2 or T cells to the system changes the result (e.g., tumor weight or TNF-α levels) to see if they could still play a role when present.

CR6: I think this combination of results can suggest that the hypothesis is partly correct. The possible reasons for this result are as follows. One reason could be the consumption of T cells and TNF-α: T cells might be used up quickly after attacking tumor cells (e.g., dying after killing them), so their recruitment appears reduced; meanwhile, TNF-α could be rapidly consumed in early anti-tumor processes, leaving little to detect. Another possibility is that IL-2 alone drives the anti-tumor effect without relying on T cells or TNF-α. For example, IL-2 might activate other immune cells (like NK cells) to kill tumors, or directly inhibit tumor cell growth even when T cells and TNF-α are low. Additionally, TRPM2 activation by ADP-ribose might mainly boost IL-2 production while suppressing pathways that promote TNF-α or T cell recruitment, making IL-2 the key player. The next experiments could include several steps. First, to test IL-2's direct role, we can treat tumor cells with IL-2 alone (without T cells or TNF-α) and see if they grow more slowly—this would show IL-2 acts independently. Second, to check if T cells are being consumed, we can look for T cell death markers in tumor tissues; higher levels would mean T cells are dying after action, explaining lower recruitment. Third, to see if TNF-α is being consumed, we can measure TNF-α receptors on tumor cells—more receptors might mean TNF-α is being taken up and used, even if levels seem low. Fourth, we can block IL-2 with antibodies; if the tumor stops shrinking, it will prove IL-2 is necessary for the effect. Fifth, we can check other immune cells (like NK cells) in tumors—if their numbers rise with IL-2, they might be helping IL-2 fight tumors. Finally, we can test if TRPM2 activation suppresses genes related to TNF-α production or T cell recruitment, to explain why their levels don't rise.

CR7: I think this combination of results can suggest that the hypothesis is partly correct. The possible reasons for this result are as follows. One reason could be the consumption of IL-2 and TNF-α: the increasing number of recruited T cells might quickly use up IL-2 (for their activation or growth) and TNF-α (for signaling), leaving little of these cytokines to be detected in samples. Another possibility is that T cells alone can kill tumor cells without relying on IL-2 or TNF-α. For example, CTLs might directly attack and destroy tumor cells through their mechanisms, such as releasing perforin or granzyme, even when IL-2 and TNF-α levels are low. Additionally, ADP-ribose activating TRPM2 might mainly promote T cell recruitment while having no effect on (or even suppressing) the production of IL-2 and TNF-α, making T cells the main force in anti-tumor activity. The next experiments could include several steps. First, to test if T cells kill tumors independently, we can isolate T cells from treated samples and co-culture them with tumor cells (without adding IL-2 or TNF-α) to see if the tumor cells die—this would show T cells act on their own. Second, to check if IL-2 and TNF-α are being consumed, we can measure their receptors on T cells or tumor cells; higher receptor levels would mean more cytokines are being taken up and used. Third, we can block IL-2 and TNF-α with antibodies and observe if T cell recruitment still reduces tumor weight—if yes, it proves T cells work without these cytokines. Fourth, we can look at the activity of T cells (like the amount of perforin they release) in samples with low IL-2 and TNF-α; higher activity

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would explain their anti-tumor effect. Finally, we can study whether TRPM2 activation directly promotes T cell recruitment by checking chemokines (substances that attract T cells)—higher levels would explain the increased T cell numbers.

CR8: I think this combination of results can suggest that the hypothesis is partly correct. The possible reasons for this result are as follows. One reason could be the consumption of T cells, IL-2, and TNF-α: as the tumor shrinks, these immune factors and cells might be used up in the process—for example, T cells could die after attacking tumors, and IL-2/TNF-α might be fully utilized in early anti-tumor responses, leaving few to detect. Another possibility is that ADP-ribose kills tumor cells through pathways that don't rely on T cells, IL-2, or TNF-α at all. For instance, it might directly damage tumor cell DNA, disrupt their metabolism, or trigger their self-destruction (apoptosis) without needing immune help. Additionally, TRPM2 activation by ADP-ribose might mainly suppress tumor growth directly, while having no effect on (or even reducing) immune-related factors like IL-2, TNF-α, and T cells. The next experiments could include several steps. First, to test if ADP-ribose acts directly on tumors, we can treat isolated tumor cells with ADP-ribose (without any immune cells, IL-2, or TNF-α) and see if they die or grow slower—this would show a non-immune pathway. Second, to check if T cells, IL-2, or TNF-α are being consumed, we can measure their receptors on tumor cells or T cells; higher receptor levels would mean more factors are being used up. Third, we can look for signs of tumor cell apoptosis (like broken DNA) in treated samples—more apoptosis would explain why tumors shrink without immune factors. Fourth, we can block TRPM2 with inhibitors and see if the tumor stops shrinking; if yes, it proves TRPM2 is driving the effect, possibly through non-immune ways. Finally, we can check for other anti-tumor molecules (not IL-2 or TNF-α) in samples—if their levels rise with ADP-ribose, they might be the real drivers of tumor shrinkage.

CR9: I think this combination of results can suggest that the hypothesis is partly correct. The possible reasons for this result are as follows. One reason could be the consumption of IL-2: the increasing recruitment of T cells might quickly use up IL-2, leading to its decreased concentration, which in turn weakens the overall anti-tumor ability. Another more concerning possibility is that the activated TRPM2 channel, instead of just promoting an anti-tumor response, may also directly or indirectly stimulate tumor growth. For example, TRPM2 activation might trigger pathways in tumor cells that promote their survival, proliferation, or resistance to immune attacks. This means the growth-promoting effect of TRPM2 activation on tumors could be stronger than the killing effect of the recruited T cells, resulting in a net increase or unchanged tumor weight. The next experiments could include several steps. First, to test if TRPM2 activation directly promotes tumor growth, we can treat tumor cells with ADP-ribose in the presence or absence of a TRPM2 inhibitor. If the inhibitor blocks tumor growth (while ADP-ribose alone increases it), this would prove that TRPM2 is responsible for the growth-promoting effect. Second, we can check which genes or proteins in tumor cells are activated by TRPM2, for example, genes related to cell division or anti-apoptosis. Third, to see if IL-2 depletion is key, we can add extra IL-2 to the system and observe if it reverses the tumor growth (i.e., tumors start to shrink). Fourth, we can analyze the type of T cells recruited: are they anti-tumor T cells (like CD8+ CTLs), or could they be regulatory T cells (Tregs) that suppress the immune response? Finally, we can use a TRPM2 knockout model (cells or animals) to confirm that without TRPM2, ADP-ribose no longer promotes tumor growth, and the anti-tumor effect of T cells and TNF-α becomes dominant.

CR10: I think this combination of results can suggest that the hypothesis is partly correct. The possible reasons for this result are as follows. One reason could be the consumption of TNF-α: the recruited T cells might use up TNF-α quickly for their activation or function, leading to its low or

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unchanged levels. Another key possibility is that activated TRPM2 not only affects the immune system but also directly promotes tumor growth. For example, TRPM2 activation might trigger pathways in tumor cells that help them grow faster or resist damage, even as more T cells are recruited. In this case, the tumor-promoting effect of TRPM2 could be stronger than the killing effect of the recruited T cells (which lack enough TNF-α to support their anti-tumor function), resulting in tumors growing or staying the same size. The next experiments could include several steps. First, to confirm TRPM2's role in promoting tumors, we can use TRPM2 inhibitors along with ADP-ribose. If the tumor stops growing or shrinks when TRPM2 is blocked, it will prove that TRPM2 activation is causing the growth. Second, to check if TNF-α is being consumed, we can measure TNF-α receptors on T cells—more receptors would mean TNF-α is being taken up and used, explaining its low levels. Third, we can add extra TNF-α to the system and see if T cells become better at killing tumors (e.g., tumor weight decreases)—this would show that TNF-α depletion weakens T cells' ability. Fourth, we can look at tumor cell growth directly: treat isolated tumor cells with ADP-ribose (without T cells or TNF-α) and see if they grow faster—this would confirm that TRPM2 promotes tumor growth directly. Finally, we can check the activity of T cells (like how many cytotoxic substances they release) when TNF-α is low; if their activity is weak, it would explain why they can't stop tumor growth.

CR11: I think this combination of results can suggest that the hypothesis is partly correct. The possible reasons for this result are as follows. One reason could be the consumption of IL-2 and TNF-α: the increasing number of recruited T cells might rapidly use up these cytokines for their activation, proliferation, or functional maintenance, leaving little to be detected in the samples, which explains their downward or unchanged concentrations. Another critical possibility is that the activated TRPM2 may have a direct tumor-promoting effect. For example, TRPM2 activation could trigger signaling pathways in tumor cells that enhance their proliferation, survival, or ability to evade immune attacks. In this scenario, the tumor-growth-promoting effect of TRPM2 activation is stronger than the anti-tumor killing effect exerted by the recruited T cells (which may lack sufficient IL-2 and TNF-α to function optimally), resulting in the tumor weight increasing or remaining unchanged despite more T cells being recruited. The next experiments could include several steps. First, to confirm that TRPM2 activation is responsible for the tumor weight increase, we can treat the experimental model with TRPM2 inhibitors along with ADP-ribose. If the tumor weight stops increasing or even decreases when TRPM2 is inhibited, it would directly prove that TRPM2 activation is the driver of tumor growth. Second, to verify the consumption of IL-2 and TNF-α, we can measure the expression levels of IL-2 receptors and TNF-α receptors on the surface of T cells. Higher receptor expression would indicate that more IL-2 and TNF-α are being taken up and utilized by T cells, supporting the consumption hypothesis. Third, we can supplement the system with exogenous IL-2 and TNF-α and observe whether the recruited T cells' killing effect on tumors is enhanced (e.g., tumor weight decreases). This would help determine if the insufficient levels of these cytokines are limiting the T cells' anti-tumor function. Fourth, we can isolate tumor cells and treat them with ADP-ribose in vitro (without T cells or cytokines) to check if their proliferation rate increases. This would confirm whether TRPM2 activation can directly promote tumor cell growth. Finally, we can examine the functional state of the recruited T cells (such as their ability to release cytotoxic molecules like perforin and granzyme) under conditions of low IL-2 and TNF-α. If their functional activity is weak, it would further explain why the increased T cell recruitment fails to reduce tumor weight.

CR12: I think this combination of results can suggest that the hypothesis is partly correct. The possible reasons for this result are as follows. One reason could be the consumption of IL-2 and T

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cells: any existing T cells might use up IL-2 quickly for their activity, and these T cells themselves could be depleted in the process, leading to their low or unchanged numbers. Another key reason is that activated TRPM2 may directly promote tumor growth. For example, TRPM2 activation could trigger pathways in tumor cells that make them grow faster or resist damage. Even though TNF-α levels are rising (which might normally fight tumors), the tumor-promoting effect of TRPM2 is stronger than TNF-α's anti-tumor effect, causing the tumor to grow or stay the same size. The next experiments could include several steps. First, to check if TRPM2 is causing tumor growth, we can use TRPM2 inhibitors along with ADP-ribose. If the tumor stops growing when TRPM2 is blocked, it proves that TRPM2 activation is the cause. Second, to test if IL-2 is being consumed, we can measure IL-2 receptors on T cells—more receptors would mean IL-2 is being used up. Third, to see if TNF-α is not working well, we can add extra TNF-α to tumor cells and check if they grow slower; if not, it means TNF-α's effect is weak here. Fourth, we can look at tumor cells directly: treat them with ADP-ribose (without T cells or IL-2) and see if they grow faster—this would show that TRPM2 promotes growth directly. Finally, we can check if T cells are dying off (by looking for T cell death markers) to explain their low numbers.

CR13: I think this combination of results can suggest that the hypothesis is partly correct. The possible reasons for this result are as follows. One reason could be the consumption of TNF-α and T cells: any existing T cells might quickly use up TNF-α for their activation or function, and these T cells themselves could be depleted during the process, leading to their low or unchanged numbers. Another key reason is that activated TRPM2 may directly drive tumor growth. For example, TRPM2 activation could trigger pathways in tumor cells that boost their proliferation or help them survive, even as IL-2 levels rise. In this case, the tumor-growth-promoting effect of TRPM2 is stronger than the potential anti-tumor effect of IL-2, which is why the tumor weight increases or stays the same despite higher IL-2 concentrations. The next experiments could include several steps. First, to confirm TRPM2's role in tumor growth, we can use TRPM2 inhibitors along with ADP-ribose. If the tumor stops growing or shrinks when TRPM2 is blocked, it will prove that TRPM2 activation is causing the growth. Second, to check if TNF-α and T cells are being consumed, we can measure TNF-α receptors on T cells (more receptors might mean more TNF-α is being used) and look for T cell death markers (to see if T cells are dying off). Third, to test IL-2's effect, we can add extra IL-2 to the system and see if it slows tumor growth—if not, it would support that IL-2's effect is weaker than TRPM2's growth-promoting effect. Fourth, we can treat isolated tumor cells with ADP-ribose (without T cells or TNF-α) and check if they grow faster—this would show that TRPM2 directly promotes tumor cell growth. Finally, we can look at IL-2's target cells (like other immune cells) to see if it's acting, but just not enough to stop TRPM2-driven tumor growth.

CR14: I think this combination of results can suggest that the hypothesis is partly correct. The possible reasons for this result are as follows. One reason could be the consumption of T cells: any T cells that are recruited might be quickly used up in the process of attacking tumor cells (for example, dying after exerting their killing effect), which is why their recruitment shows a downward or unchanged trend. Another key reason is that the activated TRPM2 may have a strong tumor-promoting effect. For instance, TRPM2 activation could trigger pathways in tumor cells that make them grow faster, multiply more, or become more resistant to the effects of cytokines like IL-2 and TNF-α. Even though IL-2 and TNF-α concentrations are rising (substances that usually help fight tumors), the tumor-growth-promoting effect caused by TRPM2 activation is stronger than the anti-tumor effect of IL-2 and TNF-α, leading to the tumor weight increasing or remaining unchanged. The next experiments could include several steps. First, to confirm that TRPM2 activation is responsible for the tumor weight increase, we can use TRPM2 inhibitors along with ADP-ribose. If

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the tumor stops growing or even shrinks when TRPM2 is inhibited, it will clearly show that TRPM2 activation is the main cause of the tumor growth. Second, to check if T cells are being consumed, we can look for markers of T cell death in the tumor tissue. A higher level of these markers would indicate that T cells are dying off after being recruited, explaining their low recruitment numbers. Third, we can add extra T cells to the system and observe if the tumor weight is affected (for example, whether it stops increasing or decreases). This would help determine if the lack of sufficient T cells is a factor in the tumor not shrinking despite higher IL-2 and TNF-α levels. Fourth, we can treat isolated tumor cells with ADP-ribose (without any T cells) and see if they grow faster. This would prove that TRPM2 activation can directly promote the growth of tumor cells on its own. Finally, we can test the combined effect of IL-2 and TNF-α on tumor cells by adding them to the tumor cells in a dish and checking if the cells grow more slowly. If they don't, it would further support that their anti-tumor effect is weaker than TRPM2's tumor-promoting effect here.

CR15: I think this combination of results can suggest that the hypothesis is partly correct. The possible reasons for this result are as follows. The main reason is likely that activated TRPM2 has a strong tumor-promoting effect. Even though ADP-ribose increases the levels of TNF-α, IL-2, and T cell recruitment—factors that usually help fight tumors—TRPM2 activation may trigger pathways that make tumor cells grow faster or resist the immune attack. For example, TRPM2 could boost tumor cell division directly or help them hide from T cells, so the tumor keeps growing despite the stronger immune response. In short, the tumor-growth-promoting effect of TRPM2 is stronger than the killing effect of the increased immune factors and T cells. The next experiments could include several steps. First, use TRPM2 inhibitors along with ADP-ribose. If the tumor stops growing or shrinks when TRPM2 is blocked, it will prove that TRPM2 activation is causing the tumor to grow. Second, check tumor cells directly: treat isolated tumor cells with ADP-ribose (without immune factors or T cells) and see if they grow faster. This shows that TRPM2 promotes tumor growth directly. Third, test if the immune factors are working: add more TNF-α, IL-2, or T cells to the system and see if the tumor stops growing. If not, it means the tumor is resisting their effects. Fourth, look at how T cells interact with tumor cells—do T cells attack them, but the tumor cells just keep growing? This would explain why more T cells don't reduce tumor weight. Finally, check for proteins in tumor cells that TRPM2 might activate to promote growth (like those that help cells divide) to find the exact pathway.

CR16: I think this combination result can prove that the hypothesis is fully contradicted. The possible reasons for this result are as follows. One reason could be that ADP-ribose activation of TRPM2 suppresses the immune response. For example, TRPM2 activation might inhibit the production of TNF-α and IL-2, or prevent T cells from being recruited to the tumor site, weakening the body's ability to fight tumors. Another possibility is that TRPM2 activation directly promotes tumor growth. It could stimulate tumor cells to multiply faster or resist cell death, leading to increased tumor weight even as immune factors decrease. Additionally, long-term treatment with ADP-ribose might cause the tumor to adapt, making it less responsive to immune attacks and allowing it to grow unchecked. The next experiments could include several steps. First, to check if TRPM2 is the cause, we can use TRPM2 inhibitors with ADP-ribose. If immune factors (TNF-α, IL-2, T cells) increase and tumor growth slows, it would show that TRPM2 is suppressing immunity or promoting tumors. Second, we can test if adding TNF-α, IL-2, or T cells directly to the tumor stops its growth. This would see if these factors can still work when TRPM2 is active. Third, we can look at the tumor microenvironment for other immune-suppressing cells (like Tregs) that might be increasing, which could explain why T cells and cytokines are low. Fourth, we can study tumor cell genes to find out if TRPM2 activation turns on genes that help tumors grow or resist immunity.

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Finally, we can try combining ADP-ribose with other immune boosters to see if they reverse the negative effects, which might help find new treatment ways.

9. Conclusion

If the combination result is CR1, it can prove that the hypothesis is fully correct, that is, increasing concentrations and treatment durations with the TRPM2 activator ADP-ribose increase production of TNF-α, IL-2, and increase recruitment of T cells, resulting in a decrease in PANC1 pancreatic cancer xenograft tumor size.

If the combination results are CR2-CR15, they can support the hypothesis that it is partly correct. Some can prove the effect of IL-2, and some can prove the effect of TNF-α, and others can prove the effect of T cells.

If the combination result is CR16, it can prove that the hypothesis is fully

incorrect that increasing concentrations and treatment durations with the TRPM2 activator ADP-ribose cannot increase production of TNF-α, IL-2, and cannot increase recruitment of T cells, and cannot result in decreased PANC1 pancreatic cancer xenograft tumor size.

In the future, we can experiment with the effects of other proteins in the TRPM2 pathway, such as NF-κB.

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