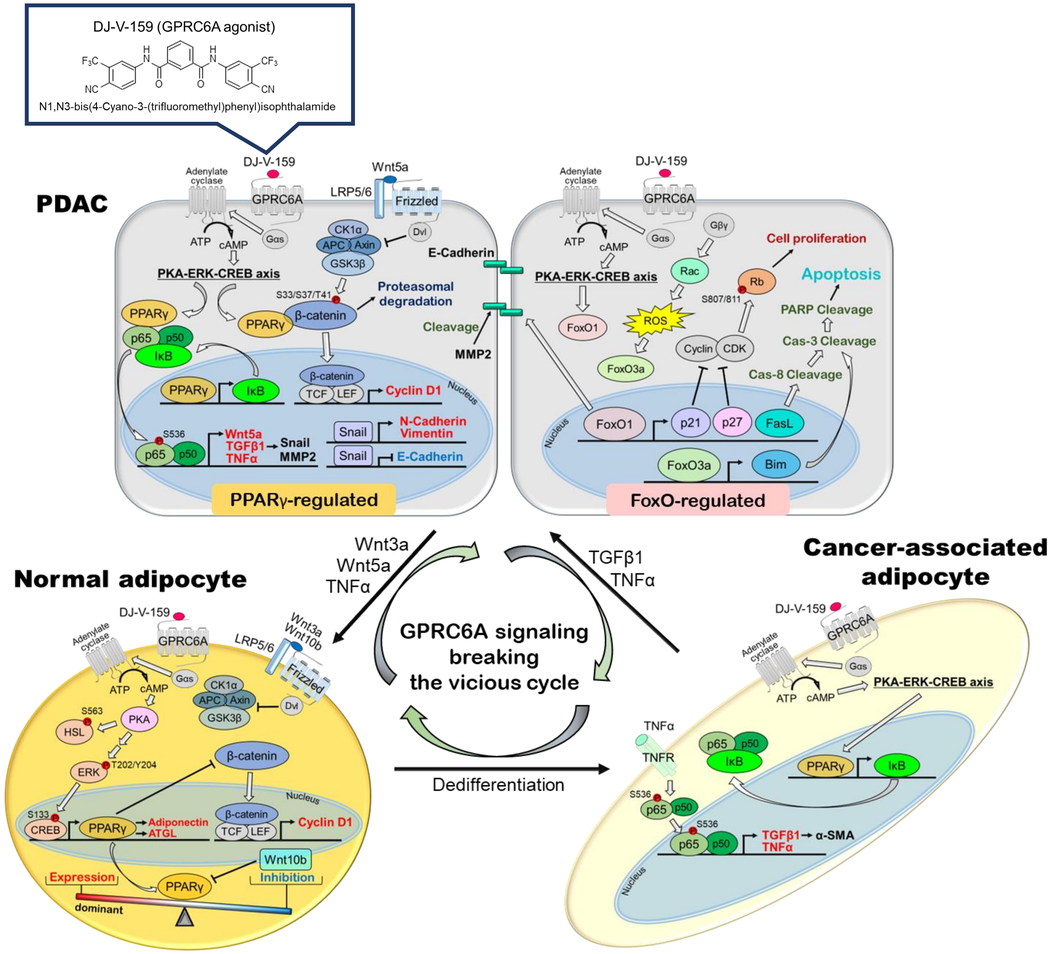
The Role of GPRC6A Activated by Osteocalcin in Pancreatic Cancer and the Tumor Microenvironment

Yuki. Nakamura[1.2] , T. Otani[1] , T. Matsunaga[2,4] , T. Matsuura[2] , Y. Takaesu[2] , H. Kido[3] , K. Egashira[3], M. Arakawa[3], Y. Kido[3]

[1] Fukuoka Dental College, Dept. of Morphological Biology, Sect. of Functional Structure, [2] Dept. of Oral Rehabilitation, Sect. of Fixed Prosthodontics
[3] Dept. of Oral rehabilitation, Sect. of Oral Implantology, [4] Matsunaga Dental Clinic, Fukuoka, JAPAN

Fukuoka Dental College

Academy of Osseointegration



Introduction

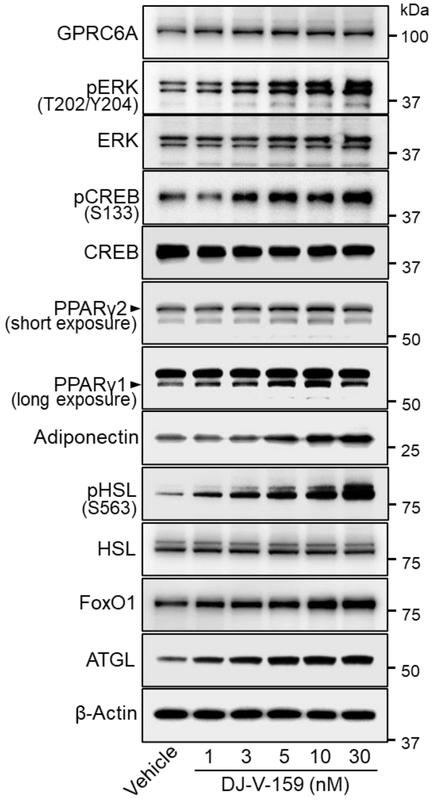
Pancreatic Ductal Adenocarcinoma (PDAC) has the highest mortality rate of all cancers worldwide. PDAC is one of the poor prognosis cancers because it spreads easily and early. It has been reported that the adipocytes adjacent to pancreas are implicated in PDAC aggressiveness.

We have researched the effects of osteocalcin (OC), a non-collagenous bone matrix protein, on the function of adipocytes so far. In this process, we have revealed that OC binds to GPRC6A, an osteocalcin receptor, and upregulation of PPARγ activity promotes metabolic activation in adipocytes. In addition, we also found that the GPRC6A receptor is expressed in PDAC.

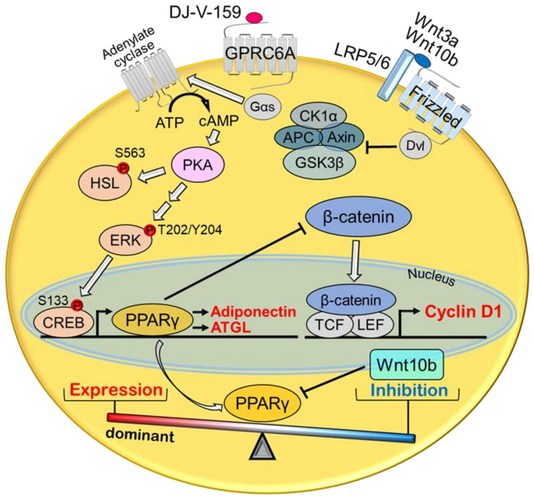
In the present study, instead of osteocalcin, we utilized a newly developed compound, DJ-V-159, to activate the GPRC6A receptor. DJ-V-159 is considered a similarly functional analog of osteocalcin.

Then, we have verified the effects of GPRC6A signaling on CAA and PDAC.

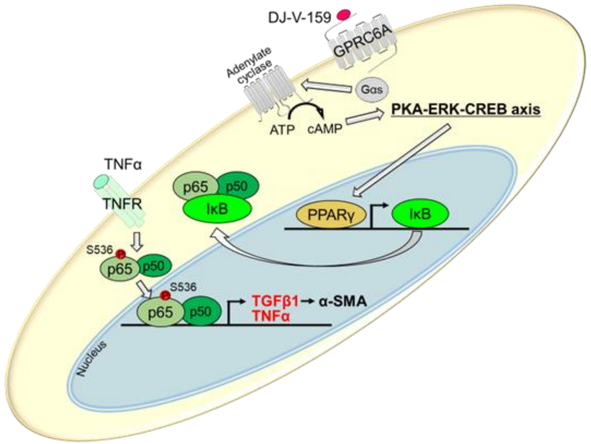
1. Preliminary study for DJ-V-159 effects on 3T3-L1 adipocytes



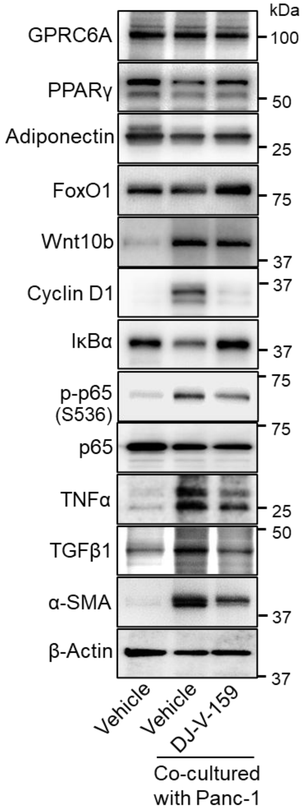
Normal adipocyte

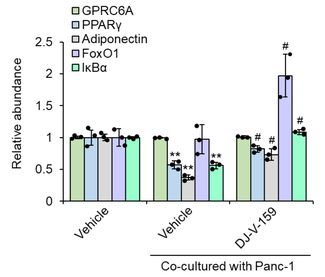


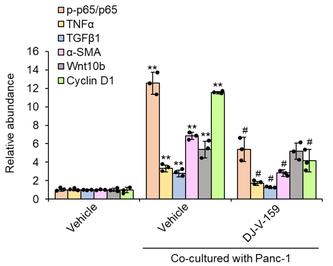
Cancer-associated adipocyte 【CAA】



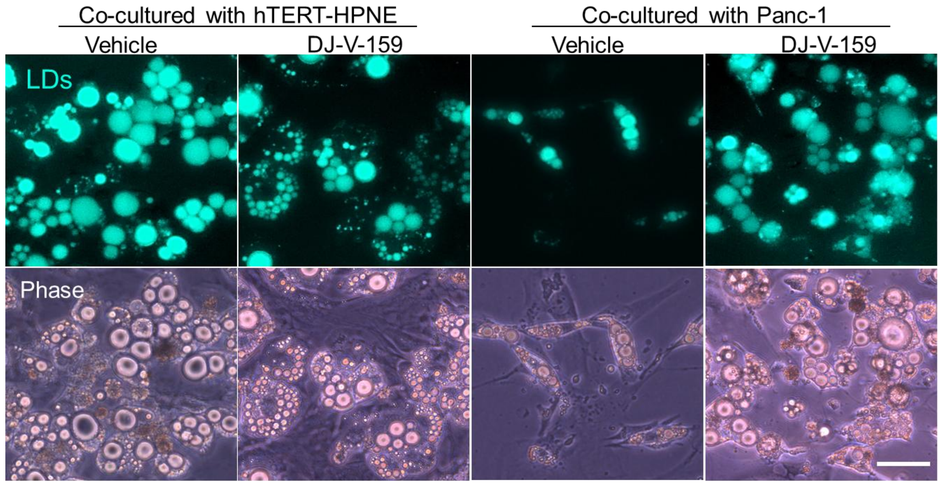
2. GPRC6A inhibits downregulation of PPARγ and NF-κB in CAA



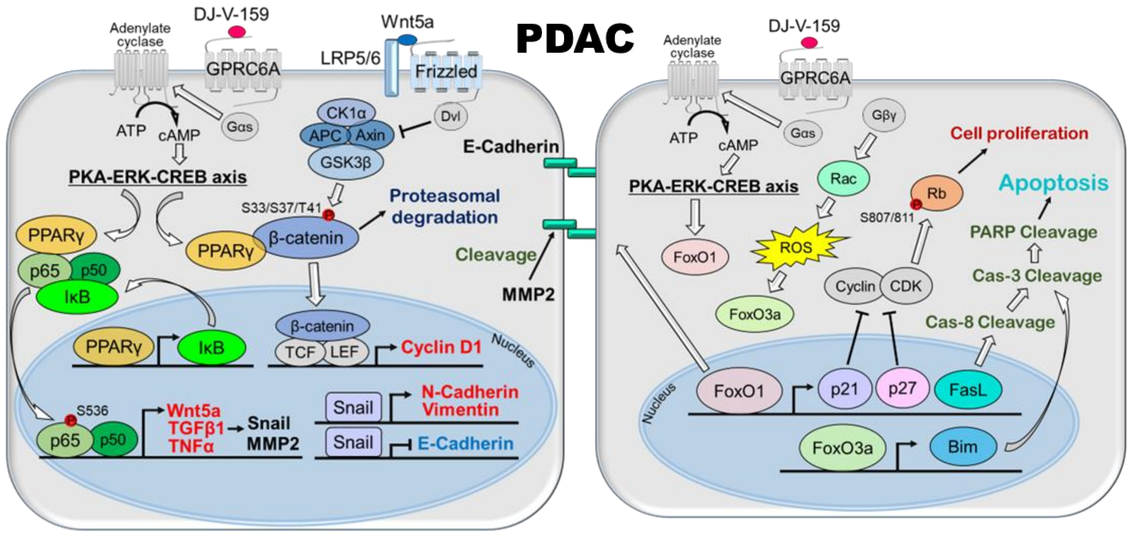




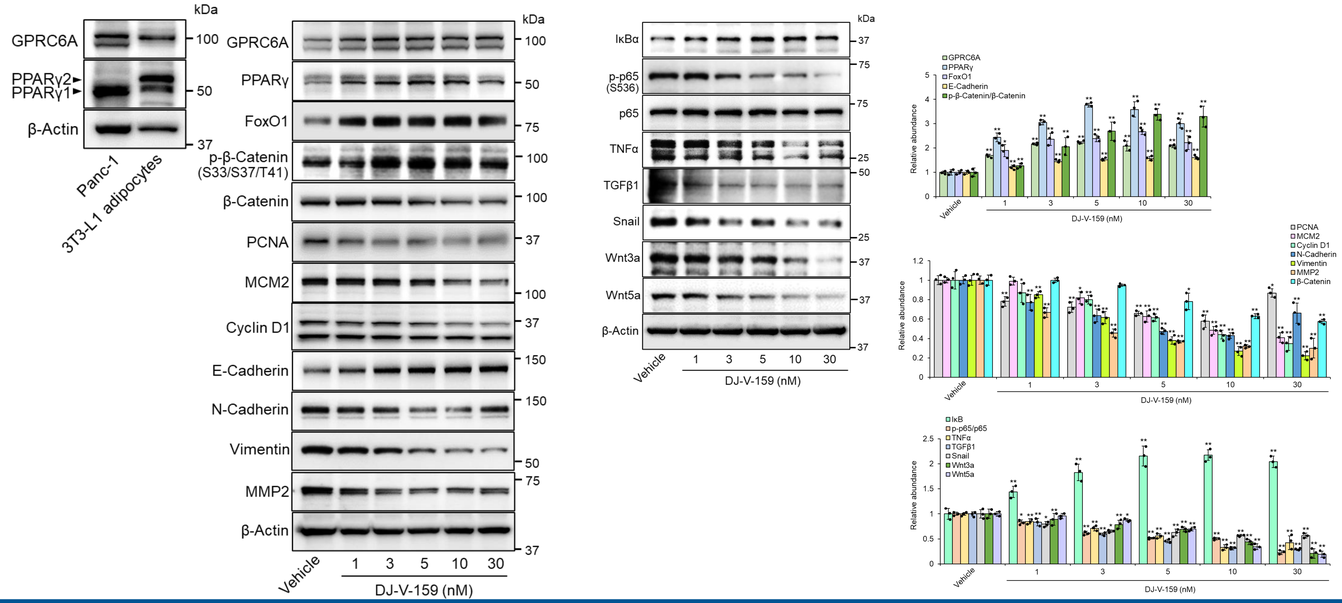
3. GPRC6A suppresses transformation from adipocytes into CAA by Panc-1



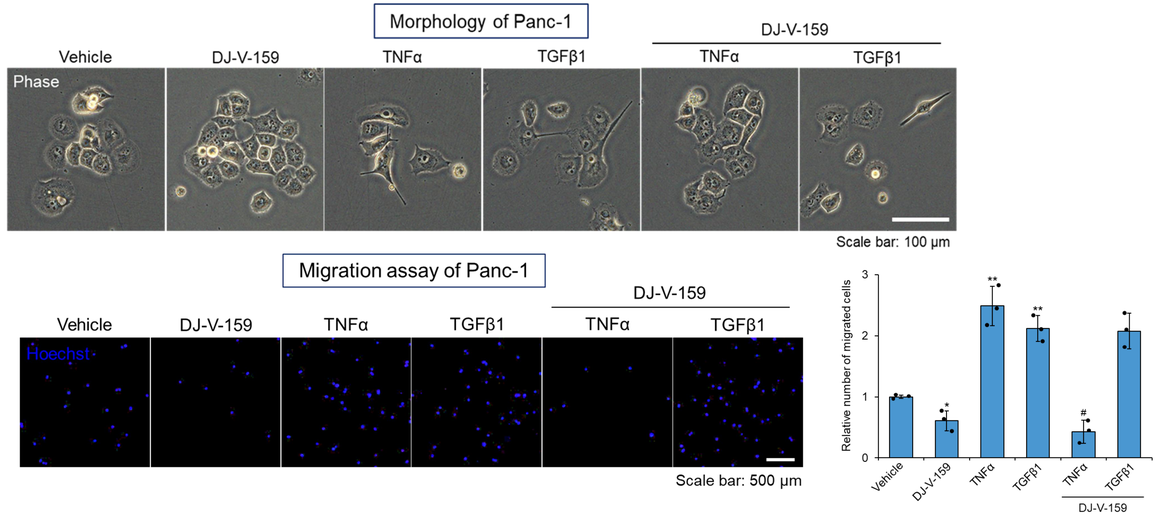
Scale bar: 50 μm

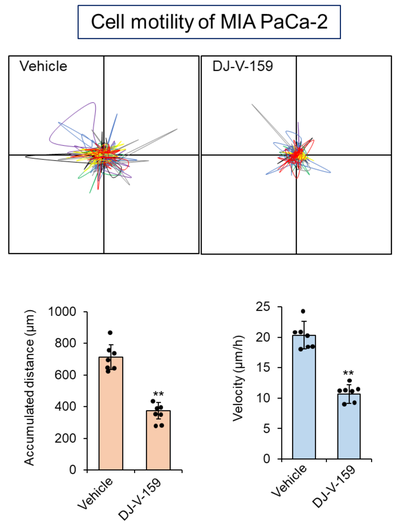


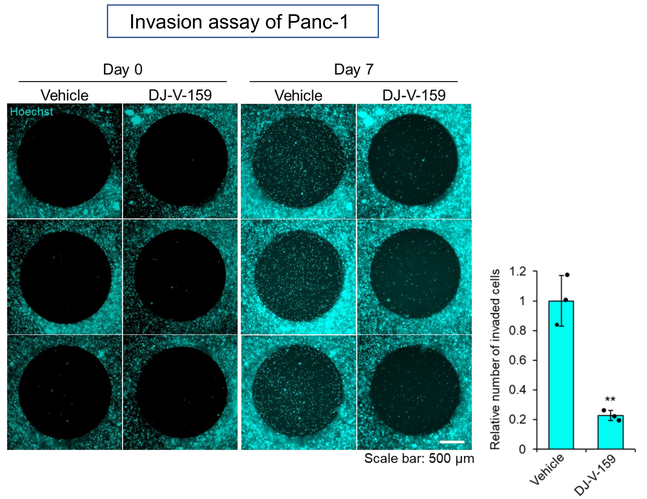
4. PPARγ induced by GPRC6A suppresses cell growth and epithelial-mesenchymal transition (EMT)



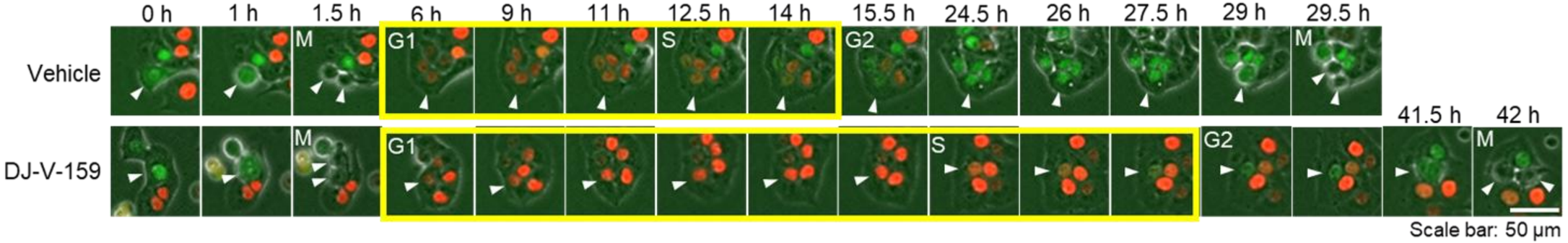
5. GPRC6A represses migration and invasion abilities



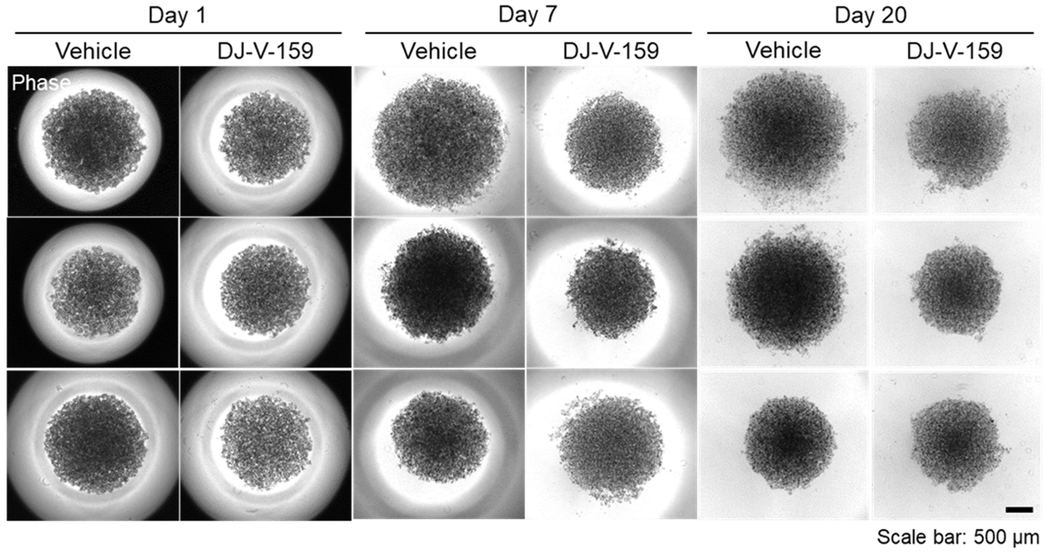


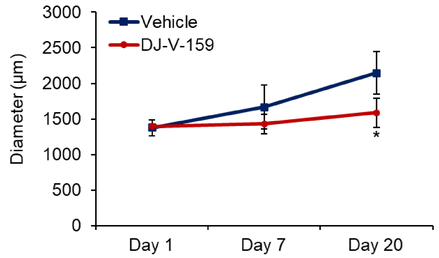


6. GPRC6A induces cell cycle delay at G1 and S phases

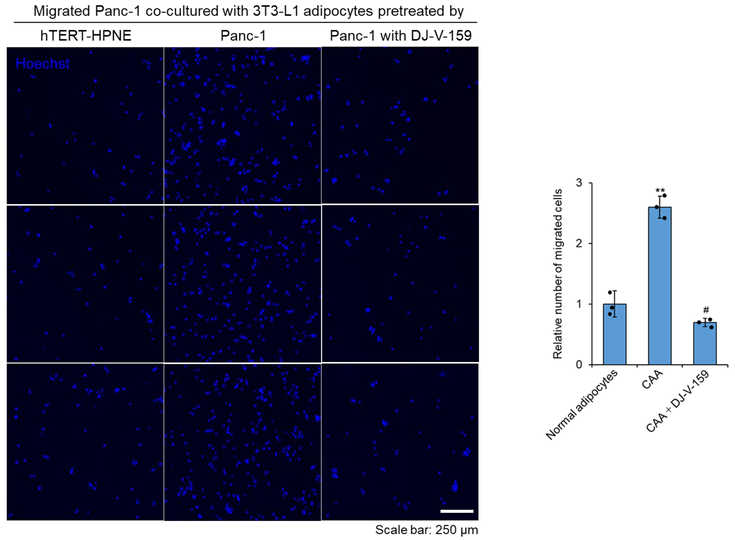


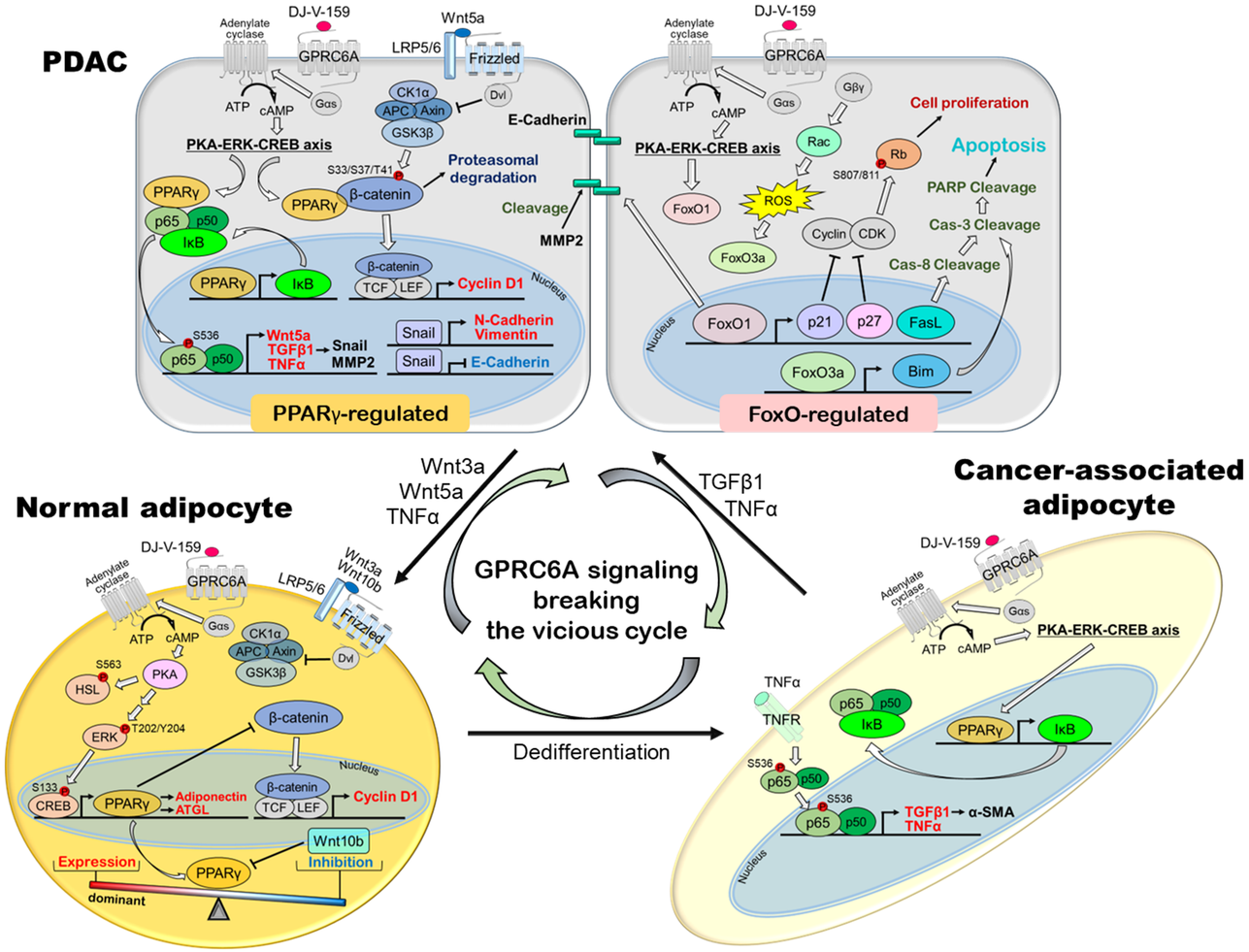
7. GPRC6A makes PDAC spheroid smaller





8. GPRC6A ameliorates the effects of CAA on PDAC migration ability





Conclusion

In this study, we have revealed the following three key findings:
1. GPRC6A signaling suppresses PDAC-induced transformation of adipocytes into CAA.

2. GPRC6A signaling ameliorates the malignant properties of CAA promoting PDAC aggressiveness.

3. GPRC6A signaling inhibits the cell proliferation and EMT in PDAC.

Taken together, these findings indicate that GPRC6A signaling activated by DJ-V-159 exerts multifaceted anti-tumor effects both PDAC and CAA. Thus, it holds promise as a potential preventive and therapeutic target for PDAC.