袁行修 教授 醫學院/醫學研究所

Background

Betel quid and its major ingredient, areca nut, are recognized by IARC as major risk factors in oral cancer development. Areca nut extract (ANE) exposure has been linked to OPMD progression and malignant transformation to OSCC. However, the detailed mechanism through which ANE acts on other cell types in the oral microenvironment to promote oral carcinogenesis remains elusive.

Methods

Immuno-profiling of macrophages associated with OPMD and OSCC was carried out by immunohistochemical and immunofluorescence staining. Phosphokinase and cytokine arrays and western blotting were performed to determine the underlying mechanisms. Transwell assays were used to evaluate the migration-promoting effect of ANE. Hamster model was finally applied to confirm the in vivo effect of ANE.

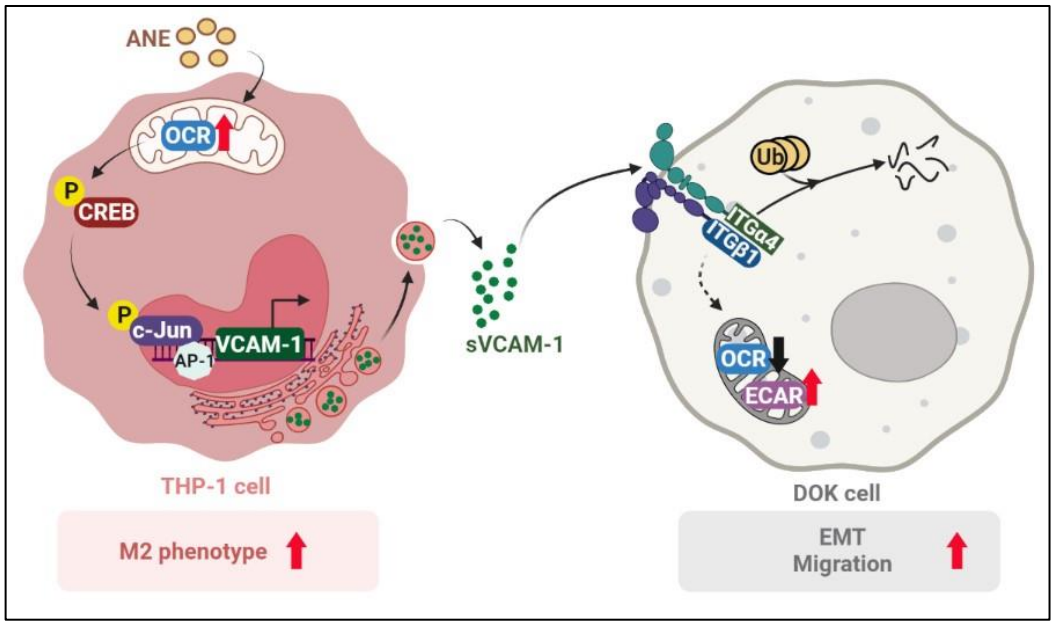
Results

We reported that M2 macrophages positively correlated with oral cancer progression. ANE induced M2 macrophage differentiation, CREB phosphorylation and VCAM-1 secretion and increased mitochondrial metabolism. Conditioned medium and VCAM-1 from ANE-treated macrophages promoted migration and mesenchymal phenotypes in oral precancer cells. In vivo studies showed that ANE enhanced M2 polarization and related signaling pathways in the oral buccal tissues of hamsters.

Conclusion

Our study provides novel mechanisms for areca nut-induced oral carcinogenesis, demonstrating that areca nut promotes M2 macrophage differentiation and secretion of oncogenic cytokines that critically activate malignant transformation of oral premalignant cells.

Keywords: Areca nut, macrophage, OPMD, OSCC, mitochondrial metabolism



Schematic drawing for malignant transformation in oral premalignant cells via ANE-induced M2 macrophage differentiation.

1. Vijayaraghavan P, Palanisamy S, Wang YY, So PB, Lin CH, Tzou SC, Yuan SS, Wang YM. Senescence-associated β-galactosidase detection in human oral cancer samples using bimetallic (Fe, Cu)-MOF-919 impedimetric immunosensor. Sensors and Actuators Reports. 2025 Jun 1;9:100271.
2. Wang YY, Chen PY, Meitei NJ, Lin YR, Lu TT, Nguyen HD, Hsu SC, Yuan SS. Copper-nitrite complexes release nitric oxide and selectively induce oral precancer and cancer cell apoptosis. Journal of Inorganic Biochemistry. 2025 Jan 20:112833.
3. Hsieh HM, Ho CM, Chen YH, Hsu WH, Wang YK, Wang YY, Yuan SS, Wu IC. Cost-effectiveness of universal esophageal cancer screening for newly diagnosed oral cancer patients. Journal of Gastroenterology and Hepatology. 2024 Dec;39(12):2778-86.
4. Yuan SS, Chan LP, Nguyen HD, Su CW, Chen YK, Chen JY, Shimodaira S, Hu SC, Lo S, Wang YY. Areca nut-induced metabolic reprogramming and M2 differentiation promote OPMD malignant transformation. Journal of Experimental & Clinical Cancer Research. 2024 Aug 20;43(1):233.

5. Sun YH, You HL, Narwane M, Koi RX, Kao CL, Yuan SS, Liao WT, Lu TT, Hsu SC. A half-sandwich Ru (II)-p-cymene nitrite complex selectively induces cell death in cisplatin-resistant malignant melanoma cells. Dalton Transactions. 2024.
6. Yuan SS, Su CW, Chan LP, Nguyen HD, Chen YK, Du JK, Cheng KH, Wang YY. Il17Rb expression is associated with malignant cancer behaviors and poor prognosis in oral cancer. Oral Diseases. 2024 May;30(4):2027-38.
7. Wang YY, Cheng KH, Hung AC, Lo S, Chen PY, Wu YC, Hou MF, Yuan SS. Differential impact of cytoplasmic vs. nuclear RAD51 expression on breast cancer progression and patient prognosis. International Journal of Oncology. 2023 Dec 7;64(2):12.

Research Team

1. Yen-Yun Wang
   https://wac.kmu.edu.tw/qur/profiles.php?id=1065015
2. Chang-Wei Su
   https://www.kmuh.org.tw/Web/WebRegistration/DocIntro/DocDetail?lang=tw&doctorID=1060197
3. Yu-Feng Chen
   https://www.kmuh.org.tw/Web/WebRegistration/DocIntro/DocDetail?lang=tw&doctorID=960266
4. Pang-Yu Chen
5. Hieu D.H.Nguyen
6. Yu-Quan Wang
7. Peng-Yu Chen
8. Anusha Rangappa
9. Yu-Ren Lin

Research Team Introduction

Our research primarily focuses on the molecular mechanisms underlying cancer progression and the development of novel therapeutic strategies. We have explored the impact of the DNA repair protein Rad51 on tumor growth and metastasis in esophageal squamous cell carcinoma, identifying potential targets for therapeutic intervention. Currently, we aim to examine the cross-talk between senescence and cancer development. Given that aging plays a key role in cancer development and progression, understanding how defective DNA repair connects

senescence to malignancy could provide valuable insights. We believe our findings may help develop new precision medicine approaches and targeted therapies for cancer patients.

Research Contacts Email: yuanssf@kmu.edu.tw