University of Prince Edward Island

Faculty of Veterinary Medicine
Summary of Dissertation

Submitted in Partial Fulfilment
of the Requirements for the

DEGREE OF DOCTOR OF PHILOSOPHY

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Prostaglandin E2 mediated inflammation and hypoxia in feline oral squamous cell carcinoma

Oral squamous cell carcinoma (OSCC) is the most common tumour of the feline oral cavity and is associated with devastating outcomes. Similar to human OSCC (HOSCC), Cyclooxygenase 2 (COX-2) expression and prostaglandin E2 (PGE2) synthesis have been demonstrated in feline OSCC (FOSCC). CD147, a known mediator of invasive behaviour, was also shown to be expressed in FOSCC. Other elements of the arachidonic acid pathway of inflammation, including microsomal and cytosolic PGE2 synthase enzymes (mPGES1, mPGES2 and cPGES) and PGE2 receptors (EP1-EP4), have not been investigated in FOSCC. Tumour hypoxia can support growing tumours by stimulating formation of new blood vessels through activity of hypoxia-inducible factor 1 alpha (HIF-1α) and expression of vascular and endothelial growth factor type A (VEGFA). This work demonstrated that FOSCC cell lines express genes for PGE2 synthase enzymes and receptors, HIF-1α and VEGFA to varying degrees. Gene expression in FOSCC cells (SCCF2) was altered by exogenous PGE2 exposure and EP4 suggesting that EP4 deserves further study in FOSCC. In biopsy samples of HOSCC and FOSCC, immunohistochemistry (IHC) revealed that a subset of tumours expressed mPGES1 and P16. High CD147 expression was more common in high mPGES1 tumours in both species, though it only reached statistical significance in the HOSCC. High p16 tumours were more common in the human oropharynx compared to the oral cavity. In vitro, 4 hours of hypoxia stimulated the expression of mPGES1. Hypoxia reduced the sensitivity of SCCF2 to cytotoxic drugs (doxorubicin and carboplatin) but not to a cyclooxygenase inhibitor (piroxicam) or an EP4 inhibitor. Interestingly, hypoxia increased the antiproliferative effect of a mPGES1 inhibitor in SCCF2 cells. These studies indicate that mPGES1 may be an important mediator of inflammation and hypoxic response in FOSCC patients, possibly serving as a therapeutic target. Based on p16 expression, it appears that FOSCC may have similarities with non-HPV-associated OSCC in people, which is reported to have a worse prognosis than HPV-associated OSCC. Further study is needed to determine the role of p16 as a prognostic indicator in FOSCC.

Publications

Walaa Hamed Shaker Nasry, and Chelsea K. Martin. In vitro gene expression of PGE2 synthase enzymes, PGE2 receptors, HIF-1α and VEGFA in feline oral squamous cell carcinoma. The Journal of Veterinary Diagnostic Investigation, December 2023 (in review)

Walaa Hamed Shaker Nasry, Kathleen Jones, Juan Carlos Rodriguez-Lecompte, Marvin Tesch, Chelsea K. Martin. Expression of mPGES1 and p16 in feline and human oral squamous cell carcinoma: A comparative oncology approach. Vet Comp Oncol. 2024 Feb 20. DOI:10.1111/vco.12967

Walaa Hamed Shaker Nasry and Chelsea K. Martin. Intersecting mechanisms of hypoxia and prostaglandin E2-mediated inflammation in the comparative biology of oral squamous cell carcinoma. Frontiers in Oncology, May 21 2021. https://doi.org/10.3389/fonc.2021.539361.

Walaa Hamed Shaker Nasry, Haili Wang, Kathleen Jones, Marvin Tesch, Juan Carlos Rodriguez-Lecompte and Chelsea K. Martin. Cyclooxygenase and CD147 Expression in Oral Squamous Cell Carcinoma Patient Samples and Cell Lines. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology volume128, issue 4 (2019) pp.400-410. https://doi.org/10.1016/j.oooo.2019.06.005

Walaa Hamed Shaker Nasry, Juan Carlos Rodriguez-Lecompte and Chelsea K. Martin. Role of COX-2 / PGE2 mediated inflammation in oral squamous cell carcinoma.Cancers 2018, 10(10), 348; https://doi.org/10.3390/cancers10100348.

Walaa Hamed Shaker Nasry, Haili Wang, Kathleen Jones, Wessel P. Dirksen, Thomas J. Rosol, Juan Carlos Rodriguez-Lecompte and Chelsea K. Martin. CD147 and Cyclooxygenase Expression in Feline Oral Squamous Cell Carcinoma. Veterinary Sciences. 2018; 5(3):72; https://doi.org/10.3390/vetsci5030072.

Walaa Hamed Shaker Nasry. 2017, Cyclooxygenase and CD147 Expression in Human and Feline Oral Squamous Cell Carcinoma. Thesis, Atlantic Veterinary College, University of Prince Edward Island. https://www.islandscholar.ca

Walaa Hamed Shaker Nasry 2011. Hepatitis B Vaccination: An Overview (Thesis, internal publication). Ain Shams University, Faculty of Medicine. Cairo, Egypt. http://srv3.eulc.edu.eg/eulc

Presentations

Walaa Hamed Shaker Nasry and Chelsea Martin. Abstract poster presentation. Expression of mPGES-1 and p16 in feline and human oral squamous cell carcinoma: A comparative oncology approach. The Canadian Cancer Research Conference, Halifax. November 12-14, 2023.

Walaa Hamed Shaker Nasry. Investigating gene expression related to inflammation and hypoxia in feline oral cancer (public presentation as part of the Mitacs Research Training Award). Atlantic Veterinary College, University of Prince Edward Island, 2021

Walaa Hamed Shaker Nasry, Haili Wang, Kathleen Jones, Juan Carlos Rodriguez-Lecompte and Chelsea K. Martin. Abstract poster presentation Comparative Study of Cyclooxygenase and CD147 Expression in Human and Feline Oral Squamous Cell Carcinoma. BHCRI/TFRI Cancer Research Conference in Atlantic Canada, Halifax. November 5-6, 2018

Walaa Hamed Shaker Nasry. Inflammation and hypoxia related mechanisms in oral squamous cell carcinoma (OSCC). Annual UPEI Graduate Studies and Research Conference, Atlantic Veterinary College, University of Prince Edward Island, 2018

Biographical Data

Born and raised in Cairo, Egypt and immigrated to PEI in 2011 with my two daughters.

Awards received

· UPEI Women's Group Bursaries. 2023
· Dr. Barbara R. Campbell Inspiration Award. 2022
· The G. Stewart MacKay Scholarship. 2022
· Prince Edward Island Women Institute Famous Five Health Scholarship. 2021
· Canadian Federation of University Women Charlottetown Graduate Scholarship. 2021
· Drs. Larry Hammell & Norma Guy Graduate Student Awards.2021
· BMO Financial Group Scholarship. 2020
· UPEI Mitacs Research Training Award. 2020
· The Regis Duffy Graduate Scholarships in Science. 2020
· Lévesque Graduate Fellowship in Nutrisciences and Health. 2019
· Zonta Club of Charlottetown 40th Anniversary Single Mother Bursary. 2019
· The Diane Kays Memorial Bursary, PEI Advisory Council on the Status of Women. 2018
· Terry Fox Research Institute – Atlantic Node and the Beatrice Hunter Cancer Research Institute Trainee Travel Award. 2018
· Phyllis Pitre Bursary, Career Development Association of PEI. 2018
· Zoetis graduate student award of distinction for AVC, UPEI. 2018
· Graduate Student Stipend Scholarship, Department of Pathology and Microbiology, Atlantic Veterinary College, University of Prince Edward Island. 2017- 2020