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Oral Presentation

TITLE	**Loss of Cathelicidin (LL-37) is associated with colorectal cancer progression.**
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ABSTRACT DETAILS:	
Background:	Colorectal carcinoma is the third most common cancer worldwide, with only 55% of patients surviving more than 5 years after diagnosis.[1] Loss of mucosal barrier integrity may contribute to carcinogenesis. Cathelicidin (LL-37) is an innate anti-microbial peptide that plays an important role promoting epithelial barrier integrity and attenuating intestinal inflammation.[2] Previous in vitro studies suggest a protective role in colonic carcinogenesis. Our recent pre-clinical data revealed that genetic knock out of cathelicidin led to increased size and number of colorectal tumours in the azoxymethane-mediated murine model of colorectal cancer.[3] Cathelicidin expression has not been characterised in human colorectal cancer.
Method:	Intensity of epithelial cytoplasmic LL-37 was assessed immunohistochemically in a tissue microarray representing 650 colorectal cancers and 50 paired normal colorectal mucosa samples. Tissue was obtained from chemotherapy and radiotherapy naïve patients collected at time of surgery for primary colonic cancer, sourced from the Grampian Tissue Biorepository. Ethical approval was granted by the Grampian Biorepository Scientific Access Group. Clinico-pathological data were available for each case, including survival for 18.2 years post-resection. Expression intensity of LL-37 was independently assessed by two observers, blind to clinico-pathological data, as absent, weak, moderate or strong. Descriptive analysis, χ^2 test, Fisher's exact test and log-rank survival analysis was performed using IBM SPSS Statistics (Version 24.0.0.0).
Results:	The expression of cytoplasmic LL-37 was weaker in colorectal cancer compared to normal colonic epithelium ($p<0.001$). Increased intensity of LL-37 expression was present in patients staged Dukes A compared to Dukes B ($p=0.004$) or Dukes C ($p=0.003$). There was no correlation of LL-37 expression to tumour site, differentiation, extra-mural venous invasion or mismatch repair protein status. Normal colonic mucosa from patients with Dukes A cancer expressed stronger cytoplasmic LL-37 compared to normal colonic mucosa from patients with Dukes C cancer ($p=0.031$). There was no relationship between LL-37 expression and overall survival.
Conclusions:	Loss of epithelial cytoplasmic LL-37 is associated with progression of colorectal cancer, confirming translation of pre-clinical data to human disease. Our study also suggests critical loss of LL-37 occurs at an early stage in carcinogenesis. There may be a global field change in LL-37 expression in distant non-malignant cells as cancer progresses. The functional impact of this warrants further investigation and may reveal new insight into the pathogenesis of colorectal cancer.
References:	1.Brenner H, Kloor M, Pox CP. Colorectal cancer. *The Lancet*. 2014;**383**(9927):1490–502 2.Gallimore AM, Phil D, Godkin A. Epithelial Barriers, Microbiota, and Colorectal Cancer. *N Engl J Med* 2013;**368**:282–4. 3.Yoshimura T, McLean MH, Dzutsev AK, *et al.* The Anti-microbial Peptide CRAMP Is Essential for Colon Homeostasis by Maintaining Microbiota Balance. *J Immunol* 2018;Epub Ahead.