Dr John Liu - RCPA Foundation Postgraduate Research Fellowship 2015 - Final Report

Colorectal carcinoma is the second most common cancer in adults. Early identification of precursor lesions is important as their removal is curative; furthermore, this identifies a group of patients at risk of developing further lesions and appropriate follow up can be instituted.

Serrated adenomas – sessile serrated adenomas and traditional serrated adenomas – give rise to 30% of colorectal carcinomas. These adenomas are characterised by unique histologic characteristics, and their diagnostic criteria have been standardised only recently. Due to risk of malignant progression detection of dysplastic serrated lesions is critical, but this is hampered by several factors. The rate of progression to dysplasia is very low, and most pathologists are unlikely to encounter sufficient examples to become familiar. Dysplasia displays a wide histopathologic spectrum and there is risk of both over- and underdiagnosis. Finally, progression to invasive carcinoma is rapid once dysplasia has occurred.

My PhD aims to identify high-risk serrated adenomas via histologic, genetic, and epigenetic methods. It is hoped this will lead to development of clinically applicable immunohistochemical markers for these lesions. The findings may also have implications in devising the most appropriate surveillance protocol for affected patients.

I was the recipient of the RCPA Postgraduate Research Award for 2016. The Award allowed me to purchase laboratory equipment, attend several courses and conferences, and apply for other awards and scholarships. This has expedited my PhD greatly, allowing me to complete two of four research projects in my first year. The first project examined mutations in *GNAS*, a putative oncogene in gastrointestinal neoplasms. I found *GNAS* mutations are present in a subset of traditional serrated adenomas, serrated tubulovillous adenomas and colorectal carcinomas. *GNAS*-mutant colorectal carcinomas are likely to demonstrate serrated molecular/morphologic features or present at advanced stage. Furthermore, due to common occurrence with *BRAF* or *KRAS* mutations, *GNAS* mutations likely have a synergistic role in the pathogenesis of serrated lesions. The second project examined the histologic features of sessile serrated adenomas with dysplasia, in conjunction with MLH1 immunohistochemistry. Four dysplasia subtypes – minimal deviation, serrated, adenomatous and not otherwise specified – are identified in this study. These subtypes differ in malignant potential and differential diagnoses. Most importantly, the minimal deviation subtype is not recognised in the World Health Organization classification, and is likely currently misdiagnosed as non-dysplastic sessile serrated adenomas.

Results from both completed projects have been published in pathology journals:

Liu C, McKeone D, Walker N, et al. *GNAS* mutations are present in colorectal traditional serrated adenomas, serrated tubulovillous adenomas and serrated adenocarcinomas with adverse prognostic features. Histopathology 2017;70:1079-1088.

Liu C, Walker NI, Leggett BA, et al. Sessile serrated adenomas with dysplasia: morphologic patterns and correlations with MLH1 immunohistochemistry. Mod Pathol 2017. (Accepted for publication post revision)