ABSTRACT

Clear cell carcinomas (CCCs) are a subtype of ovarian cancer that is understudied, and which does not respond well to conventional therapeutic strategies. There is a desperate need to clarify the genetic mechanisms of CCC to allow for the development of subtype specific therapeutics. To determine genetic changes responsible for the development of CCC, whole transcriptomes of 18 ovarian CCCs and one ovarian CCC cell line were sequenced. Somatic mutations were found in *ARID1A* in 6 samples. *ARID1A* encodes BAF250a, a key component of the SWI/SNF chromatin remodeling complex. *ARID1A* was sequenced in an additional 210 ovarian carcinomas and a second CCC cell line, and BAF250a expression was measured by immunohistochemistry (IHC) in an additional 455 ovarian carcinomas and over 3000 non-ovarian malignancies. Overall, *ARID1A* mutations were seen in 46% of CCCs and 30% of endometrioid carcinomas (EC) implicating *ARID1A* as a tumour suppressor frequently disrupted in CCC and EC. Loss of the BAF250a protein correlated strongly with the presence of *ARID1A* mutations. In two patients, *ARID1A* mutations and loss of BAF250a expression were evident in the tumour and contiguous atypical endometriosis, implicating *ARID1A* loss as an early event in tumourigenesis. Screening 3000 cases of different malignancies by IHC showed loss of BAF250a was is most frequent in cancers of endometrial origin. Reverse phase protein array (RPPA) for tumour samples with known *ARID1A* mutation status revealed a notable change pAKT-Thr308 (FDR < 1%), which may allow for targeted therapeutic strategies in *ARID1A* deficient tumours. To identify compounds synthetic-lethal with *ARID1A* deficiency, two nearly isogenic cell lines were screened along with 18 other cell lines, including ten CCC cell lines of known *ARID1A* status against a panel of kinase inhibitors, revealing several promising therapeutic compounds effective at inhibiting the growth of CCC cell lines, including GSK461364, Pelitinib, and Tovok, however these did not appear to be dependent on *ARID1A* deficiency. Collectively, these studies provided the first report of *ARID1A* as a major tumour suppressor in cancers of endometrial origin and several other tumour types; these studies have now been validated by multiple groups in diverse tumour types.