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Methylation pattern switch between low and high grade cervical intraepithelial neoplasia: Implications for progression models, robust triage and cancer risk

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The evolution of precancerous cervical lesions is poorly understood. One hypothesis, the molecular switch model, states that CIN3 could evolve straight from normal epithelium after an HPV infection without progressing through the CIN1 and CIN2 stages. To shed light on this process, we compared DNA methylation of selected biomarkers and HPV type in two groups of CIN1: CIN1 that were adjacent to CIN3 (adjacent-CIN1) and CIN1 that were the principal lesions with no CIN3 present (principal-CIN1). 354 CIN (CIN1 and CIN3) and normal tissue were macrodissected and typed for HPV from 127 women who underwent loop electrosurgical excision procedures (LEEP). Methylation of genes *EPB41L3* and the viral regions of HPV16-L1/L2, HPV18-L2, HPV31-L1 and HPV33-L2 were determined by quantitative pyrosequencing of bisulfite converted DNA. Corresponding HPV types were also obtained on paired exfoliated specimens collected before treatment. There was a highly significant trend of increased methylation with disease progression from normal to CIN3 ($p<0.0001$). CIN1 adjacent or near CIN3 (adjacent-CIN1) predominantly shared the same HPV types as the CIN3. In contrast, methylation differed substantially between adjacent-CIN1 and CIN3 ($p=0.008$); however, diagnostically principal-CIN1 had indistinguishable methylation compared to adjacent-CIN1 (*EPB41L3:* $p=0.49$; HPVme-All: $p=0.11$). HPV types and methylation levels in LEEP and corresponding exfoliated cells were similar, with 99% of CIN3 and 88% of CIN1 containing matching HPV types. Our results suggest that progression from normal epithelium to CIN1 or CIN3 can be promoted by the same persistent HPV type but occurs via distinct DNA epigenotypes, thus supporting the molecular switch model.

Figure 1: Flow chart showing the number of cases and dissected areas used for the main study (LEEP tissues, centre main panel) and the punch biopsy pilot study (top main panel). For some cases several CIN1 or CIN3 areas were dissected per cervix. Sections of five CIN1 and eight CIN3 cases had no normal epithelium. Sections of ten CIN3 cases had no adjacent- CIN1 lesions. Mean methylation levels were averaged per lesion type. HPV genotyping was done separately for all lesions. Our study also included a comparison of HPV typing data from the 127 LEEP to corresponding exfoliated cell specimens (right panel).

Recent Publications

1. Bagnati M, Ogunkolade B W, Marshall C, Tucci C, Hanna K, Jones TA, Bugliani M, Nedjai B, Caton P W, Kieswich J, Yaqoob M M, Ball G R, Marchetti P, Hitman G A and Turner M D (2016) Glucolipotoxicity initiates pancreatic β-cell death through TNFR5/CD40-mediated STAT1 and NF-κB activation. Cell Death & Differentiation 7(8):e2329.
2. Nedjai B, Viney J M, Li H, Hull C, Anderson C A, Horie T, Horuk R, Vaidehi N and Pease J E (2015) CXCR3 antagonist VUF10085 binds to an intrahelical site distinct from that of the broad spectrum antagonist TAK-779. British Journal of Pharmacology 172(7):1822-33.
3. Turner M D, Nedjai B, Hurst T and Pennington D J (2014) Cytokines and chemokines: At the crossroads of cell signalling and inflammatory disease. Biochimica et Biophysica Acta 1843(11):2563-2582.
4. Turner M D, Chaudhry A and Nedjai B (2012) Tumour necrosis factor receptor trafficking dysfunction opens the TRAPS door to pro-inflammatory cytokine secretion. Bioscience Reports 32(2):105-12.

5. Nedjai B, Li H, Stroke I L, Wise E L, Webb M L, Merritt J R, Henderson I, Klon A E, Cole A G, Horuk R, Vaidehi N and Pease J E (2012) Small molecule chemokine mimetics suggest a molecular basis for the observation that CXCL10 and *CXCL11* are allosteric ligands of CXCR3. British Journal of Pharmacology 166(3):912-23.

Biography

Nedjai B as a Senior Research Fellow co-leads the Molecular Epidemiology Lab (MEL) Research Team in Epigenetics of prostate, breast and cervical cancer. She holds a PhD in functional genomics and her aim is to identify and develop cost-effective tests for the early detection and the prediction of outcomes in cancer patients. Her recent successes include the identification of methylation biomarkers to manage women infected by papillomavirus and an alternative epigenetic approach for management of men with prostate cancer. She is an expertise in biomarkers identification and validation using deep sequencing and high through put techniques (WES, RNA seq, miRNA and methylome). Her future research will include discovery of biomarkers for early detection of epithelial cancer using a Pan Cancer approach. We have already identified a few methylation biomarkers able to predict cancer at early stage in several epithelial cancers and another aim would be to refine such biomarkers in various ethnic groups to increase the early detection potential.

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