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Characterisation of clonal and subclonal allelic imbalance at the HLA locus in a 31 patient multi-region profiled primary/metastasis clear cell renal cell carcinoma cohort

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Introduction: Metastasis is the primary cause of death in cancer. Large-scale studies of metastatic disease have not included analysis of matched primary tumours, which are required to distinguish between tumour clones with and without metastatic potential. Although the treatment of primary tumours has become more successful, five-year survival rates for metastatic renal cancer remain low at 8%. An improved understanding of the genetic differences between primary and metastatic tumours could reveal distinct therapeutic vulnerabilities between local and metastatic disease, which if exploited could improve treatment and/or prevent metastasis. Immune evasion is required for tumors progression and metastasis.

Aims: We investigated whether genomic alterations causing the loss of Human Leukocyte Antigen (HLA) alleles would facilitate immune evasion and subsequently promote proliferation and metastasis.

Methods and results: We acquired the ability to decipher potential modes of metastatic progression through simultaneous analysis of 418 primary and 278 metastatic biopsies from 31 renal cell carcinoma patients. Multiple regions from each tumour were biopsied giving us clonal resolution. AI was investigated using fluorescently labelled STR oligonucleotides that were polymorphic within the HLA locus. We showed AIHLA was significantly selected for within the metastases. Immunohistochemical analysis on 897 tumour biopsies stained for the proliferation marker Ki67 showed AIHLA did not associate with increased tumour proliferation rates. The detection of genomic alterations in tumour biopsies is confounded by infiltration from stromal DNA. Therefore, we developed a novel bioinformatics tool that purified and Characterised Allelic Imbalance in Tumours (CAIT). This was achieved through mathematical deduction of signals originating from stromal DNA. CAIT increased AIHLA detection, providing insights on AIHLA's prevalence and timing.

Discussion: These results suggest AIHLA could promote metastatic progression. The characterisation of AIHLA could increase our understanding of drug-resistance mechanisms and inform the development of immunotherapeutic agents targeting neoantigens.

Biography

Faiz Jabbar studies at University College London as a fifth-year medical student. He has completed a BSc in Immunology, Infection and Cellular Pathology in 2018, where he investigated the ability of renal cancer to evade the immune system and how it correlated with metastatic disease, cancer evolution and heterogeneity.

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