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MHC MOLECULES

Immune editing shapes the cancer landscape

Tumour cells that present neoantigens in complex with MHC class I molecules are targets for killing by $CD8^+$ T cells. Thus, tumour cells that fail to present surface neoantigens can grow out. However, it is unclear whether this 'immune editing' occurs in humans. Two studies in *Cell* now provide evidence that HLA class I genotype or loss of HLA heterozygosity are associated with immune editing, thus shaping the landscape of human cancer.

Marty *et al.* developed a new scoring scheme, which takes into account different combinations of HLA alleles that occur in individuals, to estimate the qualitative chance that peptide sequences containing specific mutations could be presented by HLA class I molecules. Using data available from The Cancer Genome Atlas, the authors used the new system to characterize the interactions between 9,176 patient HLA class I allele combinations and a set of 1,018 recurrent driver cancer mutations in oncogenes and tumour suppressor genes. They generated a score matrix that showed the individual differences in the presentation of mutations that are thought to drive oncogenesis. Remarkably, a patient's HLA class I genotype was predictive of the mutations that were more likely to emerge in their tumours. Furthermore, driver mutations were more likely to be found in peptides that were poorly presented by most MHC class I alleles.

> "a patient's HLA class I genotype was predictive of the mutations that were more likely to emerge in their tumours"

These data suggest that the specific HLA class I genotype of an individual can restrict the potential neoantigens presented on the surface of tumour cells, resulting in immune editing of a growing tumour and thus altering the landscape of cancer-associated mutations.

One potential mechanism of immune evasion by tumours is that they may lose the ability to present neoantigens by HLA loss. To investigate this, McGranahan *et al.* developed a new computational tool, LOHHLA, that determines the HLA haplotype-specific copy number from an individual's tumour and matched germline sequencing data. The authors examined the TRACERx cohort of treatment-naive patients with early-stage non-small-cell lung cancer and found that 40% had HLA loss of heterozygosity. Interestingly, loss of heterozygosity was more often seen in a subset of tumour cells (subclonally) rather than across the whole tumour cell population (clonally) and showed a tendency to be enriched in sites of tumour metastasis, indicating that it occurs later in lung cancer evolution. HLA loss was associated with an elevated nonsynonymous mutation burden, and neoantigens were found to bind more frequently to the lost allele; this suggests that immunoediting would result in the expansion of tumour cell clones that had lost a HLA allele, and this would lead to a subsequent increase in mutation rate in the expanded population.

Finally, McGranahan *et al.* carried out immune signature and immunohistochemistry analyses of lung tumours with HLA loss and found that the microenvironment showed upregulation of cytolytic activity and increased numbers of cells positive for programmed cell death 1 ligand 1 (PDL1), a receptor for the inhibitory immune cell checkpoint protein PD1. These data suggest that tumours with HLA loss have an altered immune microenvironment, which may be associated with immune evasion.

In summary, two groups have reported that HLA variation or loss is associated with immune editing of human tumours and may shape the evolution of cancer. In the future, an understanding of the HLA genotype of individual patients may help to tailor treatment regimens and predict resistance.

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ORIGINAL ARTICLES Marty, R. *et al.* MHC-1 genotype restricts the oncogenic mutational landscape. *Cell* http://dx.doi.org/10.1016/j.cell.2017.09.050 (2017) | McGranahan, N. *et al.* Allele-specific HLA loss and immune escape in lung cancer evolution. *Cell* http://dx.doi.org/10.1016/j.cell.2017.10.001 (2017)