Commentary

Commentary on Mascaux *et al.*, Immune Evasion before Tumour Invasion in Early Lung Squamous Carcinogenesis. Nature. 2019;571:570-5

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Cancer biology has long been characterised by definitive hallmarks [1,2]; acquired traits that inevitably footprint the mutational history of its transformation. It is only recently that molecular profiling techniques have offered us the opportunity to chart the sequence of these mutations—allowing us to perceive these traits, not simply as hallmarks, but as milestones in the evolution of cancer.

Squamous cell carcinoma of the lung accounts for approximately 30 percent of lung cancers and remains a world-wide health problem. Mascaux *et al.* [3] contribute to our growing understanding of carcinogenesis by demonstrating the crucial role of immune evasion in the pre-invasive stages of squamous cell carcinoma of the lung, building on previous studies implying that a breakdown in immune surveillance underpins this process [4,5]. Key to their report is the temporal information gleaned by analysing 9 distinct morphological stages in the development of this disease; from which arises the suggestion that escape from host immunity occurs prior to the cancer's capability to metastasise. Crucially, the directionality of this sequence may have important implications for detection and early prevention of lung cancer—a condition which remains largely incurable because of its presentation mainly at advanced stages.

This comes at an opportune moment in efforts centred on early detection. In terms of macroscopic disease, the NELSON trial is a randomised, controlled population-based screening study exploring volume computed-tomography in at-risk groups for lung cancer. Recently, the investigators reported a 26% reduction in lung cancer mortality in men and 39%–61% in women at 10 years of follow-up [6]—a clear indication that targeted screening is of substantial benefit. Such are the implications, that the United Kingdom National Health Service has recently invested

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£70 million in mobile CT scanning trucks to screen individuals at high risk of developing lung cancer. Despite this optimism, the long-term risks of widespread radiological screening remain unknown; more importantly, we know that cancer is a disease conceived at a microscopic, cellular level—one that can remain hidden from CT scan long before unbound clonal proliferation renders it detectable by even our most sophisticated imaging measures. In this context, the findings of Mascaux and colleagues take on a particular significance. The finding that immune evasion takes place early in the natural history of squamous cell lung carcinoma provides a platform for the identification of immune biomarkers; early changes in cellular signalling processes that facilitate immune escape could manifest in discrete serological changes—these could present an alternative, possibly more sensitive means, of screening for lung cancer, potentially at a pre-malignant stage.

The authors describe changes in absolute and relative gene expression for immune and epithelial signatures throughout lung squamous carcinogenesis indicating immune transition and sequence directionality. Functional changes that occur during immune transition are assessed through gene set enrichment in a small subset of gene ontology (GO) immune signatures at each developmental stage. While this approach provides a robust snapshot of immune function, a challenge within the field is how to assess and measure the anti-tumour response in all its granularity, including the activation of Immune Checkpoints and role of T-cell exhaustion. Immune editing in a tumour arises from the cyclical process, the Cancer Immunity Cycle, a seven stage cycle which is initiated by the release of cancer cell antigens and results in cancer cell killing [7,8]. First reported as a mechanism of characterising the antitumor immune response, multiple stages of the cancer immunity cycle are now targeted and manipulated by oncologists [7–9].

However, the treatment of metastatic non-small cell lung cancer has been transformed significantly by immunological advances, heralding the advent of immunotherapy. Immune checkpoint inhibitors now constitute first [10,11] and second-line [12,13] options in advanced disease, and there exist a subset of patients achieving long-lasting complete responses. Forays into immune checkpoint inhibition at earlier stages of lung cancer have tentatively begun, though not to the same extent; and there have been some positive results in the neoadjuvant setting [14]. Given the involvement of immune sensing, unleashing and tolerance in the incipient phases of malignant transformation suggested by Mascaux *et al.*, the question that naturally arises is whether these therapeutic options can be translated to the very source of cancer; prior to metastasis, prior to invasion, or pushed even to its conceptual limit, prior to development of cancer: an immunoprevention approach. Though at a glance, the latter may appear a relatively novel, there are precedents—particularly with virus-associated malignancies. In 1984, the government of Taiwan employed a nationwide hepatitis B vaccination program with spectacular

public health benefits—not least of which, was an 80% reduction in the incidence of hepatocellular carcinoma [15]; this constitutes one of the earliest and most successful applications of an immunoprevention strategy to date. Similar success was seen with HPV vaccination program to prevent cervical cancer [16]. Though this is a different scenario to that which may be envisaged in lung cancer, it is an indicator that immune-based prevention measures may offer us the iterative power to combat an ever-evolving disease.

The findings of Mascaux and colleagues advance our understanding of carcinogenesis in squamous cell lung cancer, with therapeutic implications for important avenues of contemporary cancer research. Further translational work is needed, with particular areas of focus that we would suggest, including: discovery and testing of immune biomarkers to facilitate earlier detection of pre-malignant disease; and clinical exploration of immune treatments, particularly targeting early treatment and chemo-preventative approaches. Our hope for the future treatment of lung cancer would be in line with the indefatigable medical adage: that prevention will prove better, and more achievable, than cure.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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