Beneficial autoimmunity in cancer control

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Many tumour antigens that do not arise from cancer cell-specific mutations (“neoantigens”) are targeted by humoral and cellular immune reactions despite their expression on normal cells. Thus, the immune system does not only detect mutations and stress-associated shifts in the immunoproteome and immunopeptidome (the sum of MHC class I-bound peptides) unique to malignant cells but also recognizes antigens expressed in normal cells, which can result in autoimmune reactions against normal structures from the tissue of origin. These autoimmune manifestations include, among others, vitiligo, thyroiditis and paraneoplastic syndromes, concurrent with melanoma, thyroid cancer and non-small-cell lung cancer, respectively. Importantly, despite the undesirable effects of these symptoms, such events can have prognostic value and correlate with favourable disease outcomes, suggesting the existence of 'beneficial autoimmunity'. For example, there is a negative epidemiological association between, on one hand, breast cancer and, on the other hand, rheumatoid arthritis or systemic lupus erythematosus. Similarly, the occurrence of dermal and endocrine autoimmune adverse events in patients receiving immune-checkpoint inhibitors can have a positive predictive value for therapeutic outcomes. Neoplasias derived from stem cells deemed 'not essential' for survival (such as melanocytes, thyroid cells and most cells in sex-specific organs) have a particularly good prognosis, perhaps because patients can tolerate autoimmune reactions that destroy tumour cells at some cost to non-malignant tissues. Recently, we obtained evidence that, in mice, experimental induction of autoimmune cholangitis can protect against the development of cholangiocarcinoma but not that of other malignancies from other cells of origin. Furthermore we have demonstrated that vaccination against normal mammary or ileal epithelial cells has oncopreventive effects against breast cancer or colorectal cancer, respectively.