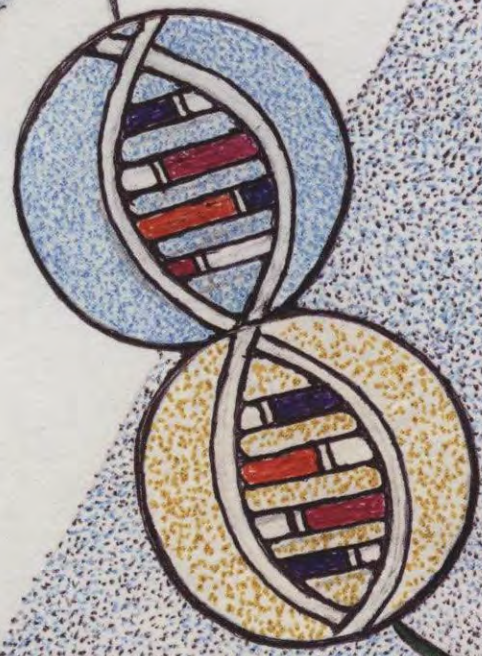


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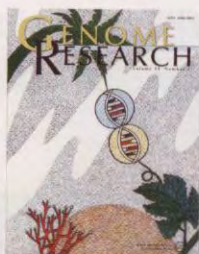
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Cover Horizontal transfer of genetic material has been demonstrated on a small scale for several organisms. In this issue, this phenomenon is demonstrated to be widespread in the plant kingdom. On the cover is a Pointillist-like view of the horizontal transfer of transposable elements between palm (*top left*) and grape (*bottom right*). The two circles depict the respective DNA molecules and leaf colors indicate the chimeric nature of plants. Horizontal branches on the “tree of life” at the *bottom left* illustrate frequent transfer during the evolution of plants. (Cover illustration by Abdelkebir El Baidouri. [For details, see El Baidouri et al., pp. 831–838.]

Research

Neo-antigens predicted by tumor genome meta-analysis correlate with increased patient survival

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John J. Spinelli,^{5,6} Brad H. Nelson,^{3,4,7} and Robert A. Holt^{1,3,8,9}

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Somatic missense mutations can initiate tumorigenesis and, conversely, anti-tumor cytotoxic T cell (CTL) responses. Tumor genome analysis has revealed extreme heterogeneity among tumor missense mutation profiles, but their relevance to tumor immunology and patient outcomes has awaited comprehensive evaluation. Here, for 515 patients from six tumor sites, we used RNA-seq data from The Cancer Genome Atlas to identify mutations that are predicted to be immunogenic in that they yielded mutational epitopes presented by the MHC proteins encoded by each patient's autologous *HLA-A* alleles. Mutational epitopes were associated with increased patient survival. Moreover, the corresponding tumors had higher CTL content, inferred from *CD8A* gene expression, and elevated expression of the CTL exhaustion markers *PDCDI* and *CTLA4*. Mutational epitopes were very scarce in tumors without evidence of CTL infiltration. These findings suggest that the abundance of predicted immunogenic mutations may be useful for identifying patients likely to benefit from checkpoint blockade and related immunotherapies.

[Supplemental material is available for this article.]

The accumulation of somatic mutations underlies the initiation and progression of most cancers by conferring upon tumor cells unrestricted proliferative capacity (Hanahan and Weinberg 2011). The analysis of cancer genomes has revealed that tumor mutational landscapes (Vogelstein et al. 2013) are extremely variable among patients, among different tumors from the same patient, and even among the different regions of a single tumor (Gerlinger et al. 2012). There is a need for personalized strategies for cancer therapy that are compatible with mutational heterogeneity, and in this regard, immune interventions that aim to initiate or enhance anti-tumor immune responses hold much promise. Therapeutic antibodies and chimeric antigen receptor (CAR) technologies have shown anti-cancer efficacy (Fox et al. 2011), but such antibody-based approaches are limited to cell surface target antigens (Slamon et al. 2001; Coiffier et al. 2002; Yang et al. 2003; Cunningham et al. 2004; Kalos et al. 2011). In contrast, most tumor mutations are point mutations in genes encoding intracellular proteins. Short peptide fragments of these proteins, after intracellular processing and presentation at the cell surface as MHC ligands, can elicit T cell immunoreactivity. Further, the presence of tumor infiltrating lymphocytes (TIL), in particular, CD8⁺ T cells, has been associated with increased survival (Sato et al. 2005; Nelson 2008; Oble et al. 2009; Yamada et al. 2010; Gooden et al. 2011; Hwang et al. 2012), suggesting that the adaptive immune system can mount protective anti-tumor responses in many cancer patients (Kim et al. 2007; Fox

et al. 2011). The antigen specificities of tumor-infiltrating T cells remain almost completely undefined (Andersen et al. 2012), but there are numerous examples of cytotoxic T cells recognizing single amino acid coding changes originating from somatic tumor mutations (Lennerz et al. 2005; Matsushita et al. 2012; Heemskerker et al. 2013; Lu et al. 2013; Robbins et al. 2013; van Rooij et al. 2013; Wick et al. 2014). Thus, the notion that tumor mutations are reservoirs of exploitable neo-antigens remains compelling (Heemskerker et al. 2013). For a mutation to be recognized by CD8⁺ T cells, the mutant peptide must be presented by MHC I molecules on the surface of the tumor cell. The ability of a peptide to bind a given MHC I molecule with sufficient affinity for the peptide-MHC complex to be stabilized at the cell surface is the single most limiting step in antigen presentation and T cell activation (Yewdell and Bennink 1999). Recently, several algorithms have been developed that can predict which peptides will bind to given MHC molecules (Nielsen et al. 2003; Bui et al. 2005; Peters and Sette 2005; Vita et al. 2010; Lundegaard et al. 2011), thereby providing guidance into which mutations are immunogenic.

The Cancer Genome Atlas (TCGA) (<http://cancergenome.nih.gov/>) is an initiative of the National Institutes of Health that has created a comprehensive catalog of somatic tumor mutations identified using deep sequencing. As a member of The Cancer Genome Atlas Research Network, our center has generated extensive tumor RNA-seq data. Here, we have used public TCGA RNA-seq data to explore the T cell immunoreactivity of somatic missense

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