Published online 29 January 2020

NAR Cancer, 2020, Vol. 2, No. 1 **1**
doi: 10.1093/narcan/zcaa001

Putatively cancer-specific exon–exon junctions are shared across patients and present in developmental and other non-cancer cells

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Received October 02, 2019; Revised January 06, 2020; Editorial Decision January 09, 2020; Accepted January 14, 2020

ABSTRACT

This study probes the distribution of putatively cancer-specific junctions across a broad set of publicly available non-cancer human RNA sequencing (RNA-seq) datasets. We compared cancer and non-cancer RNA-seq data from The Cancer Genome Atlas (TCGA), the Genotype-Tissue Expression (GTEx) Project and the Sequence Read Archive. We found that (i) averaging across cancer types, 80.6% of exon–exon junctions thought to be cancer-specific based on comparison with tissue-matched samples (σ = 13.0%) are in fact present in other adult non-cancer tissues throughout the body; (ii) 30.8% of junctions not present in any GTEx or TCGA normal tissues are shared by multiple samples within at least one cancer type cohort, and 87.4% of these distinguish between different cancer types; and (iii) many of these junctions not found in GTEx or TCGA normal tissues (15.4% on average, σ = 2.4%) are also found in embryological and other developmentally associated cells. These findings refine the meaning of RNA splicing event novelty, particularly with respect to the human neoepitope repertoire. Ultimately, cancer-specific exon–exon junctions may have a substantial causal relationship with the biology of disease.

INTRODUCTION

Aberrant RNA splicing is increasingly recognized as a feature of malignancy (1–5), potentially driving cancer progression (4) and with potential prognostic significance across many cancer types, including non-small cell lung cancer, ovarian cancer, breast cancer, colorectal cancer, uveal melanoma and glioblastoma (6–11). Due to its potential for generating novel peptide sequences, aberrant RNA splicing is also interesting as a potential source of neoantigens for cancer immunotherapy targeting (12). For instance, retained intronic sequences can give rise to numerous potential antigens among patients with melanoma, although they are not a significant predictor of cancer immunotherapy response (13), and a patient-specific neoantigen arising from a gene fusion has been shown to lead to complete response from immune checkpoint blockade (14). Novel cancer-specific exon–exon junctions have also been shown to be a source of peptide antigens (15), and represent compelling potential targets for personalized anticancer vaccines (16).

However, the ability of the adaptive immune system to target a given antigen as 'foreign' depends on a complex prior tolerogenic education, and in particular on whether or not a given antigen has been previously 'seen' by the immune system in a healthy context (17). Therefore, prediction of cancer-specific antigens depends explicitly on their sequence novelty, and thus requires a comparison with non-cancer cells.

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