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EDITORIAL

The ever-changing world of gene fusions in cancer: a secondary gene fusion and progression

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Since the Philadelphia chromosome was discovered in 1960 (Reviewed in [1]) the role of genomic rearrangement and fusion genes has continued to expand at an exponential pace. Early discoveries were in other hematopoietic tumors, sarcomas, and some uncommon carcinomas. Fusions were then discovered in more common carcinomas including a group of gene fusions that were not specific to tissue type leading to common diagnostic use and tissue agnostic therapeutics. In this issue of Oncogene, Dupain et al. [2], expand on some recent discoveries and increase the known complexity of the role gene fusions play in cancer: a second driver gene fusion (LMO3-BORCS5) in a cancer already defined by a gene fusion (Ewing sarcoma: EWSR1-FLI1) with greatly increased in expression from initial diagnosis to relapse. If past trends in gene fusions are any predictor, this rare phenomenon in a sarcoma will likely become a common diagnostic necessity across many cancers both common and rare increasing the need for more complex diagnostic tools if we are ever to fulfill the promise of precision medicine in a world where diagnostic samples are getting smaller for a variety of reasons.

Any discussion of gene fusions begins with the Philadelphia chromosome. In clinical diagnostics today we are always looking for biomarkers with clinical utility. Clinical utility can come under a number of different forms: accurate diagnosis and early detection, prognosis, therapeutic prediction (response and/or resistance), and monitoring (early detection of relapse or partial response requiring treatment changes), among others. The history of the Philadelphia chromosome fits nearly all these categories perfectly. In 1960, Nowell and Hungerford discovered that chronic myeloid leukemia (CML) almost invariably had a marker chromosome later shown by Janet Rowley to be a cytogenetic rearrangement, t(9;22)(q34,q11) (Reviewed in [1]). It was then shown that this rearrangement creates a chimeric mRNA and oncoprotein, BCR-ABL, with the ABL kinase being a key biochemical component of this driver fusion. These facts became a key diagnostic marker defining what the WHO calls today chronic myeloid leukemia (CML), BCR-ABL1 positive (accurate diagnosis). Today we often screen patients with abnormal blood counts with a test for the BCL-ABL rearrangement (screening and early detection). The t(9;22)(q34,q11) translocation was also discovered in acute lymphoblastic leukemia, but with a different BCR-ABL transcript encoding a smaller fusion protein (p190) compared with the common CML fusion oncoprotein (p210) leading to a key diagnostic and prognostic difference. As people studied the ABL oncogene, they developed a pharmaceutical, imatinib, which directly targeted the ABL kinase in addition to a few other kinases. This now created a predictive test: the presence of BCR-ABL predicting a response to therapy, and quantitative monitoring of the BCR-ABL decrease as an indicator of therapeutic response, resistance, and relapse. Overtime, resistance mutations in the ABL kinase domain were discovered and now testing for these mutations is common when monitoring shows either relapse or an incomplete response, and which may predict a response or resistance to other pharmaceutical agents [1].

As the history of BCR-ABL was progressing, a number of other gene fusions were discovered, many in acute leukemia, along with the genetic fusions of lymphocyte enhancers with oncogenes in lymphomas leading to overexpression [3]. Some sarcomas were defined as a group of tumors with diagnostically specific recurrent gene fusions [4] (i.e., Ewing sarcoma, the focus of the study by Dupain et al. [2], EWSR1-FLI1). Common carcinomas remained free from discover of their gene fusions at this time, except for thyroid carcinoma, which showed a number of translocations involving RET, especially in those exposed to radiation [5]. A landmark study in 2005 brought gene fusions to the forefront as a common driver in a common

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carcinoma, the ETS gene family members fusions in prostate carcinoma [6]. One reason this avoided discovery up to this date was that the most common lesion, TMPRSS-ERG, is caused by a small intrachromosomal deletion of 3MB not a large interchromosomal rearrangement, and it was originally the overexpression of portions of the ERG (and other ETS gene family members) mRNA that lead to this discovery. The LMO3-BORCS5 fusion in Dupain et al. [2] arises from a similar small deletion mechanism. In the last decade there has been an explosion of gene fusion discovery across all cancer types both rare and common. Recently, a number of tyrosine kinase gene fusions (i.e., the NTRK and FGFR gene families) have been discovered in common with a number of different cancers leading to the recent approval of an NTRK inhibitor and routine diagnostic testing for NTRK fusions across many cancer types [7].

Which leads us to Dupain et al. [2] and the discoveries within. While not an absolute rule, we often focus as one predominant gene fusion in cancer such as EWSR1-FLI1 as the main driver of a sarcoma known as Ewing sarcoma, an unusual tumor with a primitive neuroectodermal phenotype but a predilection for bones and soft tissues. In their previous study, Dupain et al. [8] discovered a second gene fusion in a Ewing sarcoma sample at the time of relapse. While it was shown that the fusion was present at the time of original diagnosis, its relative expression increased dramatically from the time of diagnosis to relapse (~140,000 fold increase in expression based on RT-PCR). RNA-sequencing studies have begun to reveal a near excessive number of chimeric RNAs in cancer samples, but it is uncertain at this time which are created by actual structural genomic rearrangement and which are biologically relevant without further study. Dupain et al. [2] show that this second rearrangement is a bona fide driver mutation through a number of cell based studies showing increased proliferation, tumorigenicity of xenografts, decreased sensitivity to therapeutics and cell death, and changes in gene expression.

This study has much to offer to the biology of cancer, much of which I don't have the space to discuss (and which is beyond my limited expertise). However, from the point of view of a diagnostic genomic pathologist I see this study as a harbinger of the future of precision medicine. While BCR-ABL may be the paradigm of precision medicine with a known marker used for diagnosis, monitoring, and therapeutic prediction (and as a direct chemotherapeutic target), much of the rest of cancer requires so much more than one marker and one technique (although BCR-ABL has three main techniques in its initial diagnosis: classical cytogenetics, FISH, and RT-PCR, it is primarily RT-PCR and sequencing of the RT-PCR product that are used after initial diagnosis). While Ewing sarcoma may be a rare tumor with one classic marker used for diagnosis (detectible by cytogenetics, FISH, RT-PCR, RNA-seq, etc.), the presence of this secondary gene fusion in this sample that is greatly increased at relapse and contributes to drug resistance (in general, not a direct chemotherapeutic target at this time) has me imagine a future whereby we need the full monitoring of all genomic rearrangements in all cancers at all times, in addition to the clinically relevant small nucleotide variants (by NGS) and copy number variants (by FISH or CGH), we detect on an everyday basis. In addition, current clinical guidelines for some tumors use gene expression profiles in stratification [9], and methylation profiling (a marker of gene expression) is increasingly being used to better diagnose tumors [10]. Finally, markers of immunotherapy (microsatellite instability, tumor mutation burden, and/or the expression of checkpoint molecules) are also a key clinical test for a number of different tumors [11]. At the same time, we often get very small samples that have insufficient material for the perfect battery of preferred tests, leading to a triage where only a subset of the highest yield tests are performed. However, each tumor is its own species (in addition to being in its own ecology), and as Dupain et al. [2] show any one tumor may have a very specific cause for possible tumor progression and resistance. The cumulative weight of all this information leads me to the following conclusion: if we are ever to reach the full potential of precision medicine we are going to need a way to interrogate all the genomic changes of a tumor from the individual base to the largest structural variant (and everything in-between) in addition to an understanding which genes and variants are turned on or off in each genomic context and which immune receptors are being expressed both within and adjacent to the tumor to best predict how a tumor is going to behave and respond to therapy.

Compliance with ethical standards

Conflict of interest MPP is a consultant for Neogenomics Laboratories, a company that offers cancer genomic testing, and a former employee and Scientific Advisory Board member of Dovetail Genomics, a company that offers multiple genomic sequencing solutions. The material presented in this editorial is the sole creation of the author and it does not represent, and is independent from, any current or prior employer.

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