Commentary

Aberrant ALK Tyrosine Kinase Signaling

Different Cellular Lineages, Common Oncogenic Mechanisms?

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Chromosomal translocations are typical of a select group of tumors, including most lymphomas and leukemias, many sarcomas, and rare carcinomas. In each tumor type, a specific recurrent translocation is seen in most or all cases. Compared to other oncogenic mechanisms such as point mutation, deletion, and amplification, individual translocations show the greatest specificity for particular tumor types. Accordingly, the elucidation of the gene rearrangements or fusions resulting from these translocations has yielded molecular diagnostic markers whose clinical acceptance has generally been quite straightforward. In most leukemias and sarcomas, and some lymphomas, these translocations produce specific gene fusions which encode chimeric proteins. These chimeric proteins usually function either as aberrant transcription factors or as constitutively activated tyrosine kinases (TK). Translocations that activate receptor TKs do so by fusing their catalytic domain to strongly or ubiquitously expressed proteins with dimerization or oligomerization domains. The latter can be termed dimerizing translocation partners (DTP).

In this issue of *The American Journal of Pathology*, Lawrence et al report the identification of specific gene fusions in the inflammatory myofibroblastic tumor (IMT), producing a constitutively activated chimeric anaplastic lymphoma kinase (ALK) TK.¹ These findings are significant on several levels: first, they provide a key insight into the biology of these tumors; second, they may delineate a distinct genetic, and possibly clinical, entity from the broadly defined IMT group of tumors; third, and perhaps most remarkable, they indicate that inappropriate activation of the same TK signaling pathway may be oncogenic in disparate cellular lineages, and may even result from the same translocation.

Aberrant ALK Signaling: A New Insight into the Biology of IMT

As mentioned above, chromosomal translocations seem to play a pivotal role in the biology of most lymphomas and leukemias, many sarcomas, and rare carcinomas. In almost all instances, these translocations appear to be primary genetic events, preceding any other lesion detectable by cytogenetic or molecular techniques. When they are present, they are a blessing to investigators because they represent a "Rosetta stone"² for the biology of these tumors. As primary genetic events, these gene fusions are obvious candidate necessary initiating events. Whether they are also sufficient for the genesis of these specific tumors has been more difficult to investigate, due in part to the inherent limitations of mouse models of human chromosomal translocations. More authentic mouse models of human translocations are, however, being developed^{3,4} and may help to address some of these questions. Nonetheless, the cloning of these translocations always provides a critical insight into the early biology of the tumors that harbor them.

ALK was first identified in 1994 through the cloning of the t(2;5)(p23;q35), the main translocation in anaplastic large cell lymphoma (ALCL), where it was found to be fused to the *NPM* (nucleophosmin) gene at 5q35, which encodes a nucleolar phosphoprotein.⁵⁻⁷ The resulting fusion gene encodes a chimeric constitutively activated tyrosine kinase, NPM-ALK, consisting of the N-terminal portion of NPM fused to the catalytic domain of ALK.⁵ The fusion with *NPM* results in activation of the ALK kinase domain and its expression in a deregulated and ectopic manner, both in terms of cell type (lymphoid) and cellular compartment (nucleus and cytoplasm). The ALK receptor TK is most closely related to leukocyte tyrosine kinase

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(LTK), with which it shows 79% amino acid identity in the kinase domain and extensive homology elsewhere, including the ligand-binding domain.^{8,9} Because its ligand has not yet been identified, it remains an orphan receptor, and its normal function is unknown. Initial studies using *in situ* hybridization and immunohistochemistry for ALK showed that normal ALK expression was essentially limited to the central and peripheral nervous system.^{8,9} The finding in the present study of native unphosphorylated ALK in some IMT specimens¹ suggests that there may also be a limited role for ALK outside the nervous system.

The finding of *ALK* gene fusions in IMT indicates that, at least in the subset of IMT where these fusions are found, inappropriate activation of the ALK signaling pathway may represent a critical early step in the neoplastic transformation of these myofibroblastic cells. The same portion of ALK is included in the TPM3-ALK and TPM4-ALK fusions described presently in IMT as in NPM-ALK in ALCL.^{1,5} The contribution of *NPM* to the oncogenicity of *NPM-ALK* is limited to its strong constitutive promoter and the oligomerization domain it encodes.^{10,11} *NPM-ALK* oligomerization results in constitutive ligand-independent auto- or transphosphorylation of the ALK kinase domain. The portions of the nonmuscular TPM3 and TPM4 tropomyosin (TPM) proteins involved in these fusions include their coiled coil dimerization domains. They are thus likely to play a similar generic role as DTPs within these fusions as NPM. Indeed, Lawrence et al have confirmed that the TPM3-ALK and TPM4-ALK fusion proteins in IMT are phosphorylated and activated.¹

The ALK signaling pathway is gradually being worked out. *NPM-ALK* has been shown to activate phospholipase C (PLC)- γ .¹² Experiments with mutated *NPM-ALK* constructs deficient in PLC- γ phosphorylation suggest that activation of this signaling pathway accounts for much of the mitogenic effect of *NPM-ALK*, but not its anti-apoptotic effect.¹² By co-immunoprecipitation, *NPM-ALK* is also physically associated with PI3-kinase¹² and has recently been found to activate the PI3-kinase/AKT pathway.¹³ *NPM-ALK* also interacts directly with Shc and IRS-1, but these interactions were found to be dispensable for transformation,^{11,14} and *NPM-ALK* constructs defective in their activation failed to produce any phenotype in lymphocytes.¹² There is also evidence for direct signaling from *NPM-ALK* to GRB2, but no GRB2 recognition site has been identified in *NPM-ALK*.^{12,14} Finally, *NPM-ALK* may also interact with the STAT5 signaling protein and transcription factor.^{13,15} Many of these studies have been performed in ALCL cell lines. A mesenchymal cell such as the myofibroblast may present a different set of proteins for interaction with the ALK catalytic domain and the downstream signals and pathophysiological effects could be different.

The activation of the ALK signaling pathway in IMT also identifies targets for drug development, potentially relevant to the future management of unresectable IMT. Many small molecule inhibitors of protein kinases have been designed and some appear to show clinical efficacy.¹⁶ Chimeric TKs are good candidates for this type of approach.¹⁷ For instance, the activation of PLC- γ , a key

target of *NPM-ALK*,¹² can be blocked by decoy peptides containing the PLC- γ -SH2 binding site.¹⁸

ALK+ IMT: A Distinct Clinicopathological Entity?

The entity of IMT emerged in 1995¹⁹ from the acceptance of the concept of myofibroblastic differentiation and from the recognition of the similarities among a variety of lesions with myofibroblasts and inflammatory cells, such as inflammatory pseudotumor of lung, plasma cell granuloma, postoperative spindle cell nodule, pseudosarcomatous myofibroblastic proliferation, and atypical fibromyxoid tumor. Although many of these terms suggested a non-neoplastic origin, the finding of clonal cytogenetic aberrations²⁰⁻²² and the observation of infiltrative growth, vascular invasion, and noncontiguous spread in some cases were consistent with a neoplastic process. The clinical behavior has been cautiously termed to be that of a tumor with indeterminate or low malignant potential.²³ The higher grade end of the spectrum of IMTs is reflected by the term, inflammatory fibrosarcoma.^{24,25} Tumor-related deaths are rare (<10%) and are usually due to local invasion, not distant metastases. Outside the lung, the most common sites are the mesentery, retroperitoneum, and pelvis. Three basic histological patterns have been defined: nodular fasciitis-like, fibrous histiocytoma-like, and desmoid-like,¹⁹ representing in part the substantial variation in the proportion of neoplastic myofibroblastic cells, reactive inflammatory cells, and collagenous deposits. Because of some heterogeneity in morphology and clinical behavior, the grouping of these entities under the term IMT may combine subgroups with different clinical behaviors.²⁴ There has been only limited success in predicting biological potential from histological features or ancillary studies such as DNA ploidy or p53 immunoreactivity.²⁶

The present results suggest that the lesions lumped morphologically as IMT may indeed harbor more than one discrete genetically distinct tumor entity. Lawrence et al estimate that cytogenetically detectable rearrangements of the chromosome 2 short arm, where *ALK* resides, are observed in about 50% of IMTs.¹ By ALK IHC, they found 7 of 11 cases positive; the negative cases included all older adults (age >40).¹ In a recent abstract, Coffin et al have reported 11 of 40 cases positive by IHC with the same ALK antibody;²⁷ all of the patients with ALK+ IMTs were younger than 10. In aggregate, these initial immunohistochemical data suggest that ALK+ IMTs make up about 35% of all IMTs and occur mainly or exclusively in children and young adults. So far, ALK immunoreactivity has not been associated with specific histological features, and systematic studies of prognostic correlates have yet to be done.

It is interesting to draw parallels to the effect that ALK analysis has had on our concepts of ALCL.⁷ ALK immunoreactivity, due to *NPM-ALK* and related variant *ALK* gene fusions, has been used to define a discrete genetic subset of Ki-1 ALCL, which has turned out to correspond to a distinct, prognostically favorable clinical subset as well.²⁸⁻³⁰ ALK+ ALCL tend to have a higher proliferative

rate than ALK[−] ALCL.³¹ Patients with ALK⁺ ALCL are significantly younger than their counterparts with ALK[−] tumors.^{28–30} Intriguingly, so are patients with ALK⁺ IMTs. Furthermore, although some histological, immunohistochemical, and immunogenotypic features are typical of ALK⁺ ALCL, there is still a broad overlap with ALK[−] cases, making it difficult or impossible to predict the ALK status of a given case of ALCL *a priori*. Nonetheless, given its different age distribution and clinical outcome, ALK⁺ ALCL has become accepted as a distinct clinicopathological entity. A similar fate may await ALK⁺ IMT, although the generally low malignant potential of IMT may make the identification of clinical subsets less likely. What genetic changes might underlie ALK[−] IMTs? This remains unclear, but certainly other modes of ALK activation will be investigated. In addition, some cases may contain instead rearrangements of *HMGIC*,^{22,32} a gene involved in a wide variety of benign mesenchymal tumors.^{33,34}

Lawrence et al report *TPM3-ALK* and *TPM4-ALK* fusions in IMT, along with different lines of evidence for additional variant *ALK* fusions with as yet unidentified translocation partners.¹ Will clinicopathological correlates of these alternative *ALK* fusions emerge in IMT? The number of cases is presently too low to answer this question. The potential for etiological, pathological, and clinical differences among alternative chimeric TKs within a given tumor type has been highlighted by the analysis of *RET* and *NTRK1* rearrangements in papillary thyroid carcinomas (PTC).³⁵ At least 8 types of *RET* fusions and 3 types of *NTRK1* fusions have been described.³⁶ PTCs with *RET* or *NTRK1* rearrangements occur in younger patients than PTCs lacking detectable rearrangements.³⁵ PTCs with *RET* rearrangements due to chromosome 10 inversions (*H4-RET* and *ELE1-RET* fusions) are strongly overrepresented among radiation-related PTCs.^{36–38} There is recent evidence that the normal proximity of the *ELE1* gene to *RET* in the interphase nucleus may predispose to radiation-induced rearrangements.³⁹ Pathologically, *ELE1-RET* PTCs more often show solid histology instead of the classical papillary appearance.^{36,37,40} In contrast to the findings in PTCs, variant translocations have so far not been associated with clinical, etiologic, or pathological differences in ALCL.⁴¹ As the genetic heterogeneity of *ALK* fusions in IMT becomes more fully characterized, similar issues can begin to be addressed in this tumor.

Specificity versus Promiscuity in Oncogenic Tyrosine Kinase Activation

The remarkable specificity of certain chromosomal translocations has been the subject of recent reviews.^{42,43} For translocations producing a chimeric TK, this specificity may arise in part from a requirement for a specific susceptible cell type at a specific differentiation stage, which, probably reflects the need for a suitable set of interacting signaling molecules. Other sources of tumor specificity may include the expression level of the DTP gene and, perhaps, a greater risk for expressed genes to

be rearranged. In most of these types of translocations, the DTP forms the 5' portion of the fusion gene, and thereby its promoter drives the expression of the chimeric TK. Although most DTPs are strongly or constitutively expressed, minor or uncharacterized cell type-specific differences in expression may impact on the expression level of the fusion gene, and thereby its oncogenic potential. The tertiary structure of the genes to be rearranged may be of significance insofar as transcribed genes, which are more likely to be in an open conformation, may also be more vulnerable to rearrangements. The latter hypothesis, incidentally, is not supported by the case of *ALK* rearrangements, especially in ALCL, because no putative lymphoid ALCL precursor cell expressing normal *ALK* has been identified.

Another level of specificity arises from an inherent constraint: the exon structure of the genes in question must be such that heterologous exons that can produce in-frame transcripts are available to produce full-length fusion proteins. Thus, at least one exon 5' to the catalytic domain (but 3' to the extracellular domain) of a receptor TK gene must be in the same reading frame as one or more exons 3' to the dimerization domain of the DTP gene.

Although translocations involving TK genes have previously appeared quite tumor type-specific, it is clear that point mutations as a mode of aberrant activation of specific TKs can be oncogenic in multiple cell types. For instance, activating point mutations of *KIT* are seen in mastocytosis⁴⁴ and gastrointestinal stromal tumors,⁴⁵ and *RET* activation by specific missense mutations is seen in both sporadic and familial medullary thyroid carcinomas and pheochromocytomas.⁴⁶ Moreover, *RET* activation by fusion with DTPs is also seen, but only in PTCs.³⁵

What had not been previously observed is precisely the same translocation activating a given TK in distinct cell types. The first example of this phenomenon involved the *ETV6-NTRK3* fusion. The *ETV6-NTRK3* fusion resulting from a t(12;15) translocation is found in all or most cases of congenital fibrosarcoma⁴⁷ and the related cellular mesoblastic nephroma.^{48,49} The identical translocation, both cytogenetically and at the molecular level, has also been demonstrated in a single case of acute myeloid leukemia in a 59-year-old woman.⁵⁰ The finding of *TPM3-ALK* in cases of both ALCL and IMT provides a second example of this phenomenon. Specifically, *TPM3* has been found to be fused to the *ALK* gene in rare cases of ALCL^{51,52} (most cases show *NPM-ALK*). *TPM3-ALK* may account for about 5% of ALK⁺ ALCL. *TPM3* also fuses with the *NTRK1* gene in some PTCs to form another chimeric, constitutively activated TK.³⁵ The finding of *TPM3-ALK* in IMT suggests that other *ALK* fusion partners in ALCL, namely *NPM*,⁵ *TFG*,⁵³ *ATIC*,^{54–56} or *CLTCL2*,⁵⁷ may account for some of the other ALK⁺ IMTs. Indeed, we have recently identified *CLTCL2-ALK* in an IMT (JA Bridge, SW Morris, M Ladanyi, et al, unpublished results).

Individually, certain other genes can be rearranged in specific types of both hematological tumors and solid tumors. For instance, *TLS* (also known as *FUS*) is fused to the *CHOP* gene in over 95% of myxoid liposarcomas, and

EWS can substitute for *TLS* in about 2% of cases.⁵⁸ Although the *ERG* gene is fused with *EWS* in approximately 5% of Ewing's sarcomas,^{59,60} *TLS-ERG* fusions, surprisingly, have been seen so far not in any sarcoma but only in a rare subset of acute myeloid leukemias.^{61,62} *ETV6* is involved in many different leukemia translocations, where either it acts as a DTP or contributes its ETS-type DNA binding domain.⁶³ However, there have been no instances so far of the same translocation-derived chimeric transcription factor in tumors of clearly different cellular lineages, suggesting that transcriptional deregulation may be a more cell type-specific oncogenic mechanism than deregulation of TK-mediated intracellular signaling.

TPM3-ALK and *ETV6-NTRK3* are the first instances of identical gene fusions associated with completely different tumor phenotypes, reflecting the occurrence of the same translocation in different cellular lineages, ie, hematopoietic or mesenchymal. Interestingly, transfection or retroviral transduction of NPM-ALK in rodent cells can transform both fibroblast and lymphoid lineages.^{11,12,14,64} In retrospect, these transformation data were providing an experimental clue for the clinical finding of the same ALK fusion oncoprotein in tumors from different lineages, ie, IMT and ALCL. We expect that more examples may follow.

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