Anaplastic lymphoma kinase: activating mechanisms and signaling pathways

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1. ABSTRACT

The discovery of Anaplastic Lymphoma Kinase (ALK) by Stephan Morris and colleagues twenty years ago has led to an unprecedented opportunity and provided the basis for a novel and clinically powerful stratification of human cancers. The molecular and biological characterization of ALK and the recognition of alternative mechanisms of activation of the tyrosine kinase receptors have then set the basis for the development and the subsequent application of selective small molecules. These achievements have fostered a new era in oncology, and the result of this new avenue has drastically changed the expectation of many cancer patients. Here we review the mechanisms of ALK activation and the modalities that drive ALK pathogenesis.

2. INTRODUCTION

Myriad mechanisms contribute to cell transformation. The current model predicts the acquisition and accumulation of defects over time and the selection of the best-fit phenotype(s) within a patient specific environment. This will result in the emergence of a dominant clone(s), capable of overcoming the immune response and taking advantage of host support systems (1). A similar model explains how cancer cells become resistant to therapy; a biological advantage is bestowed to cells harboring defects that allow them to overcome treatment pressure. In this way, drug selection favors the expansion of preexisting minor clones and/or facilitates the emergence of new ones (2). Although the systematic application of high throughput strategies, like next generation sequencing (NGS) (3), has identified a plethora of genomic and epigenomic defects associated with human cancer, recurrent defects are associated with a number of human cancers (4). Collectively these defects lead to deregulated activation of various signaling pathways, which alternatively and synergistically provide the neoplastic phenotype of each individual neoplasm (5). The recognition of driver mutations provides the opportunity to not only define the fingerprint of a tumor, but also to evaluate targeted therapies (6,7).

The deregulation of tyrosine-kinase (TK) activity constitutes a major mechanism in human carcinogenesis.

In neoplastic cells, abnormal TK activation can occur through several mechanisms, spanning from recurrent chromosomal translocations to gene amplifications, point mutations or gene deregulation. The aberrant expression of kinases leads to constitutive activation of multiple downstream signaling pathways that synergistically contribute to the development of neoplastic phenotypes (8). Recurrent kinase translocations are detected in up to 3% of all human tumors. This percentage increases up to 7% if non-recurrent fusions and abnormal karyotypes are considered (9). Anaplastic Lymphoma Kinase (ALK) constitutes one of the most common and well-characterized oncogenic TKs.

Twenty years ago, Stephan Morris and colleagues first described a novel Tyrosine Kinase Fusion (TKF) protein in a subset of Anaplastic Large Cell Lymphomas (ALCL) harboring the recurrent t(2;5) (p23;q35) translocation (10). This study demonstrated that in the t(2;5)(p23;q35) translocation, the nucleophosmin (NPM) gene was fused to a novel TK gene, namely ALK. In a mechanism common to other TKFs, NPM provides oligodimerization domains, which ultimately causes the dimerization of the TKF and its constitutive activation (11, 12). Since then, a long list of ALK chromosomal translocations has been described within both hematological and non-hematological tumors (8,13). The oncogenic properties of these fusions have been demonstrated *in vitro* and *in vivo* (12), leading to research and development of selective inhibitors (14) and the execution of dedicated trials (15). Crizotinib was the first of the TK inhibitors to gain accelerated FDA approval, and eventually regular approval (http://www.cancer.gov/cancertopics/druginfo/fda-crizotinib).

This review aims to characterize the molecular biology of ALK expression in normal tissues and neoplastic cells. The current understanding of the role of ALK deregulation in human carcinogenesis, the signaling pathways of ALK and the molecular mechanisms of anti-ALK therapy resistance will be addressed.

3. PHYSIOLOGICAL EXPRESSION AND FUNCTIONAL ROLE OF ALK KINASE

The ALK gene, located on chromosome 2, encodes a 210 kDa TK receptor (CD247) comprising an extracellular ligand-binding, a trans-membrane and an intracellular TK domains. ALK is closely related to the leukocyte tyrosine kinase (LTK) receptor, and the two enzymes belong to a specific subgroup of the insulin growth-factor subfamily. The extracellular domains of ALK and LTK are unique among TK receptors, as they encompass a glycine-rich region and (in the case of ALK) additional LDLa and MAM domains (16). The specific role of ALK in human development and physiology is still poorly understood. Clues about ALK function are largely derived by studies on animal models.

In D. melanogaster, ALK signaling is tightly regulated and necessary for the insect survival. ALK is involved in the differentiation of mesenchymal cells, the development of the visual system (17), the maturation of the neuromuscular junction (18) and the regulation of body size, and learning and memory (19). ALK signaling protects neuroblasts during nutrient deprivation (20) and contributes to alcohol resistance (21). These physiological roles are at least partially mediated by the Jep ligand (22), which leads to the downstream activation of the Ras-MAPK signaling pathway (23,24).

In C. elegans, the ALK-homologue, SCD-2, is required for the development of the neuromuscolar junction and for the integration of sensory inputs (22). Upon binding with its ligand HEN-1, SCD-2 controls the "dauer state" (arrest of locomotion/metabolic activities due hostile environmental conditions), by regulating the TGFβ signaling pathways (25). Notably, crosstalk between ALK and TGFβ has also been reported in D. melanogaster visceral mesodermal cells (26).

In zebrafish (D. rerio), LTK and ALK share significant structural homology (presence of MAM domain) and participate in similar biological processes. LTK contributes to neural crest development, while ALK is involved in central nervous system (CNS) embryogenesis (27). In zebrafish, the role of LTK and ALK closely resemble those reported in vertebrates (28,29).

ALK expression patterns in chickens, mice, rats and humans suggest important roles in the CNS development (30). In mice, the loss of ALK signaling results in a dramatic decrease in newborn neurons and in impaired regeneration of myelinated axons (31). ALK mRNA and protein levels significantly decrease in all tissues after birth (32). Adult ALK-deficient mice lack obvious abnormalities. Interestingly, ALK knockout (ko) mice display an increased number of progenitor cells within the hippocampus, a defect that may be associated with their subtle behavioral changes (33).

The mammalian ALK receptor is unable to bind the Jeb ligand (34), which may indicate an evolutionary divergence between mammalian and D. melanogaster ALK proteins. In mammals, the neurotropic effects of ALK seem to be mediated by other ligands, such as pleiotrophin (PTN), midkine (MK), osteoblast-specific factor-1 (OSF-1), heparin affinity regulatory peptide (HARP) and heparin-binding neurotrophic factor (HBNF) (12). However, the activating potential of these peptides remains controversial. Perez-Pinera have proposed a model in which the the activation status of the ALK receptor is physiologically downmodulated by a specific phosphatase (i.e RPTPβ/ζ). This repression is counteracted when PTN engages the receptor, leading to a higher steady state phosphorylation status of the receptor (35). Nevertheless alternative ALK ligands and/

or other and so far unknown modalities activation may also exist.

Hints on ALK effects in human physiology can potentially be drawn from patients treated with the ALK inhibitor, crizotinib. Although this drug is associated with minor side effects, occasional reports describe reduction of heart rate (36), suppression of testosterone levels and visual disturbances (37). Further studies will clarify whether these clinical symptoms are ALK-specific effects or off-target events. Indeed crizotinib can efficiently inhibit several kinases, including c-Met (11nM) and ROS1 (1.7.nM). Thus, with the introduction of new ALK Kinase inhibitors (Ki), each one with unique properties and specificity, we should be able to define the off-target effects of each compound and gain more information on the physiological role of ALK in humans (38).

The importance of ALK signaling in cell differentiation and survival and its fine-tuning during adult life provide indirect evidence of the potential oncogenic role of the kinase.

4. CHROMOSOMAL TRANSLOCATIONS INVOLVING THE ALK GENE

Chromosome translocations are catastrophically disruptive events, caused by chromosomal breaks followed by the aberrant rejoining of the DNA (39). It is unknown how frequently they may occur in normal cells, although an increased frequency is seen under certain experimental conditions (40, 41), and in individuals who bear DNA repair defects (42). Interestingly the sporadic occurrence of translocations may not lead to the neoplastic phenotype (43), suggesting that concomitant defects are needed. Supporting this theory, NPM-ALK and ATIC-ALK transcripts are detected in the peripheral blood samples of normal individual (44), confirming that ALK-like TKF may be acquired over time but they are not sufficient to induce the full transformation of hematological elements. Multiple oncogenic mechanisms can result from the chromosomal breaks and the genesis of translocations. Although species-specific mechanisms may be in place (45), active transcription of the loci involved in the DNA breaks, chromosomal proximity and multiple DNA damaging events can contribute. Indeed, oncogenic translocations can be favored by genomic instability (46,47) and it is estimated that they are causal in ~20% of hematological and non-hematological tumors (48).

In the late 90s' three distinct groups reported the presence of a recurrent translocation, t(2;5)(p23;q35), in a subset of tumors that were collectively defined as Ki-1 positive lymphoma at the time (49-51). The application of an antibody recognizing the Ki-1 (CD30) antigen had allowed the appropriate diagnosis of this unique set of lymphoproliferative disorders, currently defined as ALCL. It is now well established that the inappropriate expression of ALK gene is most frequently due to

chromosomal translocations, which is due to different and unique ALK-fusion proteins. Translocations involving transmembrane TK receptors usually occur between exons encoding the juxta-membrane region or, less frequently, the TK trans-membrane domain. Both events result in the decapitation of the extracellular region and thus ligand-binding regulation. This results in the constitutive and uncontrolled activation of the fusion via a forced dimerization, dictated by the physical structure of the peptide coded by the partner gene (52).

Following this general rule, ALK breakpoints are almost invariably located between exons 19 and 20 of ALK (53). Each translocation leads to the generation of fusion proteins with the ALK TK-domain at the 3′end and distinct peptides provided by different partners at the 5′end of the fusion capable to provide a dimerization domain. After the seminal discovery of t(2;5)(p23;q25) (NPM-ALK) in ALCLs, many ALK translocations have been described in different human cancers within a very broad range of histological types and with unique frequencies (Table 1). To date, more than 20 partner genes have been discovered to participate to ALK fusions. A complexity further increased by the heterogeneity of different ALK species derived from different breakpoint variants for each fusion gene (54).

Collectively, translocations involving ALK gene are characterized by recurrent features: (i) the transcription of ALK fusion proteins is driven by the regulatory regions of the partner gene; (ii) the sub-cellular localization of the fusion protein (nuclear, cytoplasmic and/or membranous) is determined by the partner of ALK in the translocation; (iii) the dimerization of ALK fusion proteins occurs through the translocation partner and determines the trans-autophosphorylation (i.e. activation) of the ALK catalytic domain and (iv) with rare exception, the partner gene does not contribute per se to the oncogenic properties of the fusion. Moreover, ALK partners contribute to the stabilization/protein degradation of TKF, and they can modulate the kinase activity and contribute to the resistance to ALK-inhibitors (13).

The absolute oncogenic role of ALK fusion proteins does not exclude the contribution of additional genetic imbalances for the acquisition of the neoplastic phenotype. This hypothesis is sustained by experimental data on transgenic mice, demonstrating the occurrence of ALK+ lymphoproliferative disorders only after a latency period of few months. This time interval is believed to be necessary for the acquisition of additional genetic lesions to occur and for the selection of dominant clones. Interestingly in the case of CD4-NPM-ALK transgenic mice all T-cell lymphoma derive from thymocytes suggesting that the acquisition of secondary defects is favored in cells with a high proliferation rate and prone to accumulated lesions as result of their physiological DNA remodeling along the TCR rearrangement program execution. Notably, ALK chimeric transcripts have been

Table 1. ALK-associated translocations in human tumors

Fusion protein	Translocation	Disease	Frequency (%)
NPM-ALK	t (2;5) (p23;q35)	ALCL	75-80
		DLBCL	n/a
		RMS	n/a
TMP3-ALK	t (1;2) (q25;p23)	ALCL	12-18
		IMT	50
		RCC	<5
TMP4-ALK	t (2;19) (p23;p13)	ALCL	<1
		IMT	<5
		ESCC	n/a
ALO17-ALK	t (2;17) (p23;q25)	ALCL	<1
TGF-ALK	t (2;3) (p23;q21)	ALCL	2
		NSCLC	2
MSN-ALK	t (2;X) (p32;q11-12)	ALCL	<1
ATIC-ALK	inv2 (p23;q35)	ALCL	2
		IMT	<5
MYH9-ALK	t (2;22) (p23;q11.2.)	ALCL	<1
PPFIBP1-ALK	t (2;12) (p23;p11)	IMT	n/a
CLTC-ALK	t (2;17) (p23;q23)	ALCL	2
		DLBCL	n/a
		IMT	<5
SQSTM1	t (2;5)(p23.1.;q35.3.)	DLBCL	n/a
SEC31A	t (2;4) (p24;q21)	DLBCL	n/a
CARS-ALK	t (2;11) (p23;p15)	IMT	<5
RANBP2-ALK	t (2;3) (p23;q13)	IMT	<5
SEC31L1-ALK	t (2;4) (p23;q21)	IMT	<5
C2orf44-ALK	t (2;2) (2p23;q25)	CC	n/a
EML4-ALK	inv2 (p21;p23)	NSCLC	2-5
		RCC	<5
		BC	<3
		CRC	<3
FN1-ALK	t (2;11) (q31;p15)	OC	2-4
KIF5B-ALK	t (2;10) (p23;p11)	NSCLC	<1
KLC1-ALK	t (2;14) (p23;q32)	NSCLC	<5
VCL-ALK	t (2;10) (p23;q22)	RCC	n/a
STRN-ALK	t (2;2) (2p22;p23)	Tyroid	n/a
DCTN1-ALK	inv2 (p13p23)	Spitz tumors	n/a
A2M-ALK	t (2;12) (p23;p23)	FLIT	n/a

occasionally reported as isolated genetic abnormalities in non-neoplastic lymphocytes of healthy donors (44, 55), suggesting that ALK fusion are not sufficient and may be early event along transformation. Conversely, the recent demonstration that the ectopic expression of NPM-ALK after viral transduction can lead to the transformation of human T lymphocytes from normal donors (56) provides a new layer of complexity and demands for additional studies. Overall, this experimental evidence is sustained by clinical data: ALK+ ALCLs can harbor secondary chromosomal imbalances, and can undergo the loss of "bona fede" tumor suppressor genes (58, 59), although in general ALK+ ALCL display less genetic defects than ALK- ALCL.

4.1. ALK-translocations in ALCL

Approximately 80% of ALK+ ALCL harbor the t(2;5)(p23;q35) translocation and express the NPM-ALK fusion protein. The NPM1 gene, on chromosome 5, encodes a 23kDa multifunctional protein involved in nuclear trafficking, pre-ribosomal particles transport and ribosome biogenesis. NPM can also regulate cell division, DNA repair, gene transcription and genomic stability (57). Even in the absence of t(2;5)(p23;q35), NPM expression is deregulated in several human cancers and NPM1 gene translocations/deletions are reported. NPM can indeed act as an oncogene or a tumor suppressor, depending on its expression levels: at low-to-intermediate levels, NPM controls genomic stability and regulates the p53 and ARF pathways; at high levels, NPM induces cell growth and proliferation (58). Mutations of NPM1 have been proven to be pathogenetic in a subset of Acute Myeloid Leukemia (59). The N-terminal region of NPM comprises a dimerization domain and a nucleolar localization sequence (60). The intrinsic capacity of NPM to form large homo-/hetero-dimers favors the cross-link and trans-activation of NPM-ALK fusion proteins (61,62). The physiological shuttling of NPM in different cell compartment justifies the nuclear-cytoplasmic pattern of NPM-ALK immunostaining.

About 20% of ALK+ ALCL features chromosomal translocations other than t(2;5)(p23;q35)(Table 1) and among them the t(2;3)(q25;p23) translocation involving the non-muscle tropomyosin 3 (TPM3) is the most frequent (12, 63). The N-terminal coiled-coil domain of TPM3 leads to the homo-dimerization and transactivation of the TMP2-ALK fusion protein. ALK fusions can also involve TPM4 (a TPM3 homolog), located on chromosome 19p. Both TMP3-ALK and TMP4-ALK fusion proteins localize within the cytoplasm of the neoplastic cells (12) (Figure 1).

In the t(2;3)(p23;q21) translocations, involving the TFG gene, the TGF-ALK the ALK catalytic domain is juxtaposed to variable sized fragments of the TFG 5'-region. Thus different fusion products, namely TFG-ALK$_S$ (short), TFG-ALK$_L$ (long), and TFG-ALK$_{XL}$ (extra-long) (64) can be generated. All TGF-ALK fusions contain a TFG coiled-coil oligomerization domain, which allows the TKF activation and drives its cytoplasmic localization. TFG is a cytoplasmic protein, closely associated to the endoplasmic reticulum, whose physiological role remains to be conclusively defined. Interestingly, TFG via TANK
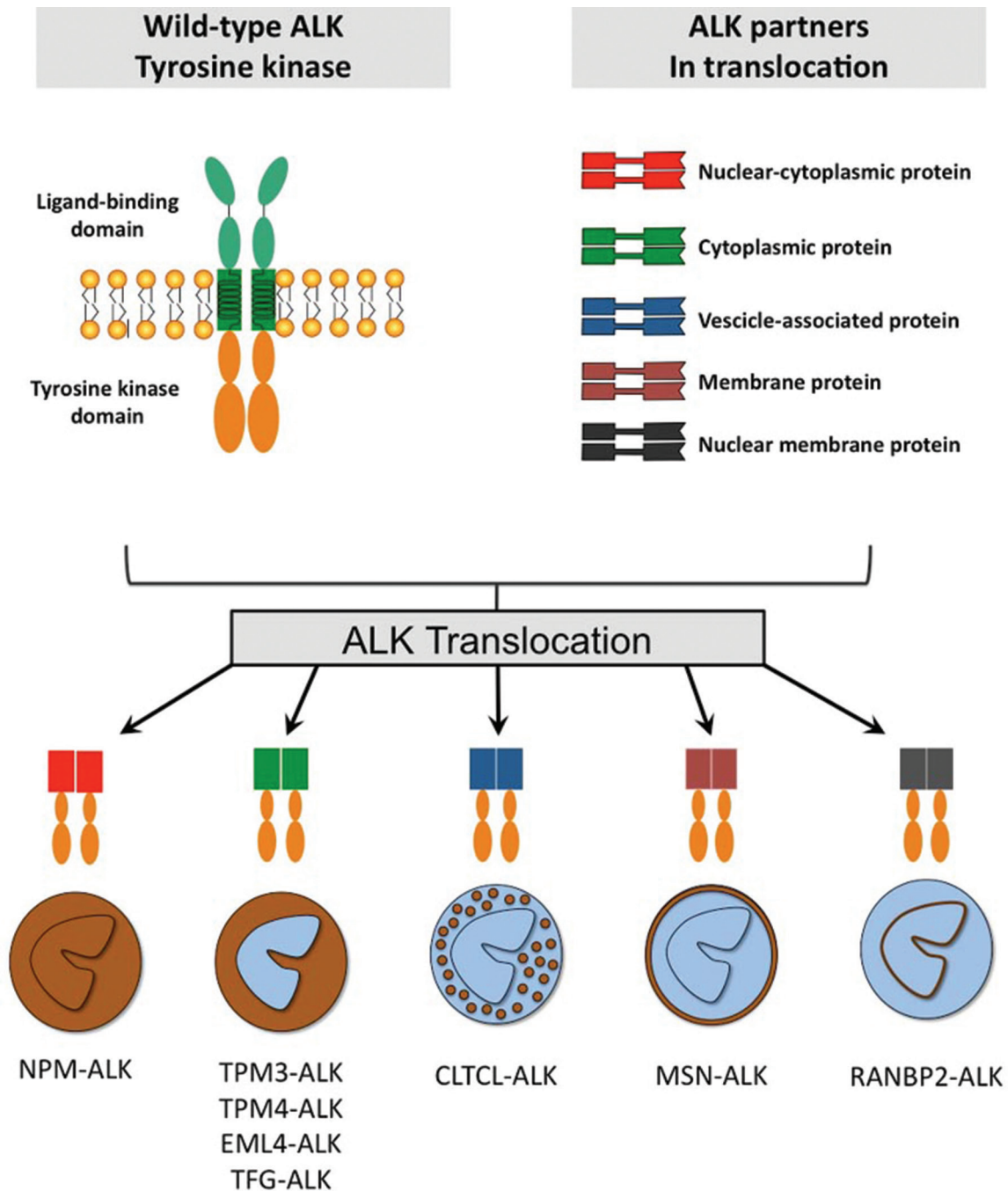
Figure 1. Schematic representation of the fusions and their corresponding cellular compartmentalization.

and NEMO can activate the NFkB pathway and it has been postulated that the TFG domain of TFG-tyrosine kinase fusions can contribute to the neoplastic phenotype, leading to concomitant activation of the NFkB pathway as well as to the oligodimerization of TKF proteins (65).

We have described a similar scenario in rare ALK+ ALCLs carrying the cytoplasmic TRAF1-ALK fusion (66-68). In TRAF1-ALK, the ALK partner binds TRAF2, leading to the constitutive activation of both canonic and non-canonical NFkB pathways (68). *In vitro* inhibition of the NFkB pathway impaired the lymphoma growth, suggesting that NFkB signaling contributes to the maintenance of the neoplastic phenotype and can be therapeutically targeted.

Other non-nuclear ALK translocations include the ATIC-, CLTCL- and MSN-ALK proteins. The ATIC

gene on chromosome 2 encodes an enzyme involved in purine nucleotide biosynthesis (5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase). The ALK fusion protein results from the cryptic inversion inv(2)(p23; q35), whose product encodes a 96-kDa TK with the ATIC N-terminal dimerization domain (69,70). Interestingly, ATIC phosphorylation enhances ALK enzymatic activity and dampens the methotrexate-mediated transformylase activity inhibition, demonstrating a novel property of this fusion and a unique contribution of the partner (71).

The CLTCL gene on chromosome 17q23 encodes a clathrin-like polypeptide, which contributes to the formation of intra-cytoplasmic endocytotic vesicles (72). The rare translocation t(2;17)(p23;q23) determines the formation of CLTCL-ALK homo-trimers, with consequent trans-activation of the TK activity. In such cases, ALK immunostaining features a characteristic cytoplasmic dot-like pattern, reflecting the TK localization on the surface of clathrin-coated intra-cytoplasmic vesicles (63,72).

The very rare t(2;X)(p32;q11-12) juxtaposes ALK and MSN genes. MSN encodes a membrane-associated protein (Moesin, MSN), implicated in the regulation of cell membrane-cytoskeleton interactions. The MSN-ALK fusion protein does not contain an oligomerization domain, but the wild-type MSN and MSN-ALK proteins hetero-dimerize, a complex capable to induce the kinase trans-activation. In these latter cases, ALK immunohistochemical staining discloses a peculiar, membrane-restricted pattern (73,74).

Other rare chromosomal translocations described in ALK+ ALCL involve the TSPYL2, ALO17 and MYH9 genes, which are respectively located on chromosomes Xp11, 17q25 and 22q11.2. The overall frequency of these translocations is <1% (67,72,75,76).

4.2. ALK translocations in other hematological disorders

ALK-translocations have been rarely reported in haematological neoplasms other than ALCL. Delsol and colleagues first described an uncommon variant of ALK-positive diffuse large B-cell lymphoma (DLBCL), now considered as a separate entity within the revised WHO Classification of hematological tumors (77). ALK-positive DLBCLs are aggressive neoplasms composed by sheets of large cells with plasmablastic features. Neoplastic lymphocytes are invariably positive for ALK (granular cytoplasmic immunostain) and express one or more plasma cell-associated marker (CD38, CD138 and EMA) (77). The most frequent chromosomal rearrangement in ALK-positive DLBCL is the t(2;17)(p23;q23), generating the CLTC–ALK fusion protein (78). Other fusions can result for the juxaposition the *NPM1*, *SQSTM1* and *SEC31A* genes to ALK (79-81). Little is

still known on the molecular biology of ALK-positive DLBCLs. As for ALK+ ALCL, the constitutive activation of STAT3 has been reported in ALK-positive DLBCLs, suggesting common mechanisms of oncogenesis in B or T-cell derived ALK+ lymphoma (82). The constitutive activation of STAT3 may also be responsible for the characteristic plasmoblastic phenotype of these lesions with a mechanism that may mirrors the one described in T-cell ALK+ ALCL (83). Interestingly, in CD4-NPM-ALK transgenic mice, the forced expression of NPM-ALK can lead to the development of either plasmablastic B-cell lymphomas or multiple myeloma (84).

ALK over-expression has been also documented in rare cases of pediatric systemic histiocytosis with a very indolent clinical course (85). One of such cases featured a t(1;2)(q25;p23) translocation, with the associated TPM3-ALK fusion transcript (85). The biology of ALK+ systemic histiocytosis is still debated, as it could represent either a true malignancy or an aberrant hyper-proliferation of accessory cells, driven by the ectopic expression of ALK. Toward this end, we have shown that the ectopic expression of NPM-ALK in mice may lead to histiocytic processes with low neoplastic potential and unable to propagate in recipient mice and/or *in vitro* (84).

Lastly rare Acute Myeloid Leukemia (AML) carrying the RAN-binding protein 2(RANBP2)-ALK have been recently described (86, 87) and in a single case failure to conventional treatment was temporarily overcome by the administration of crizotinib with the restoration of normal hematopoiesis, suggesting that RANBP2-ALK fusion acted as driver in association to additional defects in this AML (88).

4.3. ALK translocations in non-hematological disorders

ALK translocations have first reported among non-hematological neoplasms, in inflammatory myofibroblastic tumor (IMT), followed by their discovery in alveolar and embryonal rabdomyosarcoma (RMS), non-small-cell lung cancer (NSCLC) and a variety of epithelial tumors (13).

ALK fusion proteins have been reported in up to 50% of IMT and they appear to be associated with a better prognosis (89). As in ALK+ ALCL, several ALK translocation partners can be involved. These include TPM3/TPM4 (50% of cases), CLTC, CARS, ATIC, SEC31A, PPFIBP1 and RANBP2 (90-96). Of note, RANBP2-ALK, CARS-ALK and SEC31A-ALK fusions are unique/restricted of IMT, being reported only in single cases in other hematological or solid tumors (93, 97). Since RANBP2 participates to nuclear pore formation, RANBP2-ALK fusions display a typical nuclear membrane staining (97). The CARS gene on chromosome 11p15 is closely located to several tumor

suppressor genes, which could be affected by CARS chromosomal rearrangements. The deregulation of such tumor suppressors may play an important role in IMT pathogenesis (74). A novel A2M-ALK has been reported in a neonate with fetal lung interstitial tumor, proving new insights into the pathogenesis of this rare disease (98).

Among soft tissue neoplasms, rare cases of embryonal and alveolar RMS feature NPM-ALK fusion proteins. Even in the absence of chromosomal translocations, ALK expression has been reported in more than 50% of alveolar and in 23% of embryonal RMS (99). These data are further confirmed by *in vitro* studies, reporting the ALK expression and its oncogenic properties in the Rh30 RMS cell line (100).

As for epithelial neoplasms, ALK translocations have been documented in up to 6% of NSCLCs, a figure that increases with advance/metastatic tumors cases (101). ALK+ NSCLCs typically disclose glandular differentiation and arise in young patients with no story of smoking. Notably, ALK rearrangements and other NSCLC-associated genetic abnormalities (e.g. EGFR and KRAS mutations) are most commonly mutually exclusive (102), although in rare cases multiple common defects have been described. The spectrum of chromosomal imbalances in ALK+ NSCLCs is broad and several genes can be involved (EML4, KIF5B, TFG, KLC1, PTPN3 and STRN) (13, 103-106). The inv2 (p21; p23) is the most frequent translocation and leads to the juxtaposition of *EML4* and *ALK*, with the EML4 providing dimerization domains for the trans-activation of ALK TK. The ALK break point invariably involves intron 19, meanwhile different introns of the ELM4 can be affected leading to multiple EML4-ALK variants, with the variant 1 and 3 most commonly represented (90%). Interestingly from a diagnostic point of view, this could become a limiting factor which can be overcome using multiple and integrated strategies (107). The detection of ALK chromosomal imbalances in NSCLCs bears important clinical implications (108). A recent trial on ALK+ NSCLC has indeed demonstrated improved outcomes for patients treated with crizotinib plus chemotherapy compared to standard chemotherapy alone (108).

Many ALK chromosomal translocations have been reported in several other epithelial tumors, including breast, colon, renal, ovarian and squamous esophageal carcinomas. EML4-ALK fusions characterize both breast and renal (clear cell and medullary) carcinomas, while peculiar ALK rearrangements have been reported in rare colon cancer (C2orf44/WCDP-ALK), esophageal (TPM4-ALK), thyroid (STRN-ALK), renal cell carcinoma (VCL-ALK), and serous ovary (FN1-ALK) tumors. The clinical and biological meaning of such translocations has still to be clarified (109-114).

5. ALTERNATIVE MECHANISMS OF ALK ACTIVATION: GENE AMPLIFICATION AND SOMATIC MUTATIONS

Even in the absence of chromosomal translocations, several molecular mechanisms can alter ALK signaling in human cancers. Impaired expression/function of ALK TK can result from two major molecular events: (i) ALK up-regulation/amplification; and (ii) ALK gene mutations.

Amplification of the ALK locus and over-expression of ALK TK has been reported in many cancer cell lines and in human tumor samples (115), but little is known about the actual biological role of such events. ALK over-expression has been documented in tumors that occasionally bear ALK-chromosomal translocations (i.e. NSCLCs, RMS, ovarian and breast carcinoma). ALK up-regulation/amplification has also been reported in neoplasms usually not associated with ALK fusions, such as melanoma, retinoblastoma, Ewing's sarcoma and a variety of neural tumors (glioblastoma, astrocytomas and neuroblastoma) (13).

Primary glioblastoma (GB) and GB cell lines have been shown to express high levels of ALK and PNT (ALK-putative ligand). GB also features deregulated ALK signaling, which induces enhanced development and survival of neoplastic cells (116, 117). The pathogenetic role of ALK TK in GB has been further confirmed by *in vivo* models, which report the anti-proliferative effects of ALK-inhibitors in GB xenografts (117).

Amplification of ALK locus on chromosome 2 has been also reported in neuroblastoma. Of note, the amplified region encompasses both MYCN and ALK genes, with possible synergic effects in driving cell growth and survival (118). A biological link between these oncogenes is further sustained by the observation that both wild-type and activated mutant forms of ALK induce transcription and stabilization of the MYCN protein (119,120) and in a zebrafish model co-expression of activated ALK with MYCN triples the disease penetrance and markedly accelerates tumor onset (121). Of note, ALK amplification is not the only TK activating mechanism in neuroblastoma. Several lines of evidence indeed suggest that ALK activating point mutations can contribute to the acquisition of a neoplastic phenotype (118). The oncogenic potential of ALK mutations primarily resides in the perturbation of physiological processes, normally mediated by the ALK signaling pathways. Oncogenic ALK mutations have been studied by biochemical, cell culture and *in vivo* (D. melanogaster) genetic models. These analyses have led to classify ALK mutations into three major groups: (i) ligand-independent activating mutations; (ii) ligand-dependent activating mutations; and (iii) kinase inactivating (i.e. "kinase dead") mutations (122).
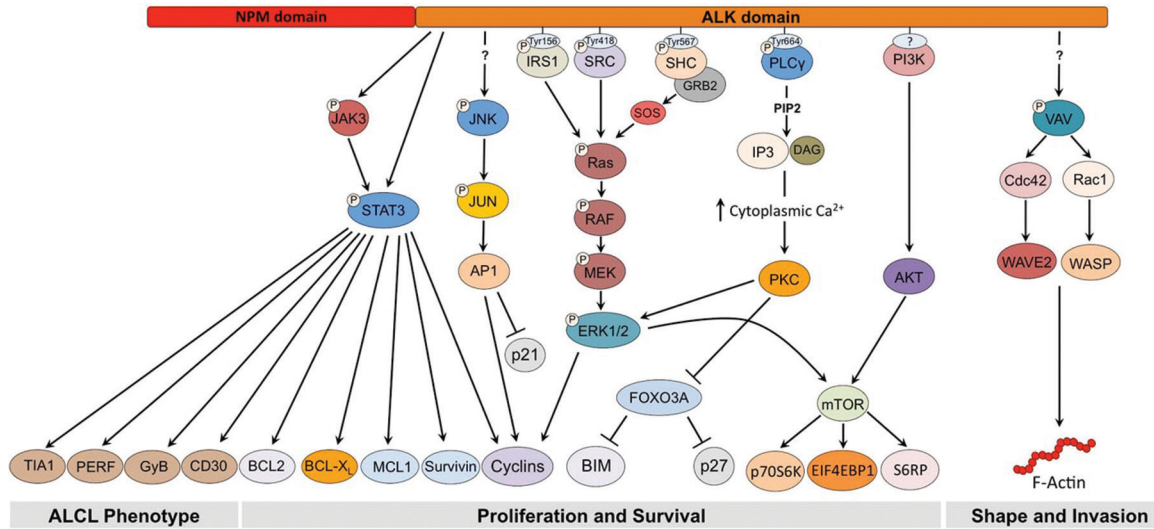
Figure 2. ALK signaling. The deregulated activation of ALK-R and ALK fusion proteins (NPM-ALK is depicted as representative ALK chimera) can elicit multiple signaling pathways, which eventually drive and maintain the neoplastic phenotype. Schematic representation of the most relative ALK driven signaling pathways.

Ligand-independent mutations (e.g. F1174I, F1174S and F1174L) generate constitutively activated TKs that induce uncontrolled cell proliferation and survival (123,124). Ligand-dependent mutations (e.g. D1091N, T1151M and A1234T) may exert pathogenic roles as passenger or driver mutations (125). Kinase-inactivating mutations (e.g. I1250T) are very rare and may contribute to the neoplastic phenotype by interfering with the remaining wild-type ALK copy (13). Point mutations and small deletions of ALK gene have been reported in neuroblastoma, lung and thyroid carcinomas as well as in crizotinib-resistant ALK+ neoplasms (126-128). Neurobalstoma constitutes a paradigmatic example to understand the biology and clinical impact of ALK point mutations. Mutations in the ALK gene are documented in 4-8% of neuroblastomas and are associated with overall poor-prognosis (123,129). Activating ALK mutations are observed both in familial and sporadic cases, with two hotspot mutations occurring in the kinase domain: (i) F1174 (mutated to L, S, I, C or V); and (ii) R1275 (mutated to Q or L). Most of neuroblastoma-associated ALK mutations have proven oncogenic also in animal and cell-culture models (123,124).

Comparison of neuroblastoma and secondary crizotinib-resistant NSCLCs /IMTs highlights significant differences in ALK derangements, as crizotinib-resistant mutations generally cluster around the inhibitor and ATP-binding sites, while neuroblastoma-associated mutations occur close to the kinase activating residues. The biological meaning of such differences is still to be clarified and further studies are needed to better illustrate the pathogenetic mechanisms underlying such differences.

6. ALK SIGNALING PATHWAYS

Chromosomal translocations, gene amplification/over-expression and DNA point mutations all concur to generate a wide spectrum of ALK variants, which can ultimately lead to the acquisition of a neoplastic phenotype. Despite the huge variety of activating mechanisms, all mutant ALK proteins exert their pathogenetic role through similar (and often overlapping) transduction pathways. For historical reasons, NPM-ALK-positive ALCL is the reference model for the study of the molecular pathways involved in ALK carcinogenesis. In the next paragraphs, the description of ALK-mediated oncogenesis will thus implicitly refer to this specific biological model (Figure 2).

6.1. Ras/ERK and JNK pathways

Constitutively phosphorylated ALK tyrosine residues act as docking sites for several downstream adaptors with SH2 (SRC homology 2) or PTB (phosphotyrosine-binding) domains. These include SHC (SH2 domain-containing transforming protein), IRS1 (insulin receptor substrate 1) and GRB2 (growth factor receptor-bound protein 2) proteins. Although, SHC, IRS1 and GRB2 bind directly to NPM-ALK, SHC and IRS1 are not essential for the acquisition of a neoplastic phenotype, since the loss of their docking sites does not preclude ALK-mediated neoplastic transformation (130). On the contrary, GRB2 seems to play a pivotal role in the ALK-mediated activation of the Ras/ERK pathway (12). GRB2 binds to NPM-ALK on Tyr567, Tyr152-156, and on the proline-rich region, Pro415-417, thus regulating ALK-mediated phosphorylation of SHP2. This activates Ras and the downstream MAPK pathway, leading to the phosphorylation of ERK-1 (MAPK3) and ERK-2

(MAPK1) (131). ERK-1 and ERK-2, in turn, phosphorylate multiple transcription factors of the AP-1 complex, thus inducing the down-regulation of p21 and the up-regulation of Cyclin D3 and Cyclin A. These events ultimately lead to the uncontrolled progression of cell-cycle and cell growth.

The AP-1 complex can be also activated by a parallel pathway, involving JNK and c-Jun, whose phosphorylation is mediated by the chimeric NPM-ALK protein (132). The AP-1 complex also determines the expression of CD30 and cytotoxic molecules, thus inducing the acquisition of the classical ALCL phenotype (133-135). These phenotypes are potentiated by STAT3 which co-synergies enhancing the transcription of these genes (Dittinger E personal communication).

6.2. PCL-γ pathway

PLC-γ directly binds to NPM-ALK on Tyr(664). The resulting activation of PLC-γ induces the hydrolysis of phosphatidylinositol to inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 and DAG, in turn, modulate the release of Ca^{2+} from the endoplasmic reticulum, with the consequent activation of protein kinase C (PKC). PKC contributes to the survival and proliferation of ALCL cells by phosphorylating and activating several downstream transcription factors (136). The pathogenetic role Tyr664 on NPM-ALK has been documented by *in vitro* studies, demonstrating a survival advantage for pro-B lymphocytes expressing wild-type (but not Y664F mutant) NPM-ALK proteins (137). However, the murine ALK lacks the docking site for the activation of the PLC-γ pathway casting some double of the tumorigenic role of this signaling.

6.3. PI3K pathway

ALK fusion proteins control cell survival through the PI3K-AKT and STAT3 pathways. NPM-ALK interacts with the catalytic subunit of PI3K (p110), inducing its phosphorylation/activation. PI3K, in turn, phosphorylates the serine/threonin kinase PKB/AKT, which provides anti-apoptotic signals via several molecular pathways (136). PKB/AKT phosphorylates FOXO3A on Tyr24, Ser256 and Ser319, thus blocking the transcription of cell-cycle arresting (p27) and pro-apoptotic (BIM1) genes (138). FOXO3A inhibition also results in the up-regulation of cyclin D2, which promotes the transition trough the G1–S phase of the cell cycle. This survival pathway is synergistically driven also by mTOR, whose activation is directly mediated by both PKB/AKT1 and ERK kinases (12).

6.4. JAK3/STAT3 pathway

The JAK3/STAT3 signaling plays a central role in NPM–ALK mediated carcinogenesis. STAT3 belongs to a family of transcription factors, whose activation is mediated by the phosphorylation of specific protein domains. Phosphorylated STAT monomers dimerize and migrate into the nucleus, where they regulate the expression of several target-genes.

In ALK+ ALCL, NPM-ALK can directly phosphorylate STAT3 or can first activate JAK3, which subsequently phosphorylates STAT3 (139-141). Upon phosphorylation, STAT3 activates several down-stream effectors, which contribute to ALCL cell phenotype (e.g. expression of CD30), survival and proliferation. In particular, STAT3 prompts the expression of several anti-apoptotic proteins, such as BCL2, BCL-X$_L$, survivin and MCL1 (139, 142). It can also promote cell-cycle progression through the activation of Cyclin-D3, c-myc and of C/EBPβ (143). Preliminary data also indicate that STAT3 may contribute to T-cell identity, by interacting with master regulators of the T-cell commitment (Pizzi M personal communication). Recent evidence finally indicates that STAT3 controls angiogenesis and anti-tumor immune functions (144, 145). Gene expression profile and more recently RNAseq data have shown that the transcriptome of ALK+ ALCL is largely depending on STAT3, as shown using either specific shRNA or selective STAT3 inhibitors (146). This has allowed the generation of classifiers, which can be used in the differential diagnosis of peripheral T-cell lymphoma (147). Remarkably, the transcriptome of ALK positive cells varies considerably when tumors derived from different lineages are evaluated (148) (Medico E. personal communication). Intriguingly, knock-down (kd) of STAT3 in ALK+ NSCLC cell lines induces only little phenotypic alterations. This suggests that even in the presence of a constitutive activated JAK/STAT3 signaling pathway the regulation of downstream genes is cell dependent (149), and mediated by the concomitant activation of antagonist/ synergist signals, unique miRNA repertoire and epigenetic landscapes. The JAK/STAT3 pathway is negatively regulated by SHP1, a tyrosine phosphatase which de-phosphorylates ALK and the ALK-associated kinases SRC and JAK. In ALCL, SHP1 expression is frequently reduced due to hyper-methylation of SHP1 promoter. SHP1 down-regulation, in turn, enhances STAT3-mediated proliferation and anti-apoptotic signals. The anti-oncogenic role of SHP1 is further demonstrated by *in vitro* experiments, indicating that restoration of SHP1 expression in ALK+ ALCL leads to NPM-ALK de-phosphorylation and partial proteasome degradation, with consequent inactivation of the JAK3/STAT3 pathway and impairment of cell growth (150). The PTPR family members provide an additional layer of regulation, controlling the phosphorylation status of STAT proteins. Several data indicate that the "oncogenic addiction" of ALK+ ALCL cells to NPM-ALK depends on the JAK3/STAT3 signaling pathway. STAT3 kd by RNAi invariably leads to ALK+ ALCL cell cycle arrest and apoptosis. This phenomenon is associated with well-defined changes in the transcription of a large number of genes, many of which are physiologically down-regulated by active (i.e. phosphorylated) STAT3. Similar results are obtained by treating ALK+ALCL cells with ALK-inhibitors or anti-ALK RNAi (151).

6.5. VAV1/Cdc42 Pathway

In ALK+ ALCL, NPM-ALK TK controls several proteins involved in the regulation of the cytoskeleton and cell migration. Of note, ALK-dependent transduction pathways closely resemble those mediated by TCR-activation and invariably require the guanine-nucleotide exchange factor, VAV1. ALK phosphorylation of VAV1 promotes the activation and re-localization of the Rho-family GTPases, Cdc42 and Rac1. These, in turn, activate PAK, WASP and WAVE2, eventually leading to F-actin polymerization and cell migration (152) (153). These molecular pathways could (at least partially) explain the peculiar morphology of ALCL cells and the distinct infiltrative pattern disclosed by ALCL at histological examination. *In vitro* and *in vivo* studies indicate that Cdc42 can act as a regulator of cell proliferation and survival. In fact, Cdc42 knock-down significantly increases the apoptotic rate of ALK-positive ALCL cell lines. Even greater growth arrest is observed when neoplastic cells are treated with a combination of ALK and Cdc42 inhibitors (153). These encouraging data may open new perspectives for the treatment of ALCL.

7. ALK ONCOGENIC SIGNALING ADDICTION AND RESISTANCE PHENOTYPES

Although ALK fusions provide strong oncogenic signals, there are many indications that suggest that they are incapable of imposing a fully transformed phenotype. However, oncogenic addiction to ALK signals varies among different type of neoplasms. It is believed that ALK+ ALCLs are quite dependent on the ALK signaling. Indeed, most ALK+ ALCL lines are sensitive to ALK inhibitors, despite being derived from end stage diseases and/or systemic leukemic processes. Nevertheless, they display a broad range of chemosensitivity with L82 and JB6 lines being very sensitive, while Karpas 299 cells display a relatively resistant phenotype. These observations are supported by the responses observed in patient derived tumor graft (PDT) models. We have shown that ALCL PDT, derived from CHOP refractory ALK+ ALCL, can display unique responses *in vivo* to anti-ALK Ki ranging from highly sensitive (154) to only partially responsive (68). Genomic and functional analyses have indicated that the responses to anti-ALK Ki were related to the genomic complexity of the corresponding ALCL PDT; the loss of TP53, BLIMP-1 and deregulation of c-myc were associated with more resistant phenotypes (68). These observations are reflected by the clinical outcomes of ALCL patients treated with conventional chemotherapy (155). Further, the activation of alternative pathways has also been proven to contribute to the neoplastic phenotype. In both human and mouse models, engagement of IGFR (156) and PDGFR (157), have been proven to provide pro-tumorigenic signals via direct and/or host related loops. Additionally, clinical trials testing the therapeutic efficacy of crizotinib in ALK+ ALCL patients have shown different degree of responses (8, 15), suggesting that ALK signaling is critical in primary ALK+ ALCL but additional events can module its addiction (158). The findings obtained in ALK+ ALCL clinical trials parallel those seen in ALK+ NSCLC patients. Notably, the majority of ALK+ lung cancer patients enjoy remarkable responses that frequently can be sustained for relatively long periods of time. Poor responders and relapses have, however, been documented. It is plausible that the carcinoma cells of TKi naïve refractory patients may have undergone a series of changes, allowing them to bypass ALK signaling requirements (158). This scenario is reflected by the different degree of sensitivity to ALK inhibitors of the EML4-ALK cell lines H3122 and H2228. The H2228 lines can undergo cell death when ALK Ki are accompanied by MEK (159) or EGFR or ERBB2/3 (148) inhibitors, contrary to H3122, which are exquisitely sensitive to ALK Ki. Interestingly, rare patients bearing EGFR mutations and EML4-ALK have been documented suggesting that both aberrations may be observed even in absence of drug selection and can contribute to the original neoplastic phenotype (160).

With the broader usage of ALK inhibitors, we have witnessed the emergence of multiple resistant phenotypes, driven by alternative mechanisms. More than one third of ALK + lung patients develop mutations within the gatekeeper site of the kinase domain or in amino acids critical for modulating the ATP kinase affinity (161). Drug resistance in the remaining patients can display gene amplification of ALK fusions or other kinases (i.e. Met), activating somatic mutations (EGFR, K-Ras), or bypass ALK signaling (158). In the latter scenario, the deregulated activation of activation of KIT, c-MET, EGFR, IGFR, AXL, ERBB can overcome ALK signaling requirements and ALK ki inhibition. Thus, it may be possible to decrease the incidence of acquired resistance by using a combination of Ki or novel multi-targ*et al*K inhibitors. In years to come, it is likely that the application of innovative tissue culture modalities will help define the molecular mechanisms of resistance and eventually guide "ad hoc" therapies for ALK resistant patients (162).

8. ACKNOWLEDGMENTS

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Abbreviations: ALCL: Anaplastic Large-Cell Lymphoma; BC: Breast Carcinoma; CRC: Colon-Rectal Carcinoma; DLBCL: Diffuse Large B-Cell Lymphoma; ESCC: Esophageal Squamous Cell

Carcinoma; IMT: Inflammatory Myofibroblastic Tumor; NSCLC: non-Small Cell Lung Cancer; OC. Ovarian Carcinoma; RCC= Renal Cell Carcinoma.

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