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THERAPEUTIC TARGETS FOR ACUTE MYELOID LEUKEMIA (AML)

L.A. Sorbera, C. Vergés, C. Dulsat

Prous Science, Provenza 388, 08025 Barcelona, Spain

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ABSTRACT

Acute myeloid leukemia (AML) is a cancer of the myeloid line of white blood cells and is characterized by the hyperproliferation of abnormal cells, which collect in the bone marrow and disrupt normal blood cell production. Replacement of normal bone marrow with leukemic cells causes a decrease in the levels of red blood cells, platelets and normal white blood cells. Symptoms include fatigue, shortness of breath, a heightened risk of bruising and bleeding, and an elevated risk of infection. Risk factors for AML have been identified, but the specific cause is still unknown. Treatment generally involves chemotherapy and, in some cases, hematopoietic stem cell transplantation. Treatment strategies for AML are currently focusing on the discovery of new drug targets and prognostic indicators, as well as the detection of residual disease subsequent to treatment. This article provides insight into the search for new and improved treatment options by detailing the putative targets for drugs currently under active investigation for AML.

INTRODUCTION

Leukemia is a malignant disease of the bone marrow and blood that is characterized by the uncontrolled accumulation of white blood cells. Leukemia is classified as either myelogenous or lymphocytic, according to the type of cell involved (myeloid precursor cells or B lymphocytes, respectively). Leukemia is further classified as either chronic or acute, based on the clinical presentation and course. Acute leukemia is a rapidly progressing form of the disease that results in the accumulation of immature, functionless cells (blasts) in the blood, bone marrow and tissues. Often the marrow can no longer produce enough normal red blood cells, white blood cells and platelets, leading to anemia, a reduced ability to fight infections and easy bruising and bleeding. Chronic leukemia progresses more slowly and allows a greater number of functional, more mature cells to be produced. Ultimately, the type of blood cell that is cancerous dictates whether the leukemia is myeloid or lymphoid and whether it is acute or chronic. Acute myelogenous (or myeloid) leukemia (AML) is the most common malignant myeloid disorder in adults, and is associated with the lowest survival rate. The median age at presentation is 70 years and the disease affects more men than women (1), although pediatric AML is not uncommon (2).

The hallmarks of AML are an abnormal proliferation of myeloid progenitor cells ("blasts") in bone marrow and a reduced rate of self-destruction and arrest of cellular differentiation. When the blast cells lose their ability to differentiate in a normal fashion and to respond to normal regulators of cell proliferation, the result is frequent infections, bleeding and organ infiltration (1). The leukemic cells are endowed with an aberrant survival advantage with respect to normal healthy cells, such that the bone marrow and peripheral blood become increasingly populated by immature blast cells that edge out normal blood cells (3, 4). Bone marrow failure is the most common cause of death in patients with AML (1). AML results from genetic alterations in molecular transcription factors that lead to arrest of cellular maturation. In addition, mutations in oncogenes, in particular the FLT3 receptor tyrosine kinase, drive cellular proliferation. In fact, FLT3 inhibitors have been the subject of intense clinical study in AML. Acute promyelocytic leukemia (APL) is an important, although comparatively rare, subtype of AML that is uniquely responsive to treatment with retinoids, and as such has a much more promising prognosis (5).

The search for effective treatment strategies for AML continues, with special attention focused on the identification of novel targets for drug development. Those targets which are currently under active investigation are discussed below (see Figure 1). Table I shows a selection of products under active development for each target.

TARGETS

Aminopeptidase N (CD13)

Aminopeptidase N, or CD13, is an *N*-terminal exopeptidase (EC 3.4.11.2) with preference for neutral amino acids. It is present on the apical surfaces of human lung, renal and intestinal epithelium and fibroblasts, as well as monocytes, granulocytes and their bone marrow progenitors. It is involved in the digestion of peptides that result from the gastric and pancreatic protease-mediated hydrolysis of proteins and induces the liberation of *N*-terminal amino acids, espe-

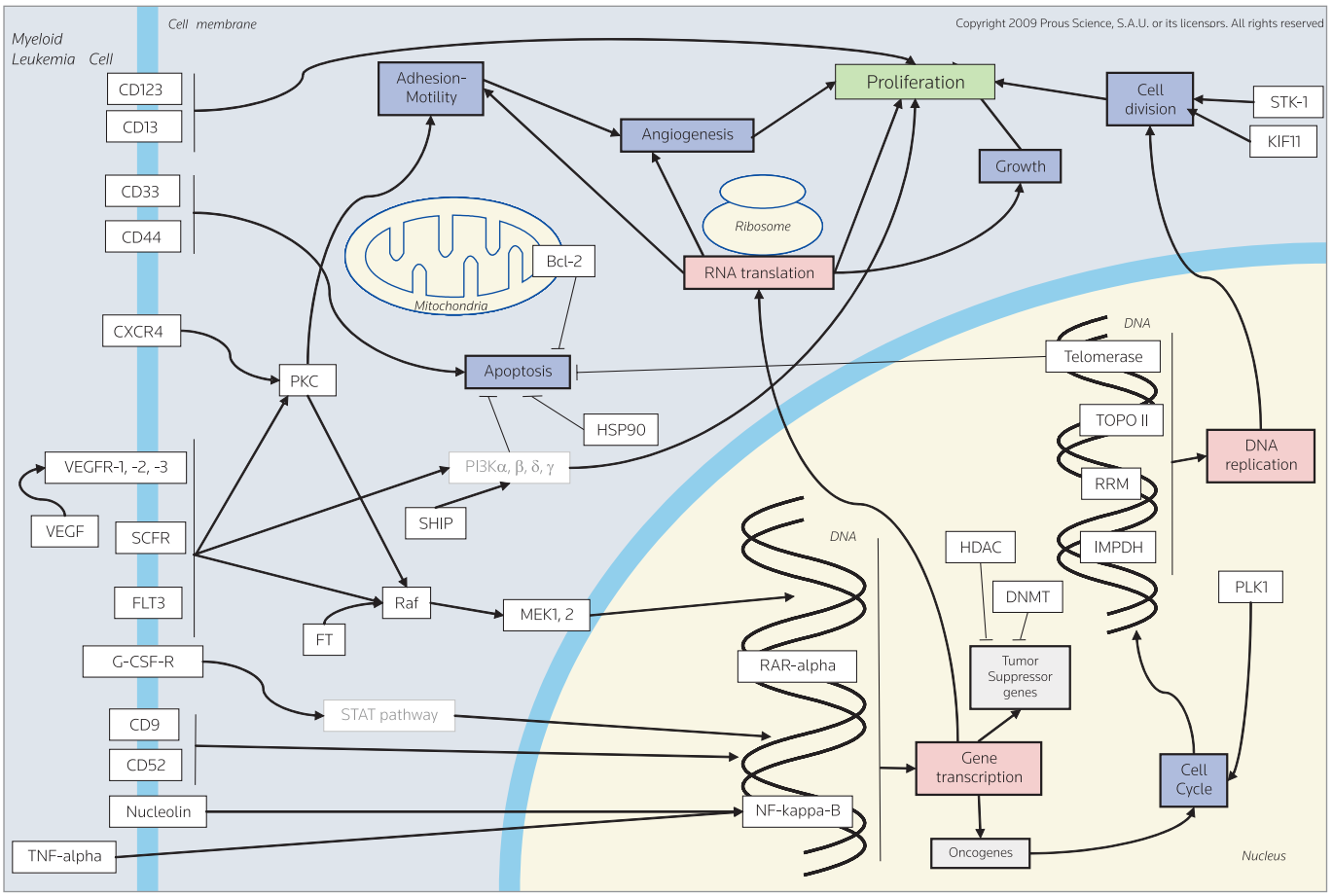

Figure 1. Acute myeloid leukemia (AML) targetscape. A diagram showing an overall cellular and molecular landscape or comprehensive network of connections among the current therapeutic targets for the treatment of AML and their biological actions. Arrow: positive effect; dash: negative effect. Abbreviations: FT, protein farnesyltransferase; RRM, ribonucleotide-diphosphate reductase; TOPO II, DNA topoisomerase II; for other abbreviations, see text.

cially those linked to alanine. It also participates in the breakdown and inactivation of neurotransmitters in the brain. It comprises a large extracellular carboxy-terminal domain that harbors a pentapeptide consensus sequence distinctive to members of the zinc-binding matrix metalloproteinase family. CD13 is believed to have a role in the metabolism of regulatory peptides by diverse cell types such as small intestinal and renal tubular epithelial cells, macrophages, granulocytes and synaptic membranes from the central nervous system (CNS). Human CD13 is involved in human coronavirus infection and defects in the gene encoding the enzyme (*ANPEP*) have been implicated in the onset of various forms of cancer. Blast cells derived from patients presenting with AML have been found to be positive for CD13, among other biomarkers. CD13 inhibitors may be potentially useful for treating certain leukemias and lymphomas, notably AML (6).

Aurora-B kinase (STK-1)

Aurora-B kinase is a member of the Aurora kinase family of mitotic serine/threonine kinases comprising three members: Aurora-A, -B and -C. All three members of the family share a common sequence and structure consisting of a highly conserved *C*-terminal catalytic domain (believed to aid proteosome degradation of the kinase at the end of mitosis) and a variable short *N*-terminal domain (that may facilitate interactions with other proteins and aid relocation of the kinase from the cytoplasm to the nucleus during mitosis). Aurora-B kinase participates in the formation and correct attachment of spindle microtubules to chromosomes, as well as in cytokinesis, regulation of chromatid separation and formation of the cleavage furrow in anaphase and telophase. Upon exit from mitosis, Aurora-B kinase is selectively degraded. The gene encoding Aurora-B kinase (*AURKB*) has been found to be amplified in breast and colorectal cancers. Overexpression of Aurora-B has been detected in several cancers and has been shown to induce tumor metastasis in murine models. Aurora-B kinase inhibitors are therefore a possible therapeutic option for cancer, including solid tumors and hematological cancers, namely AML and chronic myeloid leukemia (CML) (7-9).

Bcl-2

Bcl-2 (B-cell lymphoma 2), a member of the Bcl-2 family of proteins, inhibits the mitochondrial apoptotic pathway by preventing cytochrome *c* release and caspase-9 activation. It was first identified in human follicular B-cell lymphoma cells resistant to apoptosis and

Table I. *Select targets and products launched or being actively investigated for acute myeloid leukemia (AML) (from Prous Science Integrity®).*

Target	Product	Source	Phase
Aminopeptidase N	Tosedostat	Chroma Therapeutics	II
Aurora-B kinase	AZD-1152	AstraZeneca	I/II
Bcl-2	Oblimersen sodium	National Cancer Institute	III
CD33	Gemtuzumab ozogamicin	UCB/Wyeth Pharmaceuticals	L-2000
	Lintuzumab	Seattle Genetics	II
	AVE-9633	sanofi-aventis	I
	HuM195/rGel	M.D. Anderson Cancer Center/Targa Therapeutics	I
CD44	MAT-102	MAT Biopharma	Preclinical
	A3D8	NEXTherapeutics	Preclinical
CD52	Alemtuzumab	Baylor College of Medicine/National Cancer Institute/ University of Texas	I
CD9	AR40A746.2.3	Arius Research	Preclinical
CXCR4	Plerixafor HCl	Washington University	I/II
DNA (cytosine-5)-methyltransferase (DNMT)	Decitabine	Cilag/MGI Pharma	III
	Azacitidine	Celgene/Pharmion	I/II
DNA topoisomerase II	Amonafide	Xanthus	III
	Voreloxin	Sunesis	II
	L-Annamycin	Callisto Pharmaceuticals	I/II
	Becatecarin	National Cancer Institute	I
FLT3 (STK-1)	Midostaurin	Novartis	III
	Lestaurtinib	Cephalon	II/III
	Sorafenib	Bayer	II
	Sunitinib malate	Pfizer	I/II
	AC-220	Ambit Biosciences	I
	KW-2449	Kyowa Hakko Kirin	I
G-CSF-R (CD114)	Filgrastim	Amgen	L-1998
Heat shock protein 90 (HSP90)	Tanespimycin	National Cancer Institute	I
Histone deacetylases (HDACs)	Belinostat	National Cancer Institute/TopoTarget	II
	Entinostat	National Cancer Institute	II
	Mocetinostat dihydrobromide	MethylGene/Pharmion	II
IL-3R-alpha (CD123)	CSL-360	CSL	I
IMP dehydrogenase (IMPDH)	Ribavirin	Jewish General Hospital	II
Kinesin-like protein KIF11	Ispinesib mesylate	National Cancer Institute	I
MAPKK 1 (MEK1) and MAPKK 2 (MEK2)	ARRY-142886	University of Chicago	II
Mast/stem cell growth factor receptor (SCRF)	Imatinib	National Cancer Institute	II
	Sorafenib	Bayer	II
	Sunitinib malate	Pfizer	I/II
	AC-220	Ambit Biosciences	I
Nuclear factor NF-kappa-B	Bortezomib	Janssen-Cilag	II
Nucleolin	AS-1411	Antisoma	II
Polo-like kinase 1 (PLK1)	BI-2536	Boehringer Ingelheim	II
Protein farnesyltransferase	Tipifarnib	National Cancer Institute	III
Protein kinase C (PKC)	Bryostatin 1	National Cancer Institute	II
	3-Angeloylingenol	Peplin	Preclinical

Continuation

Table I (Cont.). *Select targets and products launched or being actively investigated for acute myeloid leukemia (AML) (from Prous Science Integrity®).*

Target	Product	Source	Phase
Raf kinase	Sorafenib	Bayer	II
Retinoic acid receptor alpha (RAR-alpha)	Tamibarotene	Nippon Shinyaku	L-2005
Ribonucleoside-diphosphate reductase	Gemcitabine Clofarabine	National Cancer Institute Genzyme	II Prereg.
SH2 domain-containing inositol phosphatase (SHIP)	MN-100	Aquinox	Preclinical
Telomerase reverse transcriptase	GRNVAC1	Geron	II
Tumor necrosis factor α (TNF-α)	Thalidomide Lenalidomide	National Cancer Institute National Cancer Institute	II II
Vascular endothelial growth factor (VEGF)	Aflibercept	National Cancer Institute	II
VEGFR-1 (Flt-1)	Sunitinib malate Cediranib Dovitinib	Pfizer National Cancer Institute Novartis	I/II I I
VEGFR-2 (Flk-1)	Sorafenib Sunitinib malate Cediranib Dovitinib	Bayer Pfizer National Cancer Institute Novartis	II I/II I I
VEGFR-3 (FLT4)	Sorafenib Sunitinib malate Cediranib	Bayer Pfizer National Cancer Institute	II I/II I

has been shown to protect a variety of cell types from programmed cell death. During embryonic development, Bcl-2 protein is widely distributed throughout the CNS and peripheral nervous system (PNS). Postnatally, Bcl-2 protein is found predominantly in the granule cells of the cerebellum, dentate gyrus of the hippocampus and throughout the PNS. Many cancer types overexpress Bcl-2, and therefore drugs inhibiting Bcl-2 activity or *BCL2* gene expression are deemed to be useful options for the treatment of cancer, including AML (10, 11).

CD33

CD33 is a 67-kDa cell-surface glycoprotein that belongs to the siglec family and participates in sialic acid-dependent cellular interactions and adhesion of myeloid cells. CD33 contains two immune-based inhibitory motifs in its cytoplasmic tail, and its engagement triggers apoptosis and suppresses the proliferation of leukemia cells isolated from AML and CML patients. CD33 is expressed during myeloid differentiation and is present on leukemic blasts in 90% of patients with AML, but not on normal hematopoietic cells or stem cells. CD33 antagonism is therefore a potential therapeutic option for AML. Likewise, expression of CD33 has been documented in some cases of childhood acute lymphoblastic leukemia (ALL) (12, 13).

CD44

CD44 is an 85-kDa multistructural and multifunctional cell-surface adhesion molecule involved in cell–cell and cell–matrix interactions, including adhesion, homing, migration and transmission of survival signals. The gene is ubiquitously expressed and has many different variants that are translated into many functionally different isoforms. It is a receptor for hyaluronic acid (HA) and can also interact with other ligands such as osteopontin, collagens and matrix metalloproteinases (MMPs). It forms a complex with hyaluronan that activates the ankyrin-based cytoskeleton Ca^{2+} mobilization, Rho signaling, phosphatidylinositol 3-kinase (PI3K)-AKT (protein kinase B) activation, NHE-1-mediated cellular acidification, transcriptional upregulation and cytoskeletal function. The HA/CD44 complex is able to trigger signaling cascades that modulate inflammation and tumor progression. CD44 is also involved in lymphocyte homing, T-lymphocyte activation and inducing the adherence of fibroblasts, lymphocytes and extracellular material (ECM). It also participates in signal transmission, drug absorption and sensitivity, pseudopod formation and cell migration. High levels of CD44 have been found on the surface of cancer cells (including hematological cancers) and it is also present in the joint synovium of patients with rheumatoid arthritis. Thus, CD44 antagonism is a possible therapeutic option for cancer, including AML (14, 15).

CD52

CD52 is a 21-kDa cell-surface glycoprotein that is expressed by B and T lymphocytes, natural killer (NK) cells, monocytes, macrophages, dendritic cells, red blood cells, platelets and hematopoietic progenitor cells. Engagement of CD52 induces lysis via activation of complement- and direct cell-mediated cytotoxicity. However, the biological function of CD52 remains unknown. The majority of low-grade B-cell lymphoproliferative disorders, including

chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia, follicular lymphoma, lymphoplasmacytic lymphoma, hairy cell leukemia and mucosal-associated lymphoid tissue lymphomas, express CD52. CD52 is also expressed in 79% and 77% of B- and T-cell lineage ALL, respectively, and in AML. Antagonism of CD52 is a possible therapeutic option for multiple sclerosis and cancer, notably AML (16).

CD9

CD9 is a cell-surface protein and member of the transmembrane-4 superfamily (tetraspanin family). It interacts with the integrin family and other membrane proteins and may participate in cell migration and adhesion. It has been shown to enhance membrane fusion between muscle cells and is involved in myotube maintenance. CD9 is also a receptor for Psg17 (pregnancy specific glycoprotein 17) and plays a role in sperm–egg fusion. It is expressed in human B-cell precursors, monocytes and platelets, and mediates platelet activation and aggregation upon binding with monoclonal antibodies. CD9 expression has been detected on the surface of AML cells and its release promotes cell growth. In addition, CD9 has been found to be aberrantly expressed in cancer cells, in which it modulates epidermal growth factor receptor (EGFR) signaling-related growth. Antagonism of CD9 may thus be a useful therapeutic strategy for cancer, including AML (17).

CXCR4

CXCR4, also known as fusin, is an α-chemokine, 7-transmembrane G-protein-coupled receptor that specifically binds to stromal cell-secreted CXCL12 (also called stromal cell-derived factor 1, SDF-1) and transduces signaling by increasing intracellular calcium ion levels. CXCR4 displays potent lymphocytic and chemotactic activity and plays a role in hematopoiesis, neuronal and cardiovascular development, the spread and progression of tumors, and the organization of the immune system. CXCR4 is found on the surface of both hematopoietic and nonhematopoietic tumor cells. It is implicated in cancer cell migration and metastasis, since it promotes tumor spread to organs where CXCL12 is expressed, such as bone marrow, while CXCL12 itself can stimulate the survival and growth of neoplastic cells in a paracrine fashion and can promote tumor angiogenesis by attracting endothelial cells to the tumor microenvironment. Furthermore, the CXCL12–CXCR4 system is involved in the migration of progenitors during embryonic development of the cardiovascular, hematopoietic and central nervous systems, among others, and has been found to be involved in several conditions, including cancer cell metastasis, leukemia cell progression, rheumatoid arthritis and pulmonary fibrosis. CXCR4 antagonism is thus a putative therapeutic option for cancers such as AML (18).

DNA (cytosine-5)-methyltransferase (DNMT)

DNMT is an enzyme (EC 2.1.1.37) responsible for DNA methylation and its maintenance. The methylation pattern, usually established during development and retained throughout life, determines differential gene expression in a tissue- and developmental stage-specific manner. Deviations from the expected methylation pattern and associated changes in gene expression could lead to tumorigenesis, establishing DNMT inhibition as a valid approach to restore DNA methylation patterns. Five human DNMTs have been identified to date, including DNMT1, 2, 3a, 3b and 3l, of which DNMT2 and DNMT3l lack enzymatic function. DNMT1 regulates tissue-specific patterns and is involved in the silencing of tumor suppressor genes in cancers. DNMT3a has DNA methyltransferase activity in de novo methylation and is essential for development. DNMT3b is associated with several cancers via the induction of aberrant methylation patterns. DNMT inhibitors include nucleoside analogues that suppress DNA methylation upon incorporation into DNA and non-nucleoside analogues that bind directly to the catalytic region of the enzyme. DNMT inhibition thus offers a promising approach for the treatment of cancer, including AML (19, 20).

DNA topoisomerase II

DNA topoisomerase II is an enzyme that plays a critical role in maintaining the proper topology and physical integrity of DNA. It makes transient double-stranded breaks and allows the passage of a second DNA duplex across the break. DNA topoisomerase II is usually ATP-dependent and the α isoform has been found to have preference for positive DNA supercoils. Since it participates in the processes of DNA transcription, chromosome disentanglement, recombination and repair, targeting DNA topoisomerase II has become a valid approach for the design of anticancer therapeutics. Additionally, mounting interest has been shown in the chemical reaction performed by topoisomerase, which is able to trigger the movement of DNA segments several orders of magnitude larger than the size of the protein. Further investigation of this class of enzymes would provide insight into the nature of triggering large-scale mechanical motions induced by biomolecular motors. DNA topoisomerase II antagonism may be a useful therapeutic approach for cancer, including AML (21).

FLT3 (STK-1)

FLT3 (STK-1) is member of the receptor tyrosine kinase family that is primarily expressed on hematopoietic stem/progenitor cells. It is mutated in approximately one-quarter to one-third of patients with AML. Mutations are mostly internal tandem duplications in the juxtamembrane domain of FLT3 and also point mutations within the tyrosine kinase domain. As with other receptor tyrosine kinases, FLT3 propagates the growth factor signal from the cell surface to intracellular processes that control critical functions such as growth, differentiation, angiogenesis and inhibition of apoptosis via sequential signaling. Oncogenic mutations in FLT3 generally lead to ligand-independent constitutive and deregulated activation of proliferation and cell growth pathways. Therefore, FLT3 inhibitors may be useful to treat hematological cancers, including AML (22-25).

G-CSF-R (CD114)

G-CSF-R (CD114), or granulocyte colony-stimulating factor receptor, is a member of the cytokine receptor superfamily that forms homo-oligomeric complexes upon binding to its ligand G-CSF. It lacks intrinsic tyrosine kinase activity but can activate cytoplasmic tyrosine kinases, including Janus kinases (JAK1, JAK2, JAK3 and TYK2), signal transducer and activator of transcription proteins (STAT1, STAT3 and STAT5) and also PI3K and mitogen-activated protein (MAP) kinase. The membrane proximal cytoplasmic region transduces proliferative

and survival signals through STAT5, whereas the distal carboxy-terminal region transduces maturation signals and suppresses the receptor's proliferative signals through STAT3. In patients with both severe congenital neutropenia (SCN) and AML, G-CSF-R acquired mutations lead to a truncated distal cytoplasmic region that mediates enhanced and prolonged activation of STAT5, thereby resulting in decreased maturation and growth arrest signaling. G-CSF-R agonism may therefore be a feasible therapeutic option for neutropenia and cancer, including both SCN and AML (26).

Heat shock protein 90 (HSP90)

HSP90 is a member of the heat shock protein (HSP) family which is composed of conserved stress proteins ubiquitously present in prokaryotic and eukaryotic cells and bacteria that serve to increase thermal tolerance. Some forms stabilize proteins in abnormal configurations by playing a role in protein folding and unfolding and in the assembly of oligomeric complexes, while others act as molecular chaperones. HSPs are characterized into the following major subclasses: HSP90, HSP70, HSP60 and small HSP. There are three types of HSP90: HSP90-alpha 1, HSP90-alpha 2 and HSP90-beta. HSP90 is highly expressed in most tumor cells, in which it plays a protective role toward damaged or mutated proteins, including v-Src, the fusion oncogene BCR/ABL and p53. Moreover, HSP90 stabilizes PI3K and AKT proteins, thus inducing the PI3K pathway and inhibiting apoptosis. It also promotes angiogenesis via the induction of vascular endothelial growth factor (VEGF) and nitric oxide synthase (NOS). Furthermore, HSP90 shows affinity for aberrant neuronal proteins, supporting the accumulation of toxic aggregates and maintaining and facilitating the transformed phenotype in neurodegenerative diseases such as Alzheimer's disease. Inhibition of HSP90 may be a feasible option for treating cancer, including hematological cancers such as AML and ALL (27, 28).

Histone deacetylases (HDACs)

HDACs are a superfamily of enzymes (EC 3.5.1) that remove acetyl groups from an ε-*N*-acetyl-lysine amino acid on a histone; this action is contrary to that of histone acetyltransferase. HDAC proteins exist in three classes: the first two classes comprise the classical HDACs and the third class consists of a family of NAD^+-dependent proteins. Within class I, HD1, 2 and 8 are principally found in the nucleus, whereas HD3 is found in the nucleus and cytoplasm and is also associated with the membrane. Class II HDACs (HD4, 5, 6, 7, 9 and 10) shuttle in and out of the nucleus according to distinct signaling cues. Positive charges on histone tails help facilitate their interaction with negatively charged phosphate groups on the DNA backbone. Acetylation neutralizes these positive charges by converting amines into amides and diminishes histone interactivity with DNA. This enables chromatin expansion and, subsequently, genetic transcription. HDAC acts by displacing these acetyl groups, thereby augmenting the positive charge of histone tails and facilitating high-affinity binding to the DNA backbone. Transcription is thus suppressed. HDAC is associated with signal transduction, notch signaling and numerous cellular processes, and is implicated in the development of certain cancers. HDAC is also believed to interact with a variety of nonhistone proteins, including transcription factors such as NF-kappa-B and coregulators. HDAC inhibitors are able to alter the activity of many transcription factors and are deemed to have potential for use in treating cancers such as AML (29).

IL-3R-alpha (CD123)

IL-3R-alpha (CD123), also referred to as interleukin-3 receptor subunit alpha, is a receptor belonging to the type I cytokine receptor family and is located on cells involved in IL-3 signaling, including pluripotent progenitor cells. It is heterodimeric and contains a unique alpha subunit 40 kb in length and consisting of 12 exons that is paired with the common beta (beta c or CDw131) chain. The gene encoding the receptor (*IL3RA*) is found in the pseudoautosomal region of the X and Y chromosomes. IL-3R-alpha mediates intracellular tyrosine phosphorylation and, in contrast to normal lymphoid progenitors, has been found to be strongly expressed and to induce proliferation and differentiation in a variety of leukemic blasts and leukemic stem cell lines. IL-3R-alpha inhibitors are believed to constitute a potential therapeutic option for hematological malignancies such as AML (30, 31).

IMP dehydrogenase (IMPDH)

IMPDH (EC 1.1.1.205) is a homotetramer enzyme consisting of a β/α barrel core domain and a smaller subdomain. The active site has binding pockets for the two substrates, inosine monophophate (IMP) and NAD. Two isoforms of IMPDH have been described. IMPDH-I is ubiquitous and mostly expressed in normal cells, whereas IMPDH-II is predominant in malignant cells. The intron structures of both genes are completely divergent and the 5′-regulatory sequences are highly different. Expression of the IMPDH-I gene (*IMPDH1*) is controlled by three distinct tissue-specific promoters, while the type II gene (*IMPDH2*) is regulated by a single promoter. IMPDH catalyzes the dehydrogenation of IMP to xanthosine monophosphate (XMP) using NAD as the proton acceptor. IMPDH plays an important role in the expression of cellular genes such as *TP53*, *MYC* and *KRAS*, being involved in transformation and progression in cancer cells. IMPDH may thus be a useful therapeutic target for cancer, including AML (32-36).

Kinesin-like protein KIF11

Kinesin-like protein KIF11, also known as kinesin-related motor protein Eg5, is a mitotic kinesin that acts at the earliest stage of spindle formation (mitosis, prophase) and forces the emerging spindle poles to move apart, driving the formation of a bipolar spindle and enabling chromosome segregation into two resulting daughter cells. It is not expressed in neurons and inhibition of its motor function prevents the formation of a bipolar spindle, causing cell cycle arrest in mitosis. Subsequently, duplicated chromosomes remain attached to the monopolar spindle in a persistent state of cell cycle arrest, resulting in apoptosis. Inhibition of this protein results in cell apoptosis followed by mitotic arrest and the formation of characteristic monoaster spindles. Agents capable of blocking KIF11 are thus considered to have potential for the treatment of cancer, including AML (37).

MAPKK 1 and MAPKK 2 (MEK1 and MEK2)

MEK1 and MEK2 are dual-specificity tyrosine/threonine protein kinases that participate in the Ras/Raf/MEK/ERK mitogen-activated protein kinase (MAPK) signaling pathway. It is known that approxi-

mately 30% of all human cancers have a constitutively activated MAPK pathway. This activation is predominantly caused by mutations in cell-surface receptors such as FLT3 (mutated in one-third of AML cases), SCFR or VEGFR. The Ras/Raf/MEK/ERK pathway and other MAPK cascades contribute to the regulation of diverse responses, including hormone and growth factor activity, cell differentiation, cell cycle progression, learning, inflammation and stress responses, as well as tumorigenesis and other pathological processes. Growth factor receptors recruit Ras guanine nucleotide exchange factors to the plasma membrane to activate Ras, a small GTPase, which then recruits and activates Raf kinases. Activated Raf phosphorylates and activates MEK1 and MEK2, resulting in the phosphorylation and activation of the mitogen-activated protein kinases ERK-1 and ERK-2, which in turn phosphorylate a wide range of effector proteins, including transcription factors. Constitutive activation of MEK1 and/or MEK2 triggers cellular transformation and inactivation of these kinases, and abrogation of their function inhibits signal propagation. MEK1 and/or MEK2 inhibition may therefore be a useful option for treating cancer, including AML (24, 38, 39).

Mast/stem cell growth factor receptor (SCFR)

Mast/stem cell growth factor receptor (SCFR), more commonly known as Kit or c-kit, is a transmembrane receptor tyrosine kinase that regulates the function of primitive hematopoietic cells, melanocytes and germ cells. Under normal conditions, the binding of the endogenous ligand stem cell factor (SCF) induces receptor dimerization, autophosphorylation and activation of multiple downstream pathways, including PI3K, phospholipase C (PLC)-γ, Src kinase, JAK/STAT and MAP kinase pathways. Mutations in SCFR have been detected in several cancers, especially gastrointestinal cancers and AML, and uncontrolled activity of SCFR due to overexpression, autocrine loops or mutational activation contributes to tumorigenesis. Targeting SCFR may therefore be a useful strategy for treating cancer, including AML (40, 41).

Nuclear factor NF-kappa-B

Nuclear factor NF-kappa-B is a protein transcription factor and intracellular mediator of the inflammatory cascade involved in the generation of adhesion molecules (ICAM-1, VCAM-1), inducible NOS (iNOS), COX-2, cytokines (e.g., IL-1β, IL-2, TNF-α, IL-6, interferon gamma) and chemokines (IL-8). Other genes that are regulated by NF-kappa-B include those encoding the IL-2 receptor, the IL-12 p40 subunit and c-Myc. Recent findings suggest that NF-kappa-B provides a mechanistic link between inflammation and cancer, controlling the ability of preneoplastic and malignant cells to resist the apoptosis-based tumor surveillance mechanism and regulating tumor angiogenesis and invasiveness. NF-kappa-B activity is closely associated with the I-kappa-B kinase complex (IKK), and aberrant or constitutive NF-kappa-B activation has been detected in many human malignancies, including solid tumors and hematological cancers such as AML and CML. It has also been reported that constitutive activation of the receptor tyrosine kinase FLT3 is responsible for IKK activation. TNF activation also results in NF-kappa-B activation and plays a role in inflammation-driven tumor progression. Inhibitors of NF-kappa-B activation may therefore represent a useful option for treating cancer, including AML (42-44).

Nucleolin

Nucleolin is a ubiquitous, nonhistone nucleolar phosphoprotein located in the nucleolus that is involved in the transcriptional control of ribosomal RNA (rRNA) genes by RNA polymerase I and II, rRNA processing, messenger RNA (mRNA) stabilization, DNA recombination and replication, ribosome maturation and assembly, transportation of ribosomal components, chromatin remodeling, cytokinesis and apoptosis. Nucleolin is highly expressed in dividing cells, while nondividing cells show nucleolin in degraded forms of various molecular sizes. Nucleolin is also found on the cell surface of cancer cells and is currently being used as a marker for the diagnosis of cancer and the development of anticancer drugs that inhibit proliferation. Nucleolin inhibitors may therefore be a useful therapeutic option for cancer, including AML (45).

Polo-like kinase 1 (PLK1)

PLK1 is a cell cycle-dependent serine/threonine protein kinase that is important for spindle assembly and chromosome segregation in cell division. Steady-state PLK1 mRNA and protein levels are regulated at the same time during cell cycle progression, being low during interphase and high in mitosis. PLK1 expression is upregulated in tissues and cells with a high mitotic index, including cancer cells, and PLK1 expression levels have been shown to have prognostic value for predicting outcomes in patients with certain cancers. Inhibition of PLK1 leads to mitotic arrest and a significant decrease in cell viability. PLK1 inhibitors may thus be useful for treating cancer, including AML (46, 47).

Protein farnesyltransferase

Protein farnesyltransferase (EC 2.5.1.58) is the enzyme that, together with protein geranylgeranyltransferase type I (EC 2.5.1.59) and type II (EC 2.5.1.60), constitutes the protein prenyltransferase family of enzymes. It is responsible for farnesylation, which involves attachment of a farnesyl group (a linear grouping of three 15-carbon isoprene units) to the carboxyl terminus of a protein bearing the four-amino-acid sequence CAAX. Farnesylated proteins (e.g., members of the Ras superfamily of small GTP-binding proteins) are involved in cell differentiation and proliferation and include several proto-oncogenes that mediate cell transformation. Because these oncogenes become functional following posttranscriptional farnesylation, protein farnesyltransferase inhibitors (FTIs) have emerged as an important class of antineoplastic agents. FTIs were principally designed to target Ras, since mutated Ras oncogenes (*HRAS*, *KRAS* and *NRAS*) play a causative role in malignant cell transformation and are frequently detected in many human tumors. FTIs are being developed to treat several types of cancer, notably AML (13, 48).

Protein kinase C (PKC)

PKC is a family of enzymes (EC 2.7.1) that phosphorylate proteins on serine or threonine residues, usually in the presence of calcium. PKCs are activated by receptor-mediated hydrolysis of membrane phospholipids that are involved in intracellular signaling for cell growth. The classical PKCs (α, β_I, β_{II} and γ) are calcium-dependent and can be activated endogenously by diacylglycerol or nonphysiologically by phorbol esters. Moreover, PKC may be the receptor pro-

tein for tumor-promoting phorbol esters. The specific physiological substrates for these enzymes are not yet known. Several calcium-independent isoforms have also been and continue to be identified. It has been reported that enzymes belonging to the PKC family embody some of the major mediators of signal transduction in melanocytes. Furthermore, they have been implicated in tumorigenesis and angiogenesis. Several PKC isoforms, including α, β_{II}, ε, ι and η, are reported to be pro-oncogenic in the skin, colon, prostate, ovary, breast, lung and brain, while PKC-δ may be antioncogenic in all tissues except the brain, where it is believed to be more pro-oncogenic. For this reason, both PKC inhibitors and activators are under development for treating cancer, including AML (49).

Raf kinase

Raf kinase belongs to a family of serine/threonine kinases. It is a downstream effector kinase of Ras proteins, members of a large family of G proteins and key intermediates in cell signaling. The Raf kinase family consists of three isoforms, Raf-1 (C-RAF), A-Raf and B-Raf. Raf-1 is ubiquitously distributed, A-Raf is abundant in urological tissues and B-Raf is ubiquitously expressed but localized mainly in the testis and neuronal tissue. Three conserved regions, CR1, CR2 and CR3, as well as various regulatory phosphorylation sites, are common to each isoform. Activated Raf potentiates a downstream signal transduction cascade that begins with the activation of MEK via phosphorylation at S218 and S222. MEK subsequently phosphorylates and activates ERK-1/2. Activated ERK-1/2 phosphorylates numerous downstream components that are implicated in a diverse range of cellular responses via the Ras/Raf/MEK/ERK pathway, from cytoskeletal alterations to gene transcription. Constitutive activation of the ERK pathway is frequently observed in human cancers characterized by tumor growth, invasion, angiogenesis and metastasis. It is often associated with the overexpression or mutation of upstream receptor tyrosine kinases such as EGFR, PDGF-R or VEGFR, increased expression of growth factor ligands or mutational activation of Ras and its downstream effectors. Aberrant signaling via this pathway may result in cell immortalization via telomerase induction; growth factor-independent proliferation and insensitivity to growth-inhibitory signals via cell cycle activation; autocrine signaling and inactivation of tumor suppressor genes, invasion and metastases via stimulation of cellular motility and extracellular matrix remodeling; angiogenesis via upregulation of proangiogenic factors; apoptosis suppression via BAD inactivation; and caspase inhibition and resistance to radiation and chemotherapy via induction of multidrug resistance genes (*ABCB*). As Raf is the key activator of the ERK pathway, therapeutic agents that specifically target Raf may be particularly effective together with agents that target other upstream targets such as growth factor ligands, receptor tyrosine kinases or Ras. Raf kinase inhibitors may therefore have potential for treating cancer, including AML (50-52).

Retinoic acid receptor alpha (RAR-alpha)

Retinoic acid receptor alpha (RAR-alpha) is a member of the retinoid receptor superfamily of nuclear receptors that also includes RAR-beta and RAR-gamma, retinoic acid X receptors RXR-alpha, RXR-beta and RXR-gamma, as well as the cytoplasmic receptors (CRABP-I and -II, CRBP-I and -II). RARs are members of the nuclear receptor NR1B family that are activated by natural vitamin A (i.e., retinoic acid), synthetic vitamin A agonists, *all-trans*-retinoic acid and 9-*cis*-retinoic acid. They form heterodimers with RXR, modulate cell differentiation and proliferation, and display antitumor activity. RAR-alpha interacts with the NCoA-3 and ASC-2 nuclear receptor coactivators and is involved in hematopoietic cell differentiation and maturation. A specific reciprocal chromosome translocation, namely t(15;17), that results in the expression of a leukemogenic fusion protein, PML-RARalpha, is the cause of APL, a subtype of AML. PML-RARalpha acts as a transcriptional repressor of RAR-alpha target genes and inhibits the activity of the transcription factor C/EBPalpha, which in turn induces the arrest of cell maturation at the stage of promyelocytes. RAR-alpha agonists have shown efficacy in the treatment of APL (53-55).

Ribonucleoside-diphosphate reductase

Ribonucleotide-diphosphate reductase (EC 1.17.4.1) is the rate-limiting enzyme responsible for the synthesis of 2′-deoxyribonucleotides (dADP, dGDP, dUDP and dCDP) from corresponding ribonucleoside 5′-diphosphates (ADP, GDP, UDP and CDP) during DNA replication. It consists of three protein components: RRM1 protein, a 160-kDa dimer with at least two different effector binding sites, RRM2 protein, a 78-kDa dimer with a nonheme iron for catalysis, and RRMB2, which is inducible by *TP53* and *TP73* and is directly involved in the p53 checkpoint for repair of damaged DNA. RRM1 mRNA levels are relatively constant throughout the cell cycle, while RRM2 mRNA is only present during late G1/early S phase when DNA replication takes place. Changes in M2 levels influence the dNTP pool and thus DNA synthesis and cell proliferation. Several studies have previously shown that tumor cells overexpress ribonucleotide-diphosphate reductase and that treatment of proliferating cells with inhibitors of the enzyme leads to apoptosis. The RRM2 protein component is used to determine the malignant potential of cells, enhancing, for example, the anchorage-independent growth of cells transformed with v-fms, v-Src, A-Raf, v-fes or c-Myc, and manipulated to overexpress the RRM2 component of ribonucleotide-diphosphate reductase. Additionally, increased RRM2 expression is associated with abnormal Raf-1 and MAPK activity and increased drug resistance in cancer cells. Therapeutic antagonism of ribonucleotide-diphosphate reductase may be useful for treating cancer, including AML (56, 57).

SH2 domain-containing inositol phosphatase (SHIP)

SHIP is an inositol polyphosphate-5-phosphatase, the expression of which is restricted to hematopoietic cells. It is a potential regulator of the PI3K pathway since it hydrolyzes the 5′-phosphate from phosphatidylinositol-3,4,5-trisphosphate (PIP_3). Its expression is restricted to hematopoietic cells and it is a negative regulator of myeloid cell proliferation, survival and end-cell activation. SHIP activators may therefore be useful for treating cancer, especially hematological cancers such as AML (58, 59).

Telomerase reverse transcriptase

Telomerase reverse transcriptase (HEST2, TP2), commonly referred to as TERT, is an enzyme involved in the repair of telomere regions of chromosomes. It consists of a protein component with TERT activity

and an RNA component which serves as a template for the telomere repeat. Telomerase adds a six-base DNA repeat sequence (TTAGGG) to the ends of chromosomes. During aging, the ends of chromosomes in mitotic cells become progressively shorter, a process thought to be due to a reduction in telomerase activity. Telomerase activity levels are influenced by the fraction of cells in the proliferative pool. The majority of cancer types express this enzyme, which is crucial for maintaining telomere length and thus ensuring indefinite cell proliferation. Shortened telomeres and high telomerase activity have been shown to correlate with disease severity in hematological cancers such as leukemias and lymphomas, especially in AML and non-Hodgkin's lymphomas. Inhibitors of telomerase activity are thus a feasible therapeutic strategy for cancer, notably AML (60, 61).

Tumor necrosis factor α (TNF-α)

TNF-α is a proinflammatory cytokine also known as cachectin that is a member of the TNF family of cytokines. It is released by activated macrophages and lymphocytes. It acts via receptors belonging to the TNF family of receptors, among which TNF receptors TNF-R1 and TNF-R2 trigger several signal transduction pathways, resulting in the activation of transcription factors such as NF-kappa-B and cFos/cJun. TNF-R1 (also known as CD120a, p55 and p60) is expressed in most tissues and is fully activated by both the membrane-bound and soluble trimeric forms of TNF. TNF-R2 (also known as CD120b, p75 and p80), however, is found only in cells of the immune system and is activated by the membrane-bound form of the TNF homotrimer. Activated factors induce the transcription of antiapoptotic, proliferative, immunomodulatory and inflammatory genes. NF-kappa-B is the major survival factor in preventing TNF-α-induced apoptosis and inhibition of this transcription factor may improve the efficacy of apoptosis-inducing cancer therapies (62, 63).

VEGF

VEGF is a major growth factor protein secreted by many cell types. The VEGF family encompasses 6 secreted glycoproteins: VEGF-A, -B, -C, -D and placenta growth factor PlGF-1 and PlGF-2. The biological effects of VEGF are mediated via interaction with one of three endothelial surface receptors: VEGFR-1 (Flt-1), VEGFR-2 (Flk-1) and VEGFR-3 (FLT4); binding to the coreceptor neurophilin enhances signaling. The VEGF/VEGFR pathway promotes a network of signaling processes that induce endothelial cell growth, migration and survival from preexisting vasculature and mediate vessel permeability. It also functions as an antiapoptotic mediator for newly formed blood vessels, as well as an inducer of the mobilization of endothelial progenitor cells from bone marrow to distant sites of neovascularization. The effect of VEGF on angiogenesis is implicated in tumor growth and metastasis, psoriasis, diabetic retinopathy and rheumatoid arthritis. VEGF levels are reported to be overexpressed in leukemic cells and elevated VEGF levels may contribute to adverse patient outcome by promoting cell growth, survival and migration and by reducing the sensitivity of leukemic cells to therapeutic agent-induced apoptosis (64-66).

VEGFR-1 (Flt-1)

VEGFR-1 (Flt-1) is a receptor tyrosine kinase belonging to the VEGFR family that is present in both transmembrane and soluble forms and plays a crucial role in regulating angiogenesis, lymphangiogenesis and vascular permeability in vertebrates. The soluble form lacks tyrosine kinase activity. Its primary ligand is VEGF-A, which binds to the receptor and induces dimerization, autophosphorylation and initiation of downstream signaling cascades responsible for endothelial cell growth, migration and survival. These pathways include the MAPK, PLCγ, PI3K/AKT and JAK/STAT pathways. The VEGF/VEGFR pathway promotes a network of signaling processes that induce endothelial cell growth, migration and survival from preexisting vasculature and mediate vessel permeability. It also functions as an antiapoptotic mediator for newly formed blood vessels, as well as an inducer of the mobilization of endothelial progenitor cells from bone marrow to distant sites of neovascularization. The VEGFR-1 pathway has also been shown to play a role in leukemia, since VEGF levels have been reported to be overexpressed in leukemic cells, and elevated VEGF levels contribute to adverse patient outcome by promoting cell growth, survival and migration and by reducing the sensitivity of leukemic cells to therapeutic agent-induced apoptosis. VEGFR-1 inhibitors may be useful for treating cancer, including AML (64, 66).

VEGFR-2 (Flk-1)

VEGFR-2 (Flk-1) is a kinase insert domain receptor (KDR) belonging to the VEGFR family. It is a receptor for VEGF-A and VEGF-C and plays a critical role in angiogenesis, regulating the growth and survival of endothelial cells in newly forming vasculature. While VEGFR-2-mediated proliferation of endothelial cells occurs via activation of the PLCγ and c-Raf–MAP signaling pathways, PI3K and focal adhesion kinase (FADK) pathways are responsible for survival and migrational signaling. The VEGF/VEGFR pathway promotes a network of signaling processes that induce endothelial cell growth, migration and survival from preexisting vasculature and also mediate vessel permeability. It also functions as an antiapoptotic mediator for newly formed blood vessels, as well as an inducer of the mobilization of endothelial progenitor cells from bone marrow to distant sites of neovascularization. The VEGFR-2 pathway has also been shown to play a role in leukemia, since VEGF levels have been reported to be overexpressed in leukemic cells, and elevated VEGF levels contribute to adverse patient outcome by promoting cell growth, survival and migration and by reducing the sensitivity of leukemic cells to therapeutic agent-induced apoptosis. Inhibitors of this receptor may be useful for treating cancer, including AML (64, 66).

VEGFR-3 (FLT4)

VEGFR-3 (FLT4) is a receptor tyrosine kinase belonging to the VEGFR family that plays a crucial role in regulating angiogenesis, lymphangiogenesis and vascular permeability in vertebrates. Ligands for the receptor include VEGF-C and VEGF-D. While it is expressed throughout the embryonic vasculature, its expression in adult tissue is correlated with transient lymphangiogenesis in wound healing. Also, activation of the VEGF-C/VEGFR-3 axis has been observed in several types of solid tumors, promoting cancer cell mobility and invasion capabilities and inducing cell metastasis. Activation of the VEGF-C/VEGFR-3 axis also induces metastasis by increasing lymphangiogenesis. It also plays a critical role in leukemic cell proliferation, survival and resistance to chemotherapy. Inhibition of VEGFR-3 may be useful for treating cancer, including AML (64, 66).

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