ajcr0000132 SupplementaryTables

Supplementary Table 1.

Proteins at the crossroad of proliferation and differentiation (Figure 2)

Interaction with the microenvironment

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
Jak2	non-receptor tyrosine kinase involved in cytokine signaling; Jak2 is indirectly activated by erythropoietin (EPO), IL-3, granuloctye-macrophage- and granulocyte-colony stimulating factor (GM-CSF and G-CSF), IL-6, thrombopoietin (TPO), growth hormone (GH), interferon gamma and prolactin	activating mutation	faster progression into S-phase	[127, 128]
Flt3	receptor tyrosine kinase involved in expansion of early progenitors; activated by Flt3 ligand	activating mutation, overexpression and altered intracellular distribution	faster progression into S-phase	[129, 130]
c-Kit	receptor tyrosine kinase involved in expansion of early progenitors; activated by Kit ligand alias stem cell factor (SCF)	activating mutation	faster progression into S-phase	[131]
CXCR4	chemokine receptor responsible for interaction with the bone marrow niche	upregulated in some cases	cytoprotection through anchoring in the hematopoietic niche and enhanced expansion	[132]

Signal Transduction

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
Ras	small GTPase which, in the GTP-bound state, activates several downstream effectors such as PI3K	N-ras and K-ras mutations	enhanced proliferation	[133]
Raf	serine/threonine kinase involved in the MAPK/ERK signaling pathway	*BRAF* mutations	enhanced proliferation	[134]
MEK	serine/threonine kinase involved in the MAPK/ERK signaling pathway	constututional activation	enhanced proliferation	[135]
MAPK/ ERK	serine/threonine kinase which is critical for the synthesis of promitotic and proproliferative genes	constututional activation and overexpression	enhanced proliferation	[135]
Pim1	serine/threonine kinase involved in cytokine signaling	overexpression	faster progression into S-phase and thus enhanced proliferation	[136]

Cdk inhibitors (CKIs)

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
p14	inhibitor of Mdm2 which leads to stabilization of p53 and hence p21	downregulated	faster progression into S-phase	[137]
p15	inhibitor of Cdk 4	downregulated	faster progression into S-phase	[138]
p16	inhibitor of Cdk 4	downregulated	faster progression into S-phase	[139]
p21	inhibitor of Cdk2 and 4	p21 deficiency cooperates with t(8;21)	faster progression into S-phase	[140]
p27	inhibitor of Cdk2 and 4	downregulated	faster progression into S-phase	[141]

Regulators of DNA synthesis

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
Tet2	methylcytosine dehydroxygenase which catalyzes the synthesis of 5-hydroxymethylcytosine	mutated	enhanced expansion of myeloid progenitors in mice	[38]

Regulators of APC/C-dependent proteolysis

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
Cdh1	activating subunit of the APC/C which is active primarily in late mitosis and G1 phase	repressed	faster progression into S-phase	[63]

Pocket proteins

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
pRb	pocket protein which binds to E2F and inhibits E2F-dependent transcription	downregulated and/or truncated	faster progression into S-phase	[142]

Cyclin-dependent kinases

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
Cdk4/6	serine/threonine kinases which are activated by cyclin D and phosphorylate pRb and are inhibited by p16	downstream target of many activating kinase mutations and deregulated signaling cascades	faster progression into S-phase	[143]

Cdk2	serine/threonine kinase which is activated by cyclin E or A and is inhibited by p21 and p27	enhanced activity	faster progression into S-phase	[144]

Cyclins

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
Cyclin D	activates Cdk4/6 is highly important for cell cycle progression	upregulated (e.g. MLL leukemia)	faster progression into S-phase	[51]
Cyclin E	activates Cdk2 regulates the G1/S transition	upregulated	faster progression into S-phase	[144, 145]

Transcription factors

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
E2F	family of transcription factors involved in cell cycle regulation and DNA synthesis		upregulated expression counteracts differentiation in vitro	[55, 146]
p53	transcription factor involved in DNA damage response and subsequent inhibition of cell cycle progression	deleted and/or mutated, deletion is often associated with mutation of the remaining allele	reduced checkpoint activity and compromised DNA damage response	[121]
c-Myb	member of the myeloblastosis family of transcription factors which is involved in the regulation of hematopoiesis	upregulated (e.g. in MLL leukemia)	important player in MLL-leukemogenesis	[39]
PU.1	ETS domain transcription factor encoded by the *SPI1* gene which is important for myeloid and B-cell development	reduced PU.1 activity in some leukemia subsets	suppression enhances pro-proliferative potential and leukemogenesis	[147]
Stat3	signal transducer and activator of transcription in response to cytokines	aberrant activation in AML	faster progression into S-phase	[148]
Stat5	signal transducer and activator of transcription in response to cytokines; the Stat pathway is activated by various cytokines (IL-2, -3, -5, -6, -7, -12, -15), prolactin, tumor necrosis factor alpha, epidermal growth factor and interferon-γ	aberrant activation in AML	faster progression into S-phase	[25, 149]
CEBPα	CCAAT/enhancer binding protein alpha is a basic leucine zipper transcription factor which can interact with Cdks	mutated	inhibition of granulocytic differentiation	[150]
HoxA9	homeobox transcription factor which is important for embryonic development	aberrant transcription of Hox genes by MLL	enhances pro-proliferative potential and leukemogenesis in cooperation with Meis1	[151]

Meis1	homeobox transcription factor which is important during development	aberrant expression in Hox- and MLL-induced leukemia, cooperation with Evi1 and regulator of cyclin D3	faster progression into S-phase and enhanced proliferation	[51, 152, 153]

Chromatin remodelers

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
MLL	Histone-lysine N-methyltransferase HRX is an important regulator of gene transcription and transcriptional memory	regulator of the Hox gene cluster and cell cycle regulators	faster progression into S-phase and mitosis	[46]

Supplementary Table 2.

Proteins during S-phase - replicating the leukemia genome (Figure 3)

Checkpoint kinases

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
ATM	ataxia teleangiectasia mutated is a serine/threonine kinase which is activated by double strand breaks	mutations are described in lymphoid malignancy	weakened checkpoint allows enhanced proliferation	[154, 155]
ATR	ataxia teleangiectasia and Rad3 related is a serine/threonine kinase which is activated by DNA damage	regulator of MLL and mediator of arsen-trioxide-induced apoptosis	weakened checkpoint allows enhanced proliferation	[74, 75, 156-159]
		mediates response to nucleoside analoga, such as cytarabine and clofarabine	S-phase arrest in the presence of nucleoside analoga	
		mediates response to topoisomerase II inhibitors such as etoposide during replication	S-phase arrest in the presence of topo-isomerase II inhibitors, such as etoposide	
Chk1	serine/threonine kinase which adds an inhibitory phosphate to Cdc25 to prevent activation of Cdk1 in response to DNA damage	repression in some cases of Fanconi anemia with higher risk of transformation	weakened checkpoint allows enhanced proliferation	[97]
Chk2	serine/threonine kinase which adds an inhibitory phosphate to Cdc25 to prevent activation of Cdk1 in response to double strand breaks	mutations and deletions may occur as rare events in myelodysplasia and AML	weakening of the DNA damage response	[160]

DNA damage response regulators

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
Claspin	regulator of the DNA damage response	differential regulation in AML cell lines	modulation of strength of the DNA damage response	[98]

Phosphatases

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References

Cdc25A	dual-specificity phosphatase which removes phosphate groups from tyrosine and serine/threonine residues and activates Cdk1, Cdk2 and Cdk4	negatively regulated by Chk1 and Chk2 and positively regulated by Jak2V617F	enhanced G1/S transitioning and S-phase progression	[161, 162]

F-box proteins

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
Skp2	F-box protein activates the SCF and mediates proteolysis of p27 and MLL	overexpressed in many cancers and aberrantly regulated in MLL-leukemia	enhanced G1/S transitioning and weakening of DNA damage response	[75, 163]

Cyclins

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
Cyclin E	activates Cdk2 regulates the G1/S transition	overexpressed	faster progression into and through S-phase	[145]
Cyclin A	activates Cdk2, regulates S-phase progression and interacts with c-Myb	overexpressed and altered intracellular distribution	faster progression through S-phase	[164-166]

Cyclin-dependent kinases

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
Cdk2	serine/threonine kinase which is activated by cyclin E or A and is inhibited by p21 and p27	high Cdk2 activity	faster progression into and through S-phase	[144]

Chromatin remodelers

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
MLL	histone modifier and target of ATR which protects damaged chromatin from replication machinery binding	disrupted by leukemogenic transloactions in MLL leukemias	weakened DNA damage response	[75]

Regulators of replication

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References

Cdc45	important regulator of early steps of replication	regulated by wild-type MLL	altered regulation of DNA binding in MLL-leukemias	[144]

Supplementary Table 3.

Proteins during G2-phase - getting prepared for genomic and cytoplasmic division (Figure 4)

Histones

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
γ-H2AX	histone which following phosphorylation at serine 139 is an indicator of DNA double strand breaks	differences in γ–H2AX loading between AML subsets	Part of the DNA damage response and possible predictor of response to therapy	[96]

Chromatin remodelers

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
SET	inhibitor of PP2A (see above) which is able to interact with p21 and inhibits cyclin B/Cdk1	aberrantly expressed in AML	weakened DNA damage response	[167]

Ubiquitin ligases

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
Mdm2	E3 ubiquitin ligase that negatively regulates p53	overexpressed in some subsets of AML	inactivation of the p53-pathway	[168]

Checkpoint kinases

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
ATM	ataxia teleangiectasia mutated is a serine/threonine kinase which is activated by double strand breaks	mediates response to chemotherapy	G2-arrest in response to chemotherapy	[154, 155, 169]
ATR	ataxia teleangiectasia and Rad3 related is a serine/threonine kinase which is activated by DNA damage	mediates response to chemotherapy	G2-arrest in response to chemotherapy	[75, 156, 170]
Chk1	serine/threonine kinase which adds an inhibitory phosphate to Cdc25 to prevent activation of Cdk1 in response to DNA damage	repression in some cases of Fanconi anemia with higher risk of transformation	weakened G2-checkpoint	[97]

Chk2	serine/threonine kinase which adds an inhibitory phosphate to Cdc25 to prevent activation of Cdk1 in response to double strand breaks	mutations and deletions may occur as rare events in myelodysplasia and AML	weakened G2-checkpoint	[160]

DNA repair proteins

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
BRCA1/2	breast cancer type 1 and 2 susceptibility proteins are involved in DNA repair	deleterious mutations	DNA damage response	[91]

Phosphatases

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
PP2A	protein phosphatase 2 is a serine/threonine phosphatase which functions in DNA damage response and cell cycle progression	frequently inactivated	weakened DNA damage response	[167]
Cdc25B	dual-specificity phosphatase which removes phosphate groups from tyrosine and serine/threonine residues and activates Cdk1	upregulated as a result of FoxM1 overexpression	faster transition into mitosis	[171]

Cyclin-dependent kinases

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
Cdk1	cyclin-dependent kinase which is an important regulator of mitotic entry	aberrantly activated by Cdc25	faster transition into mitosis	[172]

Cyclins

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
Cyclin B	activates Cdk1 at the G2/M-transition	increased expression in AML cell lines	faster transition into mitosis	[171]

Mitotic kinases

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References

Plk1	polo-like kinase 1 is a regulator of mitotic entry, centrosome kinetics and cytokinesis	overexpressed in subsets of AML	faster recovery from DNA damage response and rapid progression into mitosis	[101, 123]

Transcription factors

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
FOXM1	member of the Fox family of transcription factors with peak levels in G2 phase and mitosis and functions during mitotic entry and chromosome separation; positive regulator of various proto-oncogenic components	overexpressed in subsets of AML	faster progression into mitosis	[171]

Cdk inhibitors

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
p21	Cdk-inhibitor (see above) which, complexed with SET or following upregulation by p53, can inhibit cyclin B/Cdk1 to block mitotic entry	downregulated in subsets of AML	faster progression into mitosis	[171]

Supplementary Table 4.

Proteins during G2-mitosis - segregating leukemia chromosomes and cytokinesis of leukemia cells (Figure 5)

Chromatin remodelers

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
MLL	chromatin modifying enzyme (see above) which is supposed to mark gene promotors to avoid transient silencing during mitosis	oligomerization mediated by the septin moiety of MLL-septin fusion proteins	enhanced chromatin remodeling	[173]
MLL5	chromatin modifying enzyme which contributes to regulation of the G2/M-transition	frequently deleted	altered entry into mitosis	[174, 175]

Cyclins

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
Cyclin B	activates Cdk1 during mitosis	downregulated in the presence of truncated forms of AML1-ETO, reduced stability in the presence of a weakened mitotic checkpoint	faster metaphase to anaphase transition	[107]

Separase inhibitors

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
Securin	inhibitor of the cohesin-cleaving enzyme separase	downregulated in the presence of truncated forms of AML1-ETO, reduced stability in the presence of a weakened mitotic checkpoint	less stringent inhibition of separase	[107]

Spindle assembly checkpoint components

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
BubR1	member of the mitotic checkpoint complex (MCC) and pseudosubstrate inhibitor of Cdc20	downregulated in AML	weakens the mitotic checkpoint response	[107]
Bub1	important regulator of MCC assembly and direct inhibitor of Cdc20	downregulated in AML	weakens the mitotic checkpoint response	[108]

Mad2	member of the mitotic checkpoint complex (MCC) which inactivates Cdc20 through direct binding	Downregulated by Runx1 and the Etv6-Runx1 fusion protein, which is frequently observed in childhood ALL	weakens the mitotic checkpoint response	[176]
Blinkin	this protein mediates localization of Bub1 and BubR1 to conserved kinetochore components (hMIS12, NDC80, and Zwint-1 complexes) to facilitate stable chromatid microtubule connections	fusion protein partner of MLL	the fusion protein probably causes a dominant negative effect over the wild type protein	[110]

Mitotic kinases

Protein	Normal function	Alteration in AML	Implication for the leukemic cell cycle	References
Aurora A	mitotic kinase which is important for proper function of the mitotic spindle, chromosome alignment and cytokinesis	overexpressed in AML	overrides the mitotic checkpoint	[112]
Aurora B	chromosomal passenger protein which is important for chromosome attachment to microtubules	overexpressed in AML	hyperactivation of Aurora B is known to cause chromosomal missegregation	[116, 177]
Plk1	Plk1 is a mitotic kinase that regulates centrosome maturation, mitotic entry, spindle formation, chromosome separation and cytokinesis	overexpressed in AML	overexpression causes aberrant entry and exit from mitosis and contributes to aneuploidy	[123, 178]