Review Article

Molecular mechanisms in haematological malignancies

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Abstract

Haematopoiesis requires the constant production of large numbers of peripheral blood cells. This process is under tight control of transcription factor networks as well as cytokines, growth factors and hormones. We will review the importance of transcription factors in programming the haematopoietic lineage commitment and the role of the microenvironment and the corresponding cellular sensitivity to ensure production of mature functional cells in response to the physiological demand. Understanding the molecular mechanism of this complex process gives the opportunity to identify the underlying molecular deregulation in haematopoietic malignancies. The different levels of deregulation include hyperproliferation, block in differentiation and sensitivity to growth factors. In this review, leukaemic transformation is selected to give evidence of cell signalling deregulation. The clinical implications will be reviewed in the context of the potential opportunities in the future to identify specific therapeutic patient groups that can be defined using prognostic and predictive biomarkers.

Keywords

Haematopoiesis, haematological malignancies, leukaemia, cytogenetic aberrations, transcription factors, molecular genetics

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Introduction

The quiescent haematopoietic stem cell (HSC) compartment maintains a multipotent cell population and gives rise to oligolineage progenitors. These progenitors expand to maintain the haematopoietic compartment and differentiate into various blood lineage progenitors. Lineage positive progenitors are committed for differentiation into mature functional blood cells.

Lineage commitment in haematopoiesis

Transcription factors have a pivotal role in haematopoiesis and regulate HSC early development, survival, proliferation and lineage commitment. Transcription factors, including Runx1, SCL, Gata-2, ALL-1 and Evi-1 maintain a gene expression program unique to HSCs.[1] The maintenance of HSC self-renewal requires specific transcription factors among which are HoxB4[2], Notch1 [3] and Bmi-1.[4]

Oligolineage progenitors originate from the HSC and develop into either the common myeloid precursor (CMP) or the common lymphoid precursor (CLP), in the latter case through the down regulation of PU.1.[5] The CMPs undergo further lineage divergence into megakaryocytic/erythroid progenitors (MEPs) and granulocytic/monocytic progenitors (GMPs) upon Gata-1 and PU.1 mutually exclusive expression, respectively. C/EBPs, including C/EBPα and C/EBPε play an important role in the granulocytic branch of myelomonocytic commitment both through cell-cycle arrest [6] and the up-regulation of tissue specific genes.[7] Under the influence of PU.1, GATA-3 and Ikaros transcription factors, HSCs give rise to CLPs.[8] Upregulation of such transcription factors determine the commitment of the lymphoid lineage and subsequently the downregulation of myeloid lineage transcription factors such as GATA-1, C/EBPα, and NFE2.[9]

Differentiation of lineage committed progenitors

Upon commitment to the lymphoid lineage, lymphocyte progenitors start their maturation in the bone marrow and differentiate either as mature T cells in the thymus gland or as mature B cells in germinal centres (GCs) of secondary lymphoid organs. Lymphocyte fate is under tight regulation of mutually exclusive transcription factors and signalling pathways, which force CLP differentiation into a pro-B cell or a pro-T cell. Increased expression levels of E2A, EBF, Bcl11a[10] and PAX5[11,12] promote CLP differentiation to pro-B cells, pre-B cells and further to 'naive' B cells by the participation of the

SOX4[13] and LEF1[14] transcription factors. Consistently, PAX5 acts as a repressor by recruiting co-repressors to genes encoding NOTCH1[15], therefore direct differentiation towards the B cell lineage.

The microenvironment and the cellular sensitivity to the surrounding cytokines and growth factors allows appropriate differentiation to various mature cells in response to the physiological demand. Upon commitment, progenitors migrate to the specific microenvironment and are programmed to express lineage specific receptors, as governed by the transcription program, altering the sensitivity to the microenvironment. Lineage specific cytokines and growth factors regulate maintenance and differentiation of the committed progenitor cells. For instance, the differentiation towards the T cell lineage is promoted via the migration of CLPs to the thymus gland. The developmental progression of T cells is initiated by the downregulation of genes encoding KIT, CD44 and CD25.[16] This proceeds further to the upregulation of genes encoding the NOTCH proteins[17,18] and the response to cytokines and growth factors, such as IL-7 and morphogens, such as the Sonic Hedgehog proteins.[19]

Stem Cell Factor (SCF) supports proliferation of various haematopoietic compartments. In erythropoeisis the lineage-specific cytokine erythropoietin (Epo) works in concert with SCF to regulate the balance between proliferation and differentiation of erythroid progenitors. Epo and SCF transduce signals via multiple cooperating pathways in erythroid progenitors.[20,21] Activation of Protein Kinase B (PKB) results in phosphorylation of transcription factor Foxo3a, which results in its cytoplasmic retention and inhibition of transcriptional activation of cell cycle progression inhibitors, such as p27, p130Rb2, Btg1 and cyclin G2.[22] PKB, also activates the mTOR/eIF4E pathway[23] resulting in enhanced translation efficiency of structured mRNAs representing growth promoting transcripts (Figure 1). Decreased SCF signalling results in downregulation of PI3K, releasing active Foxo3a that promotes expression of cell cycle inhibitors initiating signals that execute terminal differentiation.

Dysregulation of haematopoiesis

The balance between proliferation and differentiation of committed progenitors is under tight control, to maintain the progenitor pool and ensure maturation in response to physiological demand. The production of increased numbers of mature blood cells during stress, requires higher progenitor proliferation rates. Concurrently, feedback mechanisms must be closely coordinated to repress progenitor proliferation and to restore physiological cell numbers when the stress is over.[24] Deregulation of this balance will result in disease.

Hyperproliferation

Myelo-Proliferative Disorders (MPD) and anaemia originate from hyperproliferative potential that can be sustained or can result in bone marrow exhaustion, respectively. Constitutive active tyrosine kinase receptors (FLT-3, cKit), activated kinases like activated Jak2 and mutant phosphatase PTEN promote proliferation and/or survival in committed progenitors that are still capable of differentiation. This results in a hyperproliferative phenotype.[9,25,26]

A common mutational event in lymphoid malignancies is the juxtaposition of genes to the BCR or TCR enhancer/promoter elements. One classical example is the BCL1 protein or CyclinD1 in the t(11;14) anomaly, where the BCL1 protein is juxtaposed to the Ig gene enhancer. The BCL1 protein is a cell cycle regulator required for the cellular maintenance of G1 progression and G1/S transition of the cell cycle. The enhancers of the Ig and BCL1 gene are exchanged leading to the possibility of overexpression of BCL1 gene with an accelerated passage through the G1 phase of the cell cycle.[28] Other similar examples are seen in mature B cell malignancies such as the t(14;18) in Follicular lymphomas[29], the t(1;14) in MALT lymphomas[30] and the t(8;14) in Burkiitt lymphomas.[31] Table 1 summarises the translocations resulting in dysregulation of proteins involved in cell cycle regulation and apoptosis. Dysregulation is a result of promoter exchange upon juxtaposition of one gene to another.

Differentiation block

In addition to hyperproliferation, a perturbed program blocking terminal differentiation plays a role in the development of leukaemia. Experimental reduction of the terminal differentiation transcription factor PU.1, results in leukaemia following failed differentiation.[5] Translocations t(8:21) and t(15;17) give rise to the fusion proteins AML1/RUNX1 and PML-RARα, both of which inhibit haematopoietic differentiation by recruiting repression complexes to target genes of the AML1 and RARα transcription factors respectively.[32, 33] This is also observed in early transformed lymphoid cells where a block in differentiation occurs either by the involvement of a transcription factor in the generation of a fusion gene or by promoter exchange with the BCR or TCR enhancer loci. The translocation t(1;19), encoding the E2A-PBX fusion protein, blocks the activity of the transcription factor E2A contributing to the onset of pre-B ALL.[34] In a recurrent chromosomal abnormality detected in T-ALL patients, t(1;14), the TAL1 gene is brought under the influence of the TCRA/D enhancer, deregulating the expression of the transcription factor TAL1 and blocks the T cell differentiation pathway giving rise to the onset of T-ALL.[35] Table 2 summarises recurrent chromosomal translocations found in leukemias that involve transcription factors.

Expression of fusion proteins in haematopoietic progenitors confers propagation in serial murine transplantation models[36,37] but is not sufficient to induce leukaemia. Cooperation events exemplified by the complementation of Flt3-ITD mutant to PML- RARα transgenic bone marrow cells results in 100% penetrance of an APL-like disease when transplanted to secondary recipients.[32] Moreover, chromosomal translocations such as the t(9;22)[38], t(14;18)[39] that are detected in CML and NHL respectively, have been also detected in normal and healthy individuals without any evidence of malignancy. Supporting this evidence is the t(12;21) in monozygotic twins. Studies have shown that although both twins may carry the t(12;21) anomaly, only the one with the additional mutation, 12p deletion, develops

precursor B acute lymphoblastic leukaemia.[40] This provides strong evidence that a second hit mutation, in addition to any other present mutation, is required for leukaemogenesis. It is in fact this combination of a proliferative switch together with a differentiation-blocking event which usually results in hematopoietic malignancy.

Growth factor sensitivity in disease

The high demand of erythrocytes in circulation is satisfied by continuous high level of erythroid progenitor expansion and differentiation in the bone marrow. Hence, negative feedback of EpoR signalling is required to prevent erythrocytosis. EpoR mutations resulting in truncations in the C-terminal region lack recruitment of the phosphatase SHP-1 resulting in constitutive proliferative signals and hypersensitivity to Epo.[41] These mutants are associated with primary familial polycythemia[42] with normal cell maturation and increased blood cell production. Hypersensitivity can be a result of loss of negative feedback but also be caused by activating mutations resulting in enhanced proliferation and/or survival. For instance the V617F *JAK2* mutation[43] is found predominantly in Polycythemia Vera (PV) patients, a myeloproliferative disorder (MPD) characterized by massive erythrocytosis. The mutation resides in the kinase inhibitory domain, resulting in constitutive JAK2 kinase activity. Pro-proliferative signal transduction pathway mutants have a central role in the pathogenesis of MPD and require cooperative events that lead to leukaemia. In human disease, constitutive activating mutations in *FLT3* are found in 30-35% of adult AML, *N-RAS* and *K-RAS* mutations in 20% and *cKIT* mutations account for 5% of cases,[27,44] supporting the hypothesis that tyrosine kinase receptor mutations represent collaborative events in leukaemogenesis together with loss or gain of function mutations in haematopoietic transcription factors such as AML1, GATA-1, C/EBPα and PU1. In addition to mutations that deregulate kinases, a number of translocations involving kinase molecules, are summarised in Table 3.

Table 1: *Dysregulation of proteins involved in cell cycle regulation and apoptosis. In these translocations, fusion genes are not generated but dysregulation is brought about by promoter exchange upon juxtaposition of one gene to another*

Chromosomal Translocation	*Gene involved*	*Function of deregulated gene*	*Associated Phenotype/disease*	*References*
t(14;18)(q32;q21)	BCL2	Apoptotic inhibition	Follicular lymphoma	29
t(11;14)(q13;q32)	BCL1	Overexpression accelerates passage through the G1 phase	Mantle cell lymphoma	28
t(1;14)(q21;q32)	BCL9	Apoptosis inhibition through NF-κB	Mucosa associated lymphoid tissue	30
3q27 rearrangements	BCL6	Bind to sequence specific DNA and repress its transcription in addition to recruiting other protein repressors; Cell cycle control; Apoptosis inhibition	Diffuse Large B cell Lymphoma	59
t(8;14)(q24;q32)	c-MYC	Constitutive activation of c-myc	Burkitt lymphoma	31

Table 2: *Transcription factors commonly involved in recurrent chromosomal translocations in leukemias*

Chromosomal Translocation	*Fusion gene*	*Fusion Protein – oncogenic function*	*Associated phenotype*	*References*
T(8;21)(q22;q22)	AML1-ETO	Recruitment of repression complex; negative dominance of ETO on AML1	AML - FAB M2 subtype	53
T(12;21)(p12;q22)	TEL-AML1	Recruitment of repression complex; negative dominance of TEL on AML1	B-ALL	54
T(15;17)(q22;q21)	PML-RARA	Dysregulation of retinoid-inducible genes involved in myeloid differentiation; Higher binding affinity for HDACs	AML – FAB M3 subtype	55
T(16;21)(p11;q22)	TLS-ERG	Seems to act as a transcriptional activator	de novo acute myeloid leukemia	56
T(1;19)(q23;p13)	E2A-PBX1	Potent transcriptional activator with pleiotropic transforming activity	pre B ALL	57
T(3;21)(q26;q22)	AML1-EVI1	Chimeric transcription factor with the dual functions of AML1 and EVI1: differentiation block (due to Runt) and stimulation of proliferation (from the zn fingers)	CML-BC of myeloid type; AML and MDS	58

Conversely, in myelodysplastic syndrome (MDS) lack of circulating erythrocytes occurs due to impaired responsiveness to Epo[45] or aberrant response to inhibitory cytokines. Epo stimulation of erythroid progenitors derived from MDS bone marrow fail to induce DNA-binding of transcription factor Stat5,[45] suggesting that dysplastic cells result from maturation commitment without the capacity to drive the terminal differentiation program.

Signalling deregulation in leukaemia transformation

Mutations that enhance the translation machinery also play a central role in enhanced aggressiveness of various human cancers including AML.[46] The D816V mutation in the kinase domain of cKit activates the PI3K/PKB/mTOR pathway conferring sensitivity to rapamycin.[47] Interestingly, rapamycin induces cell cycle arrest and apoptosis in patient-derived neoplastic mast cells harbouring the D816V *cKIT*, but not in

Table 3: *Table showing deregulated kinases involved in chromosomal translocations contributing to the onset of leukemia*

Chromosomal Translocation	*Protein kinases*	*Fusion gene*	*Associated Phenotype*	*Reference*
t(9;22)(q34;q11)	ABL	BCR - ABL	CML; ALL; AML	60
t(9;12)(q34;p13)	ABL	TEL - ABL	CML; ALL; AML	61
t(9;12)(p24;p13)	JAK2	TEL - JAK2	T-ALL; CD10+-ALL; 'CML-like' disease in transformation	62
t(9;22)(p24;q11.2)	JAK2	BCR-JAK2	Typical CML	63
t(2;5)(p23;q35)	ALK	NPM-ALK	Anaplastic large cell lymphoma	64
t(5;12)(q33;p13)	PDGFR	TEL-PDGFR	CMML	27
t(12;15)(p13;q25)	NTRK3	TEL-NTRK3	AML - FAB M2 subtype	65 66

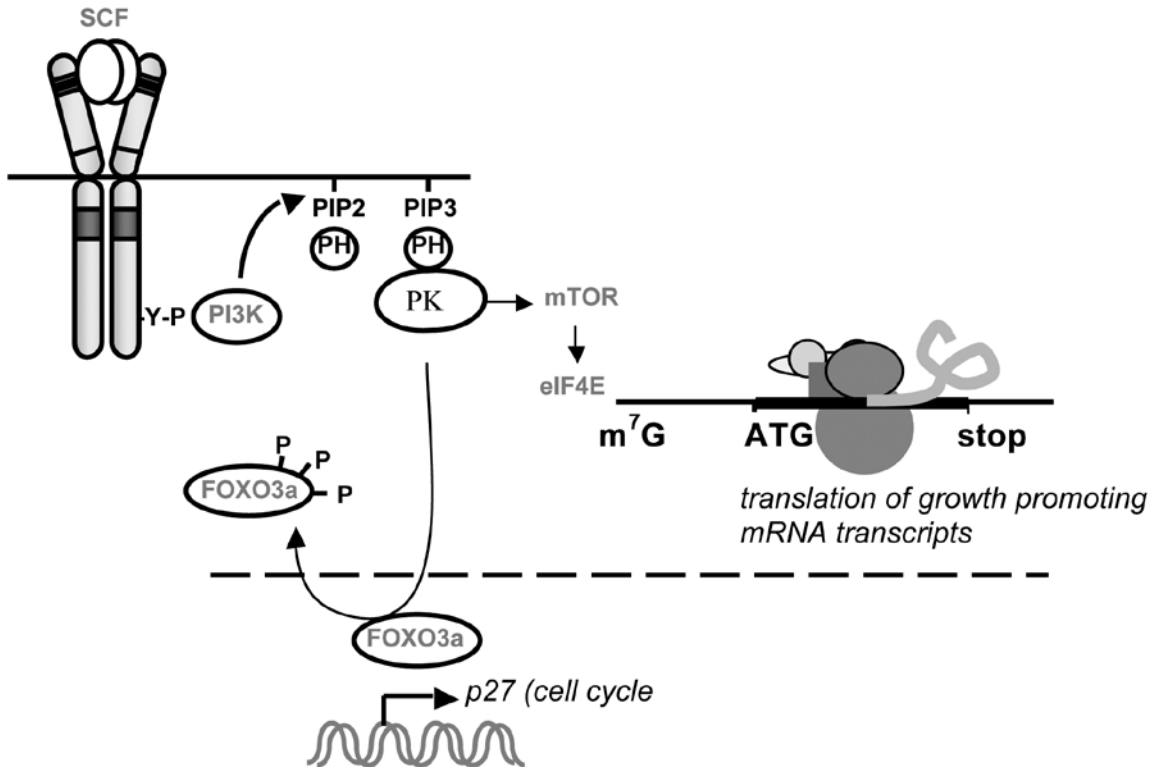

Figure 1: *Stem cell factor (SCF) signalling pathway. SCF binds to the tyrosine kinase receptor, cKit, activating the PI3K/PKB signal transduction pathway. PKB phosphorylates and redistributes Fox3a, sequestrating the molecule from the nucleus, inhibiting transcription of cell cycle inhibitors. In addition, activation of mTOR results in the translation of growth factors (eIF4E sensitive mRNA transcripts) that are otherwise not recruited to polysomes*

normal human cord-blood derived mast cells.[47] The frequency of active PI3K is higher than the incidence of mutations in *RAS* or in the receptor tyrosine kinases (RTK) *FLT3* and *cKIT*,[48] suggesting the need for targeting PI3K downstream effectors. Phosphatases that attenuate kinase activity are eligible for targeting. The phosphatases, PTEN and pp2a attenuate the PI3K/mTOR pathway, directly affecting ribosome biosynthesis and translation initiation.[23,49] The leukaemic potential of BCR/ABL-expressing cells can be inhibited by pharmacological activation of the phosphatase pp2a.[50] This suggests a central role of deregulated PI3K/mTOR/translation machinery in chronic myeloid leukemia (CML).

Conclusion and Further Directions

The knowledge of the molecular mechanism underlying specific groups of patients gives the opportunity to identify specific therapeutic targets that can be treated with known, or offer the opportunity to develop, specific pharmaceutical agents. To achieve this goal, patients are required to be classified into therapeutic groups. As mentioned above, activation of the PI3K pathway by various molecular aberrations classifies patients into a risk group that is sensitive to rapamycin treatment. Patients with cytogenetic abnormalities inv(16) (p13q22), and t(8;21) (q22;q22) are classified as core binding factor (CBF) leukemias (Table 2). These patients are represented into both the good and poor prognostic groups. Poor prognosis is driven by mutations in the *cKit gene*.[51] The identification of cKit mutations in CBF leukaemia cases is today used as a predictive biomarker strategy that will allow the use of specific tyrosine kinase inhibitors, such as Imatinib, in the treatment of such cases. Specific tyrosine kinase inhibitors are also available for *Jak2* positive myeloproliferative disorders (MPD); and ABL translocations (Table 3). Although still being tested in clinical trials, FLT3 inhibitors are showing promising results in AML patients that carry FLT3 mutations (approximately 30% of AML patients).[52] The BCR/ABL product of the translocation t(9;22)(q34;q11) is efficiently and directly targeted by the tyrosine kinase inhibitor, Imatinib. Molecular studies of the acquired mutations in the BCR/ABL molecule give predictive information on resistance to therapy. Knowledge of these mutations has been used to develop new therapeutic drugs to minimise the burden of resistance to therapy in CML patients.

Hence, patients will benefit from the identification of additional biomarkers that could predict clinical outcome at diagnosis. In addition, prognostic markers that can potentially serve as targets for novel agents are continuously investigated. Taken together, this knowledge will ensure informed therapeutic decisions and allow clinicians to use specific targeted therapies.

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