

## REVIEW

# Signaling revisited in acute promyelocytic leukemia

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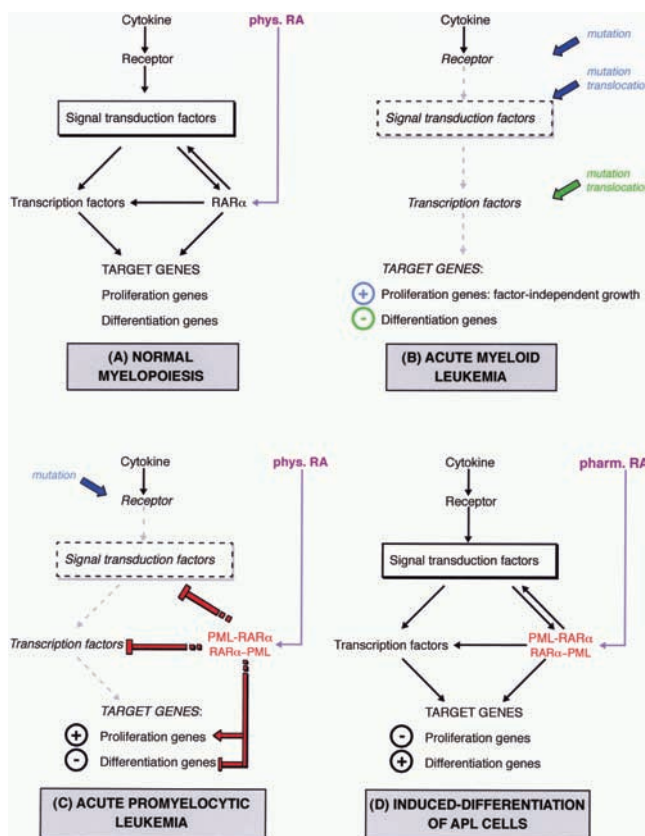
Although transcription factors are still the main focus to understanding leukemogenesis, recent results strongly suggest that alteration of a receptor and/or subsequent signaling plays a critical and co-operative role in the pathogenesis of acute myeloid leukemia (AML). The t(15;17) translocation, found in 95% of APL, encodes a PML-RAR $\alpha$  fusion protein. A main model proposed for acute promyelocytic leukemia (APL) is that PML-RAR $\alpha$  exerts its oncogenic effects by repressing retinoic acid-inducible genes critical to myeloid differentiation. Dysregulation of these genes may result in abnormal signaling, thereby freeing pre-leukemic cells from controls which normally induce the onset of differentiation. It is also likely that treatment of APL cells by retinoic acid induces *de novo* up-regulation of the same genes which are dominantly repressed by PML-RAR $\alpha$  and whose expression is required for reactivation of the differentiation program. Identification of such genes together with the signaling pathways interrupted at the early stages of leukemia transformation and reactivated during retinoic acid-induced differentiation in APL cells will contribute to the development of new molecular targets for treatment of leukemia.

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## Introduction

Hematopoiesis is organized as a hierarchy of events articulated by both a genetic commitment and growth factors. Lapidot and others have identified an acute myeloblastic leukemia (AML)-initiating cell capable of establishing human leukemia in SCID mice, strongly suggesting that a hierarchy of leukemic stem/progenitor cells exists in human AML.<sup>1–3</sup> Indeed, human AML cells are likely to arise from hematopoietic progenitors developing through the myeloid pathway. The development of normal hematopoietic progenitor cells is under the control of cytokines. Since differentiation occurs at the level of late progenitors, it is likely that genes critical to growth and differentiation of these cells are under the control of cytokines and growth factors through their specific transduction pathways (Figure 1, panel A). Leukemic progenitors become factor-independent as transformation is taking place. Genes critical to growth and differentiation may be the targets of transcription factors or co-factors involved in chromosomal abnormalities.<sup>4–6</sup> However, it is noteworthy that expression of specific abnormal proteins such as PML-RAR $\alpha$  is not sufficient to induce a complete leukemic phenotype, strongly suggesting that secondary mutations are required to cause AML.<sup>7–11</sup> Signal transduction abnormalities such as those due to mutations/rearrangements in cytokine or growth factor receptors can lead to constitutively activated tyrosine kinase molecules such as the FMS-like receptor tyrosine-kinase 3



**Figure 1** Signal transduction cross-talks are central to normal and leukemic hematopoiesis: altered cell responses to RA in the presence of cytokines. (A) In normal hematopoietic progenitor cells, genes critical to proliferation and differentiation are under the control of cytokines and physiological (phys.) RA concentrations. A functional link exists between stimulation by cytokines and retinoic acid receptors (RARs) activation. (B) In AML cells, constitutive activation of transduction pathways as a result of mutations or translocations provides proliferative and survival signals and renders hematopoietic cells growth factor independent. Chromosomal abnormalities implicating transcription factors mostly result in impaired differentiation. (C) In APL cells, genes critical to proliferation and differentiation are dysregulated by PML-RAR $\alpha$ . Alteration of signal transduction co-operates with PML-RAR $\alpha$  to induce APL. (D) In APL cells treated with pharmacological (pharm.) RA concentrations, cross-talks exist between RA and cytokine signaling pathways to inhibit proliferation and induce differentiation. In (B) and (C), dotted arrows and boxes represent alterations of signaling.

(FLT3).<sup>12–13</sup> Such abnormalities are frequently found in AML and in acute promyelocytic leukemia (APL) suggesting that these other hits are required for a full malignant phenotype. In such a model, activated tyrosine kinase may mainly provide proliferative and survival signals to hematopoietic cells while a second event such as a fused transcription factor may confer

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a proliferative and/or survival advantage but mostly result in an impaired differentiation (Figure 1, panel B).

Although transcription factors are still the main focus to understanding leukemogenesis, recent results strongly suggest that alteration of a receptor and/or subsequent signaling plays a critical and co-operative role in the pathogenesis of AML<sup>14</sup> (Figure 1, panel B). Accordingly, we should be shifting to include equally transcription and signal transduction in our models of transformation. To this extent, it now becomes increasingly important to identify genes which are the common or specific targets of these abnormal proteins and which, through their dysregulation and induced regulation, control transformation and induced-leukemia cell differentiation, respectively.

### Activated transduction pathways in acute myeloid leukemia

Increasing attention has been recently given to receptor cytosolic signaling. Indeed, aberrations in cytokine and growth factor function are likely to play a major role in malignant transformation. Myeloid leukemia transformation may involve: (1) production of a growth factor in an uncontrolled fashion resulting in autocrine growth; (2) dysregulation of a specific growth factor receptor leading to alteration of subsequent signaling, or; (3) direct alteration of signal transduction proteins (Figure 1, panel B).

The hypothesis of an autocrine loop in human leukemia is unlikely. Indeed, factor-independent growth is likely to represent one of the early stages in leukemia development that may result in autonomous growth of primitive leukemia cells<sup>15</sup> rather suggesting a constitutive activation of receptor pathways.<sup>16–17</sup>

Dysregulation of a specific growth factor receptor may lead to alteration of subsequent signaling. Indeed, a large variety of structural alterations found in hematopoietic growth factor receptors may lead to constitutive activation of receptor signals which consequently result in the stimulation of mitogenic signal transduction pathways and the subversion of the mechanisms controlling cell growth (Figure 1). Constitutively activated receptors which contain single point mutations (eg, macrophage colony-stimulating factor receptor, FLT3 receptor) or activating internal tandem duplication (ITD) mutations (eg, FLT3 receptor) can induce myeloproliferative disorders<sup>12,13,18</sup> and are linked to components of the Ras-MAP kinase signaling pathway. This suggests that those receptor mutations may induce constitutive activation of Ras<sup>19</sup> which is known as an important factor in the malignant growth of myeloid cells.<sup>20</sup> It is well established that ITD in the juxta-membrane region that results in constitutive activation of FLT3, confers interleukin 3 (IL-3)-independent growth to hematopoietic cells.<sup>21</sup> Constitutive tyrosine phosphorylation of the signal transducer and activator of transcription 5 (STAT5) is mostly associated with autophosphorylation of the FLT3 receptor which has often been linked to tandem duplications of the FLT3 gene.<sup>22</sup> Furthermore, FLT-3 ligand and granulocyte colony-stimulating factor (G-CSF) have a potent synergistic effect in the proliferation of hematopoietic progenitor cells *ex vivo*<sup>23</sup>. Receptor deletion/mutant studies have shown that activation of the Ras-mitogen activated protein (MAP) kinase pathway is necessary for G-CSF-induced proliferation. It is well recognized that in patients with severe congenital neutropenia the progressive acquisition of G-CSF receptor mutations significantly correlates with transformation into acute leukemia.<sup>24–28</sup> Furthermore, mutations in the G-CSF

receptor gene resulting in the truncation of the carboxy-terminal region have been detected in a subset of patients with severe congenital neutropenia transforming to acute leukemia.<sup>24–28</sup> Such mutations confer clonal expansion to neutrophilic progenitor cells and the resulting truncated receptors have been shown to act in a dominant-negative manner over wild-type receptors to enhance proliferation and restrain maturation.<sup>29</sup> As a result, ligand-mediated G-CSF receptor internalization by truncated receptors is impaired and is associated with prolonged activation of STAT.<sup>30</sup> In t(8;21)-positive AML cells, the fusion protein blocks differentiation mediated by G-CSF. However, in these cells STAT1 and STAT3 have normal activities suggesting a functional G-CSF signaling which allows pharmacological concentrations of G-CSF to induce transient *in vivo* differentiation.<sup>31</sup> Translocations involving a receptor tyrosine kinase such as Tel-PDGFR $\beta$ <sup>32</sup> can also be found in hematologic malignancies. Such receptors contain a tyrosine-kinase domain associated with an oligomerization domain which stabilizes interactions between adjacent cytoplasmic domains and constitutively activates the tyrosine kinase<sup>33</sup> thus abrogating growth factor dependence of hematopoietic cells.<sup>34</sup> A similar mechanism has been described for translocations involving non-receptor tyrosine kinases such as Tel-Abl.<sup>35,36</sup>

Direct alteration of a signal transduction protein such as Ras which is activated by mutation can be involved in malignant cell growth.<sup>20</sup> Furthermore, in juvenile chronic myelogenous leukemia, loss of the neurofibromatosis type 1 (NF1) gene, a Ras GTPase activating protein, leads to aberrant growth of hematopoietic cells through a Ras-mediated hypersensitivity to granulocyte-macrophage CSF (GM-CSF) receptor.<sup>37,38</sup> Although activation of Ras is not linked to a specific receptor, the possibility that direct alteration of a protein linked to a specific growth factor signaling pathway may be involved in myeloid leukemia transformation remains to be verified.

### Acute promyelocytic leukemia

Human APL is associated with five reciprocal translocations always involving the retinoic acid receptor alpha (RAR $\alpha$ ) gene fused to the promyelocytic leukemia (PML), nucleophosmine (NPM), promyelocytic leukemia zinc finger protein (PLZF), nuclear mitotic apparatus (NuMA), or STAT5b genes.<sup>39,40</sup> Abnormal activities of these fusion proteins are likely to result from the dysregulation of their partners respective functions. RARs are retinoic acid (RA)-dependent transcription factors<sup>41</sup> involved in the control of hematopoietic cells differentiation.<sup>42,43</sup> Interestingly, PML, PLZF and STAT5b are involved in the control of transduction of the cell mitogenic and survival signals.<sup>44–47</sup> In more than 95% of APL, the specific translocation t(15;17)<sup>48</sup> creates a PML-RAR $\alpha$  and reciprocal fusion proteins. PML-RAR $\alpha$  is thought to involve an oncogenic transcriptional repression of RA-target genes (Figure 1, panel C). Complete remission of patients with APL can be obtained with all-*trans* retinoic acid (RA) which induces differentiation of PML-RAR $\alpha$ -positive leukemic cells.<sup>49–52</sup> Although PML-RAR $\alpha$  and RAR $\alpha$ -PML fusion proteins play a critical role in APL leukemogenesis as demonstrated in transgenic mice, they do not confer a fully malignant phenotype in murine promyelocytes.<sup>53–55</sup> Indeed, FLT3 ITD mutation was found to co-operate with PML-RAR $\alpha$  to induce an APL-like disease in a mouse model.<sup>56</sup>

As external signals such as cytokines regulate limited expansion and maturation of hematopoietic progenitor cells

in the bone marrow, fusion proteins may promote leukemia transformation in these cells by repressing RA-target genes thereby disrupting signaling pathways leading to differentiation (Figure 1, panel C). This, in association with other genetic dysregulations, may contribute to full leukemic transformation.

### PML-RAR $\alpha$ target genes

In APL cells, pharmacological concentrations of RA switched PML-RAR $\alpha$  activity from repression to activation<sup>57</sup> (Figure 1, panel D). Although RA-regulated genes which are involved in triggering differentiation in APL cells remain elusive,<sup>58</sup> a number of potential PML-RAR $\alpha$  targets have been described such as: (1) the granulocytic differentiation marker CD18;<sup>59</sup> (2) type II transglutaminase<sup>59</sup> which is implicated in the activation of cytokines,<sup>60,61</sup> signal transduction,<sup>62</sup> and the induction of apoptosis;<sup>63,64</sup> (3) p21<sup>WAF1/CIP1</sup>, a mediator of growth inhibition which plays a role during commitment to differentiation of RA-treated APL cells;<sup>65</sup> (4) caspase 3 and ubiquitin-activating enzyme E1-like (UBE1L) which mediate PML-RAR $\alpha$  degradation;<sup>66,67</sup> (5) the CCAAT/enhancer binding protein  $\epsilon$  (c/EBP $\epsilon$ ), a myeloid transcription factor.<sup>68,69</sup> c/EBP $\epsilon$  is the only example of a gene up-regulated by RA in APL cells and dominantly repressed by PML-RAR $\alpha$ , whose expression is required for reactivation of the differentiation program.<sup>57</sup> Using the NB4 APL cell line which can undergo *in vitro* granulocytic differentiation when treated with RA,<sup>70</sup> subtraction cloning was applied to identify novel genes which are up-regulated during RA-induced differentiation of leukemic promyelocytes and genes regulated in the course of *in vitro* differentiation of normal human hematopoietic stem/progenitors cells along the myeloid lineage were selected. Two of these genes encode potential signal transduction factors which are PML-RAR $\alpha$  targets in myeloid leukemia cells: (1) ASB-2 (ankyrin-repeat-containing protein with a SOCS Box-2) which inhibits growth and promotes commitment in myeloid leukemia cells<sup>71</sup> and PRAM-1 (PML-RAR $\alpha$  target gene encoding an Adaptor Molecule) a novel adaptor protein.<sup>72</sup>

### Retinoic acid and normal myeloid differentiation

The role of specific cytokines in regulating myeloid cell proliferation and differentiation is well established. Although, RARs are dispensable for granulopoiesis,<sup>73</sup> a role of RA in the commitment of hematopoietic progenitors into the granulocytic lineage has been proposed<sup>74-77</sup> (Figure 1, panel A). In addition, when added to cultures of bone marrow cells in the presence of G-CSF and stem cell factor, a RAR antagonist reduced neutrophil differentiation suggesting that serum retinoids promotes differentiation.<sup>73</sup> Furthermore, overexpression of wild-type RAR $\alpha$  or dominant-negative forms of RAR $\alpha$  including PML-RAR $\alpha$  block granulocytic differentiation at the promyelocytic stage.<sup>75,78</sup> RAR $\alpha$  is likely to inhibit neutrophil differentiation in its non-liganded state and to promote differentiation when liganded. To this extent, the relationship between RAR activity and other important regulators of myelopoiesis and particularly those cytokines and growth factors which regulate myeloid progenitor growth and differentiation is an important issue that has to be systematically investigated. Johnson *et al*<sup>79</sup> have emphasized the role of specific cytokines in modulating RAR activity in different *in vitro* models of myeloid differentiation showing a direct functional link

between stimulation by cytokines, such as IL-3 and GM-CSF, and ligand-dependent as well as ligand-independent RAR activation. The observation of a ligand-independent activation of RARs might shed new light on the mechanisms by which RAR activity can be modulated during hematopoiesis and also suggests a molecular basis for the differential sensitivity of human acute myelogenous leukemia cells to retinoids. Altogether, this work revealed a novel point of convergence of signaling pathways important for myeloid differentiation.

### Signal transduction factors in APL

A number of signal transduction pathways can be activated in induced-differentiation of myeloid leukemia cells.<sup>80</sup> Beyond the importance of finding synergistic effects between different inducers for more efficient treatments of leukemia, potential cross-points between different signaling pathways may allow identification of key molecules controlling maturation in leukemia cells. Therefore, here we will focus on synergisms which may help in revealing such critical signaling cross-points and allow useful molecular mechanisms to be deciphered by which differentiation and growth arrest could be induced more efficiently in leukemia cells.

Synergistic effects of retinoid and interferon alpha (IFN $\alpha$ ) signaling was first reported in human myeloid leukemia cell lines as well as in patients with acute myelogenous leukemia.<sup>81</sup> This was confirmed in NB4 in which IFN was shown to potentiate RA-induced growth arrest and differentiation.<sup>82</sup> Retinoic acid induced expression of STAT1 and STAT2,<sup>83-85</sup> as well as IFN-responsive factor 1 (IRF-1)<sup>83</sup> and p48<sup>85</sup> which play central roles in IFN specific signaling and are known to be involved in differentiation and anti-proliferative functions.<sup>85,86</sup> Retinoic acid induced tyrosine phosphorylation of STAT1 and STAT2.<sup>83</sup> In addition, RA treatment induced IFN- $\alpha$  synthesis and enhanced IFN-induced STAT activation in NB4 cells.<sup>87,88</sup> Furthermore, IFN $\gamma$  (but not  $\alpha$  or  $\beta$ ) induced slight maturation and growth suppression in retinoid-resistant NB4-R1 cells, partially restoring a co-operative RA response.<sup>82</sup> It is remarkable that treatment of NB4-R1 cells by RA did allow induction of IRF-1 but not of STAT1, p48 and IFN $\alpha$ .<sup>88</sup> These results together with the fact that, in U-937 monocytoid cells, ectopic expression of a phosphorylation-deficient STAT1 suppressed RA-induced differentiation as well as expression of the G-CSF receptor,<sup>89</sup> strongly suggest that STAT1 is a main cross-point between the RA and IFN signaling pathways.

Early observations have established that HL-60 and U937 cells could be primed by RA to differentiate in response to cyclic AMP (cAMP)-inducing agents.<sup>90</sup> In NB4 cells, it has been shown that a decrease protein kinase A (PKA) activity blocked RA-induced maturation.<sup>91</sup> Although pharmacological concentrations of RA are required to differentiate APL cells, sustained PKA signaling allowed near physiological levels of RA to induce NB4 cell differentiation. This suggests that cAMP plays a key role in physiological responsiveness to RA. RA and cAMP cross-talk may define discrete maturation steps. Indeed, Ruchaud *et al*<sup>91</sup> defined two discrete steps in the maturation process of NB4-R1 cells: (1) an RA-dependent priming that maintains proliferation while cells become competent to undergo maturation in response to retinoids; (2) a cAMP-dependent trigger allowing RA-primed cells to undergo terminal maturation. These authors speculated that uncoupling RA and cAMP action might be responsible for the so-called RA resistance of NB4-R1 cells. Finally, the possibility that cAMP may be required for lineage-restricted differentiation

stage is suggested by the fact that G-CSF activates PKA in granulocytic but not monocytic differentiation of HL-60 cells.<sup>92</sup> Potential cross-talks have also been identified between RXR $\alpha$  and cAMP signalings. Indeed, maturation of retinoid-resistant cells was obtained following treatment with both retinoid X receptor and PKA agonists.<sup>93</sup> *In vitro* PKA phosphorylation of RXR $\alpha$  has an important role in the cross-talk between RXR $\alpha$  and cAMP signaling pathways. Although it is established that PKA-dependent phosphorylation is required for RA-cAMP cross-talk, secondary effectors likely to activate cAMP to trigger differentiation have not as yet been identified.

Recently, arsenic trioxide (As<sub>2</sub>O<sub>3</sub>) has been identified as an alternative therapy in patients with both RA-sensitive and RA-resistant APL. As<sub>2</sub>O<sub>3</sub> triggers apoptosis and a partial differentiation of APL cells in a dose-dependent manner, and a strong synergy exists between a low concentration of As<sub>2</sub>O<sub>3</sub> and the cAMP analogue, 8-CPT-cAMP, in fully inducing differentiation of NB4, NB4-R1 and fresh APL cells. This synergism could be blocked by an antagonist of PKA. These results thus support the existence of a novel signaling cross-talk for APL differentiation.<sup>94</sup>

Myeloid differentiation is controlled by cytokines, including G-CSF, which act in part through the activation of the STAT family. STAT transcription factors and especially STAT1, are constitutively activated in a number of human AML cell lines and might contribute to their autonomous proliferation.<sup>95</sup> The fact that RA induces the G-CSF receptor<sup>96</sup> as well as RAR( $\alpha/\beta$ )<sup>97</sup> may suggest that G-CSF and RA either co-operate or partly share a common signaling pathway to induce differentiation in APL cells. Indeed, RA and G-CSF act synergistically to reduce the proliferation of normal hematopoietic progenitor cells<sup>98</sup> and to induce differentiation of APL cells.<sup>99</sup> A strong synergistic interaction between G-CSF and RA exists to induce leukocyte alkaline phosphatase activity in APL cells.<sup>97</sup> Retinoic acid and G-CSF co-operate to induce neutrophilic maturation in the t(15;17)-harboring HT93 cells<sup>100</sup> as well as in acute myelogenous leukemia with a t(2;17;4) aberration.<sup>101</sup> Furthermore, G-CSF renders PLZF-RAR $\alpha$ -positive APL cells sensitive to RA and is clearly beneficial when associated with RA in patients expressing this fusion protein.<sup>102</sup> This synergism between RA and G-CSF, together with the fact that RA induces G-CSF receptor transcripts strongly suggests a cross-talk between the RA and G-CSF signaling pathways.

PRAM-1, an RA-inducible gene, is a first example of an adaptor molecule whose expression is inhibited and superinduced when PML-RAR $\alpha$  is expressed alone and in the presence of RA, respectively. The co-ordinated induction of PRAM-1, the SKAP-HOM adaptor and the tyrosine kinase lyn protein expression by RA in NB4 cells, together with the capacity of these proteins to associate with each other, represent a good basis to further investigate whether PRAM-1, SKAP-HOM and lyn are functionally linked in a common RA-signaling pathway.<sup>72</sup> The evidence that PRAM-1 mRNA expression is inhibited by PML-RAR $\alpha$  together with the association of PRAM-1 with other above-mentioned RA-induced proteins, suggests that the fusion protein may indirectly dysregulate the organization of molecular complexes and therefore disrupt signaling events important for myeloid differentiation.<sup>72</sup> The fact that lyn plays a major role in G-CSF receptor signaling<sup>103</sup> points to PRAM-1 complexes as a potential link between RA and G-CSF signaling pathways. Also, IL-3 and GM-CSF were recently shown to enhance RAR activity upon myeloid differentiation, revealing a novel point of convergence of RA and cytokine signaling pathways important for myeloid differentiation.<sup>79</sup>

The synergism observed between RA and G-CSF for inducing differentiation as exemplified by PLZF-RAR $\alpha$ -expressing APL cells, together with enhanced RAR $\alpha$  activity in IL-3- or GM-CSF-treated myeloid cells, and the likelihood that PRAM-1 belongs to both RA and G-CSF signaling, strongly suggest a unified view of transformation in which RA induces differentiation through molecules at a cross-point between RA and specific cytokine receptor signalings. These observations must encourage the investigation of combinations of RA and hematopoietic growth factors in myeloid leukemia.

Identifying the signaling pathways interrupted at early stages in leukemia transformation and reactivated during RA-induced differentiation in APL cells and specially those molecules at a cross-point between different signaling pathways, will contribute to the development of new molecular targets for treatment in order to force differentiation and growth arrest of human leukemia cells.

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