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Extra View

Oncoproteins, heterochromatin silencing and microRNAs

A new link for leukemogenesis

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The pathogenesis of acute myeloid leukemias involves complex molecular events triggered by diverse alterations of genomic DNA. A limited number of initiating lesions, such as chromosomal translocations generating fusion genes, are constantly identified in specific forms of leukemia and are critical to leukemogenesis. Leukemia fusion proteins derived from chromosomal translocations can mediate epigenetic silencing of gene expression. Epigenetic deregulation of the DNA methylation status and of the chromatin "histone code" at specific gene sites cooperate in the pathogenesis of leukemias. The neutralization of these crucial oncogenic events can revert the leukemia phenotype. Thus, their identification and the study of their molecular and biological consequences is essential for the development of novel and specific therapeutic strategies. In this context, we recently reported a link between the differentiation block of leukemia and the epigenetic silencing of the microRNA-223 gene by the AML1/ETO oncoprotein, the product of the t(8;21) the commonest AML-associated chromosomal translocation. This finding indicates microRNAs as additional epigenetic targets for leukemogenesis and for therapeutic intervention in leukemias.

In a large number of leukemias the primary mutational events involve chromosomal translocations, leading to the formation of fusion genes.[1] The molecular and biological consequences of this event depend on the nature of the genes involved in the fusion. Often these genes encode transcription factors, whose function is altered by the fusion.[2] Many of these factors are able to modify chromatin structure. The notion that alterations of chromatin structure can initiate the carcinogenic process derives from studies carried out on acute promyelocytic leukemia (APL), an acute myeloid leukemia (AML) subtype. In most APL cases, the chromosomal translocation t(15;17) generates a fusion gene encoding the PML/RARα fusion protein, that is fundamental for leukemogenesis.[3] The APL-fusion product was the first example of an oncogenic transcription factor acting by recruiting to its target genes a chromatin modifying protein complex. The oligomerization capability of the PML/RARα fusion protein generates a multimeric complex, including multiple PML/RARα molecules and the retinoid receptor RXR, which stabilizes the recruitment of a number of chromatin remodeling proteins.[4-7] Among the chromatin remodeling proteins participating to the PML/RARα complex there are corepressors, such as N-CoR and SMRT, histone deacetylases, histone methyltransferases, polycomb group proteins and others.[8-12] All these proteins heavily modify the chromatin "histone code" to repress transcription. In addition, the PML/RARα oncogenic complex also comprises DNA-methyltransferases and methyl-CpG binding activities, which induce stable DNA methylation on the promoters of PML/RARα target genes.[13-15] The mechanistic model derived from the PML/RARα oncoprotein highlighted the importance of epigenetic changes in the altered gene regulation mediating the pathogenesis of leukemia and have guided the investigation regarding other leukemia fusion proteins.

The most frequent chromosomal rearrangement in AML is the t(8;21) chromosomal translocation, that produces a chimeric gene and a fusion protein generated by a portion of the AML1 (also named RUNX1) transcription factor fused to the corepressor ETO protein. The molecular and biological activities of the resulting AML1/ETO protein have been intensively studied. The AML1 moiety of the fusion protein retains the DNA binding activity, whereas the ETO moiety conveys several new properties to the fusion molecule including: (1) several docking sites for the corepressors SMRT, N-CoR and Sin3A and the histone deacetylases HDAC1, 2 and 3; (2) a dimerization domain that initiate the formation of omo-oligomers of the fusion protein, that increase its effects on target genes and associated proteins. Thus, the AML1/ETO protein can function as a transcriptional repressor of AML1-regulated genes. However, this is only part of the story. The AML1/ETO fusion protein appears to exert its effects in different manners (Table 1 lists some examples). Actually, a direct transcriptional repression by AML1/ETO through the AML1 DNA-binding activity has been demonstrated for few genes, notably the cell cycle regulator $p14^{ARF}$ and the tumor suppressor neurofibromatosis-1 (NF1).[16,17] A number of transcription factors are repressed because of their physical interaction with the AML1/ETO protein. Likely, the

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Table 1 **Examples of putative or established epigenetic targets of AML1/ETO**

	Target	Biological function	Mechanism of targeting by AML1/ETO
↑	Plakoglobin	Hematopoietic stem/progenitor cells self-renewal	Unidentified epigenetic deregulation[23]
↑	Jagged1		Unidentified epigenetic deregulation[24]
↓	C/EBPα	Hematopoietic lineage regulators	Physical interaction blocking C/EBPα auto-regulation[18]
↔	PU.1		Physical interaction[20]
↔	GATA-1		Inhibition of GATA-1 acetylation[21]
↓	E proteins		Displacement of coactivators at E-box site[22]
↓	microRNA-223		Binding to AML1 consensus[40]
↓	GM-CSF	Colony-stimulating factors	Inhibition of AML-1b activity[53]
↓	Interleukin-3		Binding to AML1 consensus[54]
↓	c-FMS	Macrophage colony-stimulating factor receptor	Binding to the intronic AML1 consensus[55]
↓	Lysozyme	Myelomonocytic granule protein	Unidentified epigenetic deregulation[56]
↔	RARα-RXR	Retinoid receptors	Physical interaction[19]
↓	$p14^{ARF}$	Cell cycle and apoptosis regulators	Binding to AML1 consensus[16]
↑	BCL-2		Binding to AML1 consensus[57]
↓	NF1	Oncogenes or oncosuppressor	Binding to AML1 consensus[17]
↑	c-jun		Activating Jun N-terminal kinase (JNK) pathway[58]

The arrows indicate the up (↑), down (↓) or unchanged (↔) expression levels of putative or established AML1/ETO-epigenetic targets classified according their biological function. Reference numbers are indicated.

repressor protein complex carried by AML1/ETO is driven to target genes of these transcription factors and affects their activity. This control mechanism involves key regulators of hematopoietic differentiation, such as the CCAAT/enhancer binding protein C/EBPα, PU.1 and the retinoid receptor RARα-RXR heterodymer.[18-20] The same mechanism, based on a direct protein:protein interaction and displacement of p300/CBP coactivators, blocks the activity of hematopoietic regulator GATA-1 and of a subset of E-box binding proteins (E proteins), including E2A, HEB and E2-2.[21,22] Further complexity to the functional activity of AML1/ETO, is added by studies, mostly originated by microarray screenings, showing that the expression of this fusion protein can induce upregulation of gene expression. Significantly, more in depth analysis of the mechanisms underlying AML1-ETO induced gene upregulation revealed that, in some cases, this effect depends on the corepressor binding moiety of AML1/ETO, thus suggesting that unidentified epigenetic mechanisms mediate the transcriptional effects. Among the genes upregulated by AML1/ETO, the induction of Jagged1, suggests that the Notch pathway may be affected, while induction of Plakoglobin and β-Catenin indicate that AML1/ETO can increase the activity of the Wnt signaling system.[23,24] In this context, it is biologically relevant that the expression of AML1/ETO into hematopoietic stem/precursor extend their self-renewal potential, while it blocks the proliferation and differentiation of committed myeloid progenitors in vitro, and causes pre-leukemic myeloproliferative disorders in vivo.[16,25-27]

Recent evidence suggests microRNA (miRNA) genes as new epigenetic targets in cancer. Their altered regulation by oncogenic proteins and specifically by leukemia fusion proteins is potentially of great relevance in the pathogenesis of leukemia. MiRNAs are noncoding RNA of 19–24 nucleotides encoded by phylogenetically conserved genes. MiRNAs derive from long, capped and polyadenylated stem-loop precursor (pri- and pre-miRNAs) processed by the RNase III endonuclease Drosha and Dicer. The precursor RNAs can be transcribed from independent transcriptional unit or derive from intronic/exonic gene regions. MiRNAs inhibit protein translation or induces mRNA degradation, respectively through an imperfect or perfect base pair binding to the 3- untranslated (UTR) sequences of target mRNAs.[28,29] The imperfect matching between miRNAs and their targets implies that each miRNA can bind different mRNAs. Moreover, recent evidences suggest that miRNAs can bind to the 5' UTR and, in specific conditions upregulation of translation can result from their binding to mRNA.[30,31] Overall, in normal cells every miRNA posses an enormous regulatory potential. To date, >500 miRNAs are known in humans. They are involved in diverse physiological processes including development, cell differentiation, proliferation and apoptosis. MiRNA expression is indeed, highly regulated according to the cell's developmental lineage and show restricted expression profiles in adult tissues, including the haematopoietic cell system.[28,29,32] MiRNA expression profiles have shown unique miRNA signatures relevant for the pathogenesis, diagnosis and prognosis of myeloid and lymphoid leukemias.[33-35] Interestingly, similarly to lineage-specific hematopoietic transcription factors, miRNAs expressed in hematopoietic cells have been found mutated or altered by chromosomal translocations in diverse leukemias, indicating their role in the pathogenesis of these malignancies.[36] MiRNAs and their targets genes are now regarded as a potential new class of tumor suppressors or oncogenes. Moreover, a potential oncogenic role of altered miRNA activities has been reported as a consequence of hypermethylation of their genomic regions, thus unraveling a still largely unexplored area dealing with the epigenetic transcriptional silencing of miRNA genes in tumor development and progression.[37-40]

Very little is known, however, about transcriptional regulation of miRNA genes and on the factors responsible for their basal and tissue-specific expression. Evidence indicates that the information for transcription and sequential processing of miRNAs are present in the upstream regions of their genes. In general, these regions contain a

larger number of regulatory motifs when compared to the promoters of protein-coding genes.[41] Interestingly, miRNAs and transcription factors regulating their function can control each other function in negative feedback loops.[40,42-46] We recently described a direct correlation between the transcriptional and epigenetic regulation of miRNA-223, a miRNA highly specific for hematopoietic cells, and the differentiation fate of myeloid precursors.[35,42,47,48] During myelopoiesis miRNA-223 levels rise progressively and the suppression of this increase blocks granulocytic maturation. We found that miRNA-223 levels are modulated by the competitive binding to its upstream region of two CCAAT-box binding proteins, the Nuclear Factor I (NFI-A)[49] and the C/EBPα,[50] for CAAT elements present on the pre-miRNA-223 promoter.[42] NFI-A maintains miRNA-223 at low levels, while its replacement by RA-induced C/EBPα activation results in miRNA-223 upregulation and granulocytic differentiation. Moreover, we identified and validated NFI-A as a miRNA-223 target.[42] Of note that C/EBPα is a transcription factor involved in myeloid differentiation and in the repression of genes promoting cell growth, whereas NFI-A has been implicated in DNA replication and in the control of cell growth.[49-51]

The importance of miRNA-223 in the regulation of myeloid differentiation prompted us to investigate the possibility that leukemia fusion proteins could epigenetically inhibit its expression. We found that miRNA-223 is a direct transcriptional target of the AML1/ETO.[40] The expression of AML1/ETO triggers the heterochromatic silencing of genomic regions generating the miRNA-223 by recruiting diverse chromatin remodeling enzymes at an AML1-binding site present on the pre-miRNA-223 gene. Thus, miRNA-223 is one of the genes that can be directly repressed by the AML1/ETO fusion protein by virtue of its own transcriptional activity. The effects of AML1/ETO on miRNA-223 gene include both histone deacetylation and DNA methylation. Epigenetic miRNA-223 gene silencing can be reversed by pharmacological treatment with demetylating agents that also restored myeloid differentiation in t(8;21)-AML blasts in vitro. The relevance of the miRNA-223 silencing was also highlighted by the consequences of its ectopic expression that, alone, is sufficient to reprogram myeloid differentiation in distinct myeloid leukemia subtypes, independently from the presence of a specific genetic lesion.[40,42] Therefore, miRNA-223 appears as an additional pathogenetic target for a leukemia fusion protein, which may represent a key event linking the epigenetic silencing of a miRNA locus to the differentiation block of myeloid precursors underlying leukemogenesis.

The potential biological implications of this regulation are far-reaching. Since each miRNA represses the expression of multiple target proteins, the suppression of its expression expands the oncogenic activity of the fusion protein, involving genes that are not regulated by AML1/ETO with any of the mechanisms described above. In addition, novel mechanisms of action of miRNAs are being discovered, including their nuclear localization, their binding to the 5' UTR, their ability to modify mRNA stability and to increase protein expression.[30,31,52] The complexity of the biological activities of either miRNAs or AML1/ETO oncoprotein may explain the complex patterns of protein coding and non-coding genes found in microarray-based or proteomic expression screenings. Transcription factors, miRNAs and chromatin remodeling activities may act as ultimate determinants for the correct organization of cell-type specific gene programs in hematopoietic differentiation, whose de-regulation cause the differentiation block underlying the pathogenesis of different myeloid leukemia subtypes.

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