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MLL-r Leukemia

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Introduction

25 years ago the HTRX, HRX, ALL-1, MLL gene, now renamed to KMT2A, has been discovered at chromosome 11q23 and shown to be rearranged with two different genes, AF4 and ENL, due to balanced chromosomal translocations. These two chromosomal translocations - discovered in the labs of Carlo Croce and Michael Cleary-were the starting point for a new field of research associated with acute leukemia [1,2].

Until today, more than 80 genes have been discovered to be fused with the Centro metric portion of the MLL gene (direct MLL fusions), all diagnosed from bone marrow aspirates containing the leukemic cells in AML, ALL or MLL patients [3]. Noteworthy, reciprocal MLL alleles (fusing "translocation partner genes" with the telomeres portion of the MLL gene) have been identified in the same patients and have been also characterized (n=120). This leads to a rather complex picture of genetic rearrangements, with partner genes that encode proteins that exert their biological activity in nearly all cellular compartments.

In general, the MLL protein is hydrolyzed by Taspase1 [4] and forms a multiprotein complex that is necessary for marking up and to activate promoters of transcribed genes in a given human cell [5-7]. This process requires bound transcription factors on target promoters (ubiquitous and specific ones). The link between MLL and these transcription factors comes with MENIN and LEDGF, both bound to the very N-Terminus of the MLL protein complex. At least for MENIN we know that it is able to directly interact with a large variety of many different transcription factors. Due to this interaction, specific chromatin marks are being set that allow binding of RNA polymerase II.

Noteworthy, direct MLL fusion proteins bind to subset of MLL target genes. In all yet investigated cases, these MLL-X fusion proteins cause a dramatic activation of gene transcription of these target genes. To this end, direct MLL fusion complexes behave like a dominant-positive versions of the wild type MLL protein complex.

Vice versa, reciprocal X-MLL fusions exhibit quite specific properties that depend on the fusion partner. Moreover, 4 out of 5 tested reciprocal X-MLL fusion proteins displayed clear oncogenic features [8,9]. Thus, a picture emerges where MLL-r leading to AML are depend on direct MLL fusions, while reciprocal MLL fusions may account for ALL diseases.

This large plethora of MLL fusion partners have led to the hypothesis that direct MLL fusions are the driver of the leukemia disease. This is obviously true for AML which is usually associated with an increase of HOXA gene transcription in conjunction with MEIS1 [10]. The latter genes are directly targeted by the direct MLL fusion proteins and transcription is therefore enhanced. However, there are also data available where reciprocal MLL fusions, not associated with any HOXA or MEIS1 gene activation, can exert oncogenic activities as well.

So the emerging picture is quite complex and not as straight forward as assumed years ago. This is important to know because most efforts trying to develop novel drugs for the treatment of MLL-r acute leukemia are targeting the MLL-X fusions (BETi, MEN1i, DOT1Li, etc.). So it can be assumed that these novel drugs will show therapeutic effects in AML patients, but will potentially fail in ALL patients [11].

Therefore, new approaches have to be taken into account. We have shown exemplarily for the most frequent t (4;11) translocation - associated with proB ALL - that there are indeed novel treatment options. Treatment of cells expressing MLL-AF4 or AF4-MLL with HDACi showed that (1) MLL-AF4 can be competitively inhibited in its oncogenic function by the reactivation of endogenous MLL (inhibition of HDAC1 and HDAC1), and that (2) AF4-MLL can be compromised as well because the bound P-TEFb needs HDAC3 activity [12,13]. Moreover, we have shown that a dominant negative form of Taspase1 is also able to "cure" the cells from the oncogenic AF4-MLL fusion protein [8], by simply inducing a rapid turn-over [14]. In all these experiments, wild type proteins were not affected, which is important in terms of finding a "better treatment" modality.

Conclusion

MLL-r leukemia is an important disease entity and MLL-r leukemia patients still have a poor outcome. Diagnosis of MLL-r leukemia is a challenging task and being provided to the scientific community at no costs by the Frankfurt "Diagnostic Center of Acute Leukemia" (DCAL; http://web.uni-frankfurt.de/fb14/dcal). The pathology of MLL-r leukemia is also challenging and far away from being understood. We can recapitulate the disease in the murine model system when using a few MLL fusions, but many studies using other MLL fusions have failed already. Therefore, we still have several questions that need to be solved in the future: (1) why a disease progression in humans is quick (infant leukemia) while taking 6-12 months when testing the same oncoprotein in murine cells; (2) what are the precise target cells that are permessive for distinct MLL fusions; (3) why there is "latency in disease devoplement" when secondary mutations are not required; (4) what is the precise mechanisms of oncogenic transformation. There is plenty to do...let's get started.

References

1. Gu Y, Nakamura T, Alder H, Prasad R, Canaani O, et al. (1992) The t(4;11) chromosome translocation of human acute leukemias fuses the ALL-1 gene, related to Drosophila trithorax, to the AF-4 gene. Cell 71: 701- 708.

2. Tkachuk DC, Kohler S, Cleary ML (1992) Involvement of a homolog of Drosophila trithorax by 11q23 chromosomal translocations in acute leukemias. Cell 71: 691-700.
3. Meyer C, Hofmann J, Burmeister T, Gröger D, Park TS, et al. (2013) The MLL recombinome of acute leukemias. Leukemia 27: 2165-2176.
4. Hsieh JJ, Cheng EH, Korsmeyer SJ (2003) Taspase1: a threonine aspartase required for cleavage of MLL and proper HOX gene expression. Cell 115: 293-303.
5. Marschalek R (2011) Mechanisms of leukemogenesis by MLL fusion proteins. Br J Haematol 152: 141-154.
6. Scholz B, Marschalek R (2012) Epigenetics and blood disorders. Br J Haematol 158: 307-322.
7. Marschalek R (2016) Systematic Classification of Mixed-Lineage Leukemia Fusion Partners Predicts Additional Cancer Pathways. Ann Lab Med 36: 85-100.
8. Bursen A, Schwabe K, Rüster B, Henschler R, Ruthardt M, et al. (2010) AF4-MLL is capable of inducing ALL in mice without requirement of MLL-AF4. Blood 115: 3570-3579.
9. Wächter K, Kowarz E, Marschalek R (2014) Functional characterization of different MLL fusion proteins by using inducible Sleeping Beauty vectors. Cancer Letters 352: 196-202.
10. Ayton PM, Cleary ML (2001) Molecular mechanisms of leukemogenesis mediated by MLL fusion proteins. Oncogene 20: 5695-5707.
11. Marschalek R (2015) MLL Leukemia and Future Treatment Strategies. Arch Pharm (Weinheim) 348: 221-228.
12. Ahmad K, Katryniok C, Scholz B, Merkens J, Löscher D, et al. (2014) Inhibition of class I HDACs abrogates the dominant effect of MLL-AF4 by activation of wild-type MLL. Oncogenesis 3: e127.
13. Ahmad K, Scholz B, Capelo R, Kahn AS, Marschalek R, et al. (2015) AF4 and AF4-MLL mediate transcriptional elongation of 5-lipoxygenase mRNA by 1,25-dihydroxyvitamin D3. Oncotarget 6: 25784-25800.
14. Sabiani S, Geppert T, Engelbrecht C, Kowarz E, Schneider G, et al. (2015) Unraveling the activation mechanism of Taspase1 which controls the oncogenic AF4-MLL fusion protein. EBioMedicine 2: 386-395.