A Meta-Narrative Review of RUNX1-RUNX1T1 and its Relativity to CBF Disruption Within the Adult Population

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Guiding Research Question

If RUNX1-RUNX1T1 gene fusion is present, is there a block in differentiation through disruption of the CBF complex, influencing AML diagnosis and treatment?

Background Information

- Acute Myeloid Leukemia (AML) is an aggressive subgroup of leukemias developed from a deviant hematopoietic stem cell, prevented from differentiating into a mature cell.

- Core Binding Factor (CBF) is disrupted by the translocation of chromosomes 8 and 21. This balanced translocation generates the RUNX1-RUNX1T1 fusion gene on the derivative chromosome 8, resulting in t(8;21)(q22;q22.1). These events cause a blockage of hematopoietic stem cell differentiation and ultimately lead to leukemia transformation (Beghini, A. 2019).

- Using Fluorescence in situ hybridization (FISH) and Karyotyping, molecular translocation can be detected, visualized, and associated with chromosomes 8 and 21 [t(8;21)(q22;q22)].

- A multitude of treatments are used in CBF AML, such as: Chemotherapy, High Dose Anthracycline/Cytarabine (HDAC), and Gemtuzumab Ozogamicin (GO). (Beghini, A. 2019; Borthakur, et al. 2021; Kuykendall, et al. 2018). The impact of mutations and chromosomal abnormalities influence the outcome in AML.

Significance of the Study

Although it is mostly seen in children, CBF AML represents 10–15% of adult AML diagnosis. (Opatz, et al., 2020). This form of leukemia is difficult to treat due to the impact of mutations, chromosomal abnormalities, and clinical variables that influence the outcome in AML (Opatz, et al., 2020). **This study will investigate how gene fusion and translocation disrupt core binding factor (CBF) for the purpose of understanding how AML is diagnosed and treatment.**

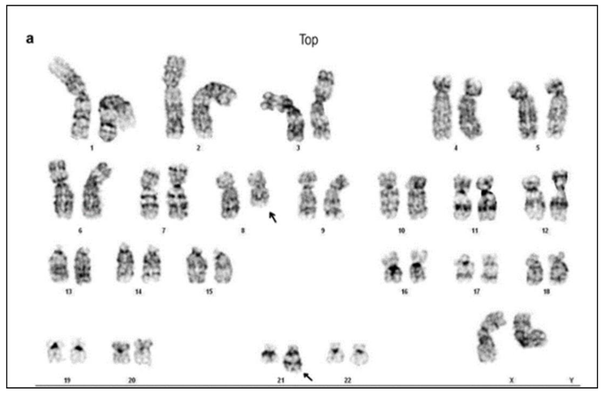

Figure 1: Conventional cytogenetic analyses of AML-M4 with t(8;21)(q22;q22)). ***a***. G-banded karyogram of 19/20 marrow cells metaphases. Arrows indicate the t(8;21) translocation.

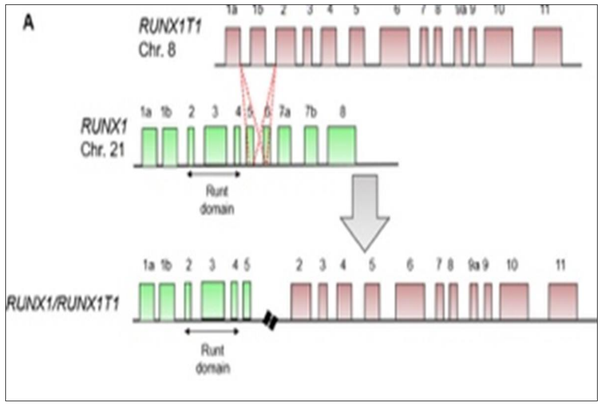

Figure 2: Structure of the RUNX1/RUNX1T1 fusion gene and protein (Swart & Heidenreich, 2021)

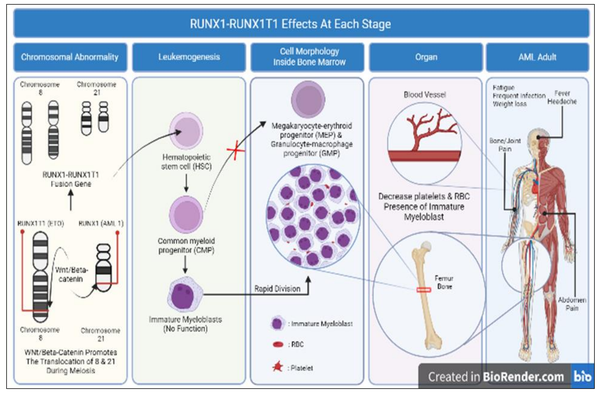

Figure 3: This chart provides an insight into the consequences of the RUNX1/RUNX1T1 fusion gene at its origin in the chromosomal level.to the visible symptoms on the human body.

Methodology

	PubMed (nih.gov)	Atlasgeneticsoncology.org
Identification	Records identified through database searching (n = 970)	Additional records identified through other sources (n = 100)
	Keywords: Acute Myeloid Leukemia (AML): (n = 940) t(8;21)(q22;q22): (n = 100) RUNX1-RUNX1T1 fusion gene: (n = 6) Core Binding Factor (CBF): (n = 24)	
Screening	**Records after filtering and duplicates removed (n = 1063)**	
	Records screened (n = 7)	Records excluded (n = 3)
	Studies relating to our research topic. **Keywords**: Acute Myeloid Leukemia (AML) t(8;21)(q22;q22) RUNX1-RUNX1T1 fusion gene Core Binding Factor (CBF)	**Duplication of Information (Sample Size and Methods)** Diversion from our topic and methods
Eligibility	**Full-text articles assessed for eligibility (n = 4)**	**Full-text articles excluded, with reasons (n = 3) Duplication of Information (Sample Size and Methods)**
Included	**Studies included in qualitative synthesis (n = 4)**	

Table 1: Research Process Flowchart

Inclusion:

- Patients with RUNX1/RUNX1T1-rearrangement (age in years, median (range) 54 (16–79)) and diagnosed with CBF Leukemia.
- Translocation between chromosomes 8 and 21 [t(8;21)(q22;q22)] underlies the RUNX1/RUNX1T1 fusion.

Exclusion:

- AML with other mutated genes:
  - FLT3, NPM1, DNMT3A, IDH1, IDH2, TET2, TP53, NRAS, CEBPα, and WT1
- RUNX1 in other various types of hematological malignancies:
  - acute lymphoblastic leukemia (ALL), myelodysplastic syndromes (MDS), myeloproliferative neoplasm (MPN), chronic myelomonocytic leukemia (CMML), congenital bone marrow failure (CBMF)
- inv(16)(p13q22): CBFB-MYH11 fusion, block of RUNX1 transcription program

Results

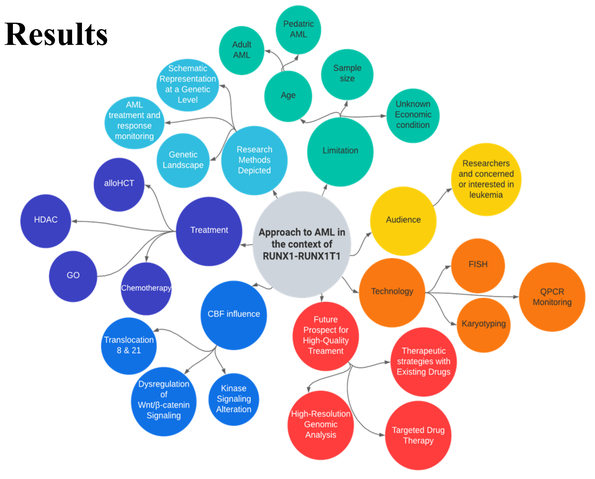

Figure 4: Displayed is a meta-narrative review of the number of articles that correspond to each sub-theme of the approach to AML in the context of RUNX1-RUNX1T1 fusion gene, including the utilization of treatments, its detail on correlation to CBF complex, how the research method was depicted, limitations, audience, technology, and treatment

Discussion

The study objectives focused on 1) understanding the mechanisms of CBF and RUNX1/RUNX1T1, one of the leukemia-causing mutations and 2) the differentiation and development of targeted therapy approaches in CBF leukemia.

Moreover, CBF can influence the AML diagnosis and the therapy used to treat the cancer. Two component factors of CBF are RUNX1 and RUNX1T1. Bone marrow sampling is tested for chromosomal abnormalities by karyotyping and FISH. Although, the presence of additional cytogenetic abnormalities does not predict the outcome in t(8;21) AML, (Grimwade, et al. 2022) further molecular studies are performed to detect specific mutations in genes which may influence the outcome of the disease, (Beghini, A. 2019.) Additionally, the use of high-resolution genomic analysis may assist in understanding the heterogenous nature of AML and lead to the development of new targeted strategies for CBL AML.

Strengths

The articles involved were selected by the association of RUNX1/RUNX1T1 to AML in adults leading to cytogenetic abnormalities in CBF function. Furthermore, the focus was on a CBF AML subgroup, and the specifics of treatments were clear, precise, and abundant with information.

Conclusion

One of the most important aspects of the study was the understanding of genetic abnormalities and the use of genetic analysis in developing future treatment strategies for leukemia. The correlation of RUNX1-RUNX1T1 gene generated on the derivative chromosome 8 will result in t(8;21)(q22;q22.1), a balanced translocation.

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