WHITEPAPER

FISH and Cytogenetic Analysis: Probing for CLL and MDS

EMPIRE GENOMICS
a Biocare Medical Company

BIOCARE MEDICAL

FISH and Cytogenetic Analysis: Probing for CLL and MDS

Fluorescence in situ hybridization (FISH) probes have become a cornerstone of cytogenetic analysis in hematological malignancies. These targeted probes allow for the detection of specific chromosomal abnormalities associated with various leukemias and myelodysplastic syndromes (MDS). This white paper will explore the importance of certain FISH probes for Chronic Lymphocytic Leukemia (CLL) and Myelodysplastic Syndromes (MDS), focusing on:

- **ATM/TP53 extended and D13S319/LAMP1/CON12 Extended FISH probes for CLL:** These probe sets target critical chromosomal regions frequently involved in CLL.

- **MECOM Break Apart FISH probes for MDS:** This probe set detects rearrangements of the MECOM gene, a crucial abnormality in a subset of MDS patients.

CLL and FISH Probes

Chronic Lymphocytic Leukemia (CLL) is the most common chronic leukemia in adults, and one of the most common leukemias according to the American Cancer Society. Specific chromosomal aberrations are associated with disease prognosis and treatment response. FISH probes offer a rapid and sensitive method for detecting these abnormalities.

- **ATM/TP53 Extended FISH probes:**
  - o Deletions on chromosome 11q can occur in CLL, and when they do, the ATM gene (11q22.3) is lost in this region. The ATM gene plays a vital role in DNA damage response, and loss of ATM function can contribute to disease progression.[1]
  - o TP53 (17p13.1) is a tumor suppressor gene that has been found to be mutated or deleted in cases of CLL. TP53 dysfunction can lead to uncontrolled cell growth.[2]

- **D13S319/LAMP1/CON12 Extended FISH probes:**
  - o Deletions on chromosome 13q are another abnormality in CLL.
  - o D13S319 (13q14.2) deletions have been found in 10-29% of CLL cases.[3] Researchers are continually trying to locate a potential tumor suppressor gene that might be located near this chromosome area.
  - o The LAMP1 gene codes for a glycoprotein called lysosomal-associated membrane protein 1 (LAMP-1), which helps break down waste, foreign materials, and can act as an activation marker for releasing molecules to fight infection. LAMP1 (13q34) deletions occur less frequently but may hold prognostic significance.[4]
  - o Trisomy of chromosome 12 can be found in around 20% of CLL cases. The alteration is associated with atypical morphological and immunophenotypic features, high proliferative rates, and NOTCH1 mutations.[5]

Clinical Significance in CLL

The identification of chromosomal aberrations using FISH probes can impact the clinical management of CLL patients:

- **Risk Stratification:** Certain FISH abnormalities, like deletions TP53 or ATM, are associated with a more aggressive disease course and poorer prognosis.[6]

- **Treatment Selection:** FISH results can help guide treatment decisions. 13q deletions were found to have a favorable clinical course and best overall survival.[7]

- **Monitoring Response:** FISH probes can be used to monitor a patient's response to treatment by tracking the biological fitness of patients, especially in cases of CLL with TP53 defects.[8]

MDS and MECOM Break Apart FISH Probes

MDS is a group of bone marrow disorders characterized by abnormal blood cell production, according to the American Cancer Society. FISH and cytogenetic analysis play a crucial role in potentially diagnosing and classifying MDS subtypes.

- **MECOM Break Apart FISH probes**:
  - o MECOM, located on chromosome 3q26, encodes a protein involved in normal cellular development.
  - o Rearrangements of the MECOM gene are found in a subset of MDS patients, particularly those with poor prognoses.[9]
  - o The gene is frequently mutated in hematological malignancies of myeloid origin, including acute myeloid leukemia (AML)[10]
  - o AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2) is a WHO-recognized disease entity, characterized by aberrations involving MECOM at 3q26.2 and RPN1 (ribophorin I) at 3q21.[10]

Clinical Significance in MDS

The identification of MECOM rearrangements using FISH probes has significant implications for MDS patients:

- **Diagnosis:** MECOM abnormalities can help confirm a diagnosis of MDS, particularly in cases with complex cytogenetics.[11]
- **Prognosis:** The presence of MECOM rearrangements may also associated with a higher risk of developing MDS associated acute myeloid leukemia (AML).[9,11]
- **Treatment Decisions:** Studies have found that identifying high-risk patients with MECOM abnormalities may influence treatment approaches because of the poor prognosis. Many different clinical studies are being investigated that could affect future prognosis.[12]

Conclusion

FISH probes like ATM/TP53 extended, D13S319/LAMP1/CON12 extended, and MECOM Break Apart FISH probes play a vital role in the cytogenetic analysis of CLL and MDS. These targeted probes provide valuable information for risk stratification, treatment selection, and monitoring disease course. As our understanding of these malignancies continues to evolve, the role of FISH probes is likely to become even more crucial in guiding personalized medicine approaches for patients with CLL and MDS.

To learn more about the science of FISH and the associated FISH probes, please visit our website at www.empiregenomics.com
Or send us an e-mail info@empiregenomics.com

1. Guarini A, Marinelli M, Tavolaro S, Bellacchio E, Magliozzi M, Chiaretti S, De Propris MS, Peragine N, Santangelo S, Paoloni F, Nanni M, Del Giudice I, Mauro FR, Torrente I, Foà R. ATM gene alterations in chronic lymphocytic leukemia patients induce a distinct gene expression profile and predict disease progression. Haematologica. 2012 Jan;97(1):47-55. doi: 10.3324/haematol.2011.049270. Epub 2011 Oct 11. PMID: 21993670; PMCID: PMC3248930.

2. Campo E, Cymbalista F, Ghia P, Jäger U, Pospisilova S, Rosenquist R, Schuh A, Stilgenbauer S. TP53 aberrations in chronic lymphocytic leukemia: an overview of the clinical implications of improved diagnostics. Haematologica. 2018 Dec;103(12):1956-1968. doi: 10.3324/haematol.2018.187583. Epub 2018 Nov 15. PMID: 30442727; PMCID: PMC6269313.

3. Khalid K, Padda J, Syam M, Moosa A, Kakani V, Sanka S, Zubair U, Padda S, Cooper AC, Jean-Charles G. 13q14 Deletion and Its Effect on Prognosis of Chronic Lymphocytic Leukemia. Cureus. 2021 Aug 2;13(8):e16839. doi: 10.7759/cureus.16839. PMID: 34522485; PMCID: PMC8424995.

4. Antić D, Dencić-Fekete M, Tomin D, Djunić I. Monosomy 12 and deletion of 13q34 in a case of chronic lymphocytic leukemia with concomitant lung cancer. Vojnosanit Pregl. 2010 Oct;67(10):864-6. doi: 10.2298/vsp1010864a. PMID: 21061845.

5. Tsagiopoulou M, Chapaprieta V, Duran-Ferrer M, Moysiadis T, Psomopoulos F, Kollia P, Papakonstantinou N, Campo E, Stamatopoulos K, Martin-Subero JI. Chronic lymphocytic leukemias with trisomy 12 show a distinct DNA methylation profile linked to altered chromatin activation. Haematologica. 2020 Dec 1;105(12):2864-2867. doi: 10.3324/haematol.2019.240721. PMID: 33256389; PMCID: PMC7716362.

6. Puiggros A, Blanco G, Espinet B. Genetic abnormalities in chronic lymphocytic leukemia: where we are and where we go. Biomed Res Int. 2014;2014:435983. doi: 10.1155/2014/435983. Epub 2014 May 22. PMID: 24967369; PMCID: PMC4054680.

7. H Beverly P. Nelson, Rohit Gupta, Gordon W. Dewald, Sarah F. Paternoster, Steven T. Rosen, LoAnn C. Peterson, Chronic Lymphocytic Leukemia FISH Panel: Impact on Diagnosis, American Journal of Clinical Pathology, Volume 128, Issue 2, August 2007, Pages 323–332, https://doi.org/10.1309/21TN2RUWKR827UW2

8. Zent CS, Kay NE. Management of patients with chronic lymphocytic leukemia with a high risk of adverse outcome: the Mayo Clinic approach. Leuk Lymphoma. 2011 Aug;52(8):1425-34. doi: 10.3109/10428194.2011.568654. Epub 2011 Jun 8. PMID: 21649549; PMCID: PMC3448554.

9. Chantana Polprasert, Chantiya Chanswangphuwana, Weerapat Owattanapanich, Smith Kungwankiattichai, Ekarat Rattarittamrong, Thanawat Rattanathammethee, Wasithep Limvorapitak, Supawee Saengboon, Pimjai Niparuck, Teeraya Puavilai, Jakrawadee Julamanee, Pirun Saelue, Chinadol Wanitpongpun, Chajchawan Nakhakes, Kannadit Prayongratana, Chantrapa Sriswasdi, Adisak Tantiworawit; Clinical Characteristics and Outcomes of Myeloid Neoplasms with Mecom Rearrangement: Results from a Nationwide Multicenter Study. Blood 2023; 142 (Supplement 1): 4213. doi: https://doi.org/10.1182/blood-2023-180100

10. Bobadilla, D., Enriquez, E. L., Alvarez, G., Gaytan, P., Smith, D., & Slovak, M. L. (2007). An interphase fluorescence in situ hybridisation assay for the detection of 3q26.2/evi1 rearrangements in myeloid malignancies. British Journal of Haematology, 136(6), 806–813. https://doi.org/10.1111/j.1365-2141.2007.06505.x

11. Liu K, Tirado CA. MECOM: A Very Interesting Gene Involved also in Lymphoid Malignancies. J Assoc Genet Technol. 2019;45(3):109-114. PMID: 31554743.

12. Demir D. Insights into the New Molecular Updates in Acute Myeloid Leukemia Pathogenesis. Genes (Basel). 2023 Jul 10;14(7):1424. doi: 10.3390/genes14071424. PMID: 37510328; PMCID: PMC10378849.