

## The MEFV gene and clonal myeloid disorders

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The relationship between the MEFV gene (MEFV), which is mutated in familial Mediterranean fever (FMF) disease and located on 16p13.3, and clonal myeloid disorders has been a subject of concern, and there have been studies undertaken in an effort to explain this situation<sup>1-3</sup>. In these studies, it was speculated that MEFV is a cancer susceptibility gene because the protein encoded by this gene, pyrin, is closely related with interleukin-1 $\beta$  (IL-1 $\beta$ ) and nuclear factor- $\kappa$ B (NF- $\kappa$ B) pathways, which play a part in carcinogenesis. It is proposed that when the mutations in MEFV alter pyrin synthesis, the subsequent abnormalities developing in either pyrin structure or function disrupt these pathways and lead to development of myeloid malignancy. Therefore, point mutations in MEFV in patients with myeloid neoplasms were analyzed. However, each study resulted in similar but unexplainable results with this hypothesis, suggesting the presence of a relationship developing via other mechanisms. Recent evidence suggests that  $\alpha$ -thalassemia myelodysplastic syndrome (ATMDS) might be one of those alternative mechanisms. ATMDS is an acquired form of  $\alpha$ -thalassemia that arises in the context of a clonal myeloid disorder<sup>4,5</sup>. This condition may develop with deletions in the  $\alpha$ -globin gene on chromosome 16 in band 16p13.3 neighboring MEFV, and is a well-characterized acquired disorder in patients with hematologic malignancy. In this yet to be enlightened relationship, ATMDS seems to explain the results achieved in the studies that could not be explained by the previous hypothesis. Therefore, we herein want to draw attention to this clinical condition.

The basic hypothesis of the studies is the fact that disruption in pyrin synthesis is responsible for carcinogenesis via some mediator pathways. It is considered that the genetic variants that disrupt pyrin synthesis are the point mutations in MEFV. If this hypothesis is correct, the most devastating form of point mutations

should be the homozygous or compound heterozygous forms, and these forms are expected to be the most frequently detected form in the cancer patients studied. However, the most frequently detected form in patients was clearly heterozygosity<sup>1</sup>. Thus, the MEFV mutations that disrupt the pyrin synthesis should be a genetic alteration other than point mutations. Regardless of the type of genetic alterations, if the mediator mechanisms in cancer development are the IL-1 $\beta$  and NF- $\kappa$ B pathways, as suggested by the studies, the corresponding MEFV changes should also be detected in patients with all other hematologic malignancies in which these pathways play a part. However, of those, the MEFV changes in hematolymphoid malignancies were detected to be lower than in the general population<sup>3</sup>. Thus, the mediator mechanisms in cancer development might be pathways other than the IL-1 $\beta$  and NF- $\kappa$ B pathways. Taking into consideration these two basic results that cannot be overlapped with the previous hypothesis, one may speculate that there might be other MEFV mutations acting with other mechanisms in this relationship. With its clinical and molecular features, ATMDS might be a candidate for this role.

Acquired  $\alpha$ -thalassemia arising in the context of a clonal myeloid disorder has been termed ATMDS<sup>4-6</sup>. Although the term ATMDS is accurate in most cases, acquired  $\alpha$ -thalassemia is not unique to MDS and has been reported in patients with other malignant hematologic disorders (e.g., acute myeloid leukemia [AML], myeloproliferative disorder [MPD]). ATMDS can result from two molecular defects: 1-acquired deletion of the  $\alpha$ -globin gene cluster limited to the neoplastic clone, and 2-inactivating somatic mutations in ATRX, a chromatin remodeling gene. Although rare, deletional-type ATMDS has the potential to affect the neighboring MEFV located on 16p13.3<sup>7</sup>. On the other hand, the proteins that cause ATMDS due to their deficiency or abnormality play a

central role in  $\alpha$ -globin gene expression in normal and abnormal hematopoiesis.  $\alpha$ -globin gene expression is under a tight epigenetic regulation. Molecular aberrations in any gene whose product is predicted to play a part in this epigenetic network cause complex multisystem disorders<sup>4</sup>. As is known, myeloid malignancies are among the epigenetically best-characterized neoplasms<sup>8,9</sup>. Epigenetic lesions occur in MDS and AML, and compared with genetic lesions, they are more frequent and recurrent. Epigenetic changes in all types of myeloid malignancies are related to DNA methylation and histone acetylation<sup>4,8,9</sup>. It has been shown that aberrant DNA methylation patterning resulting from perturbed epigenetic regulation plays a role in leukemogenesis<sup>8</sup>. Indeed, the proteins that cause ATMDs due to their deficiency or abnormality are involved in the establishment or maintenance of DNA methylation<sup>4</sup>. In brief, ATMDs may have a part in this relationship, with “deletion” as the type of mutation and “epigenetic mechanism” as the pathway.

The striking result of the studies was the high frequency of heterozygosity for point mutations, as the most frequently detected MEFV variant in patients with myeloid malignancies<sup>1-3</sup>. The frequency of heterozygosity was also higher than in healthy controls (17.5% vs 16.9%)<sup>1</sup>. Why is heterozygosity higher in patients than controls, and more importantly, how can heterozygosity disturb pyrin synthesis so severely? A valid hypothesis should be able to explain these questions. This can be properly explained by the ATMDs hypothesis: myeloid neoplasms naturally develop in some FMF heterozygotes. These individuals acquire a deletion in MEFV in the context of the myeloid malignancy. In these cases, a deletion and a single mutation of FMF in MEFV are present, and pyrin synthesis is disturbed as severely as seen in the homozygous form. If the patients are from a population with a high frequency of FMF, as was seen in these studies, the point is in question in more cases. Further, when patients with hematologic neoplasms are studied, this coexistence is encountered more frequently. Namely, the cases are selected FMF heterozygotes and the carrier frequency of MEFV variants in these patients is found to be higher than in the normal population. As is known, ATMDs is suggested to be more

common than generally realized<sup>5</sup>. The second remarkable result is the fact that the highest rate of heterozygosity among hematologic malignancies was found to be in MDS (27.3% vs 10.7%)<sup>1,2</sup>. This result is a contributing finding to ATMDs. Although ATMDs has been reported in patients with other malignant hematologic disorders, it is more commonly associated with MDS<sup>4</sup>. Therefore, heterozygosity is expected to be higher in patients with myeloid neoplasm than in healthy controls, and higher in MDS compared to other malignant hematologic disorders, as was also observed in these studies.

In conclusion, we suggest that ATMDs may explain the results of the previous studies and may play a part in this relationship under the scope. The deletional subtype of ATMDs may be one of the MEFV mutations seen in myeloid malignancies. If only the point mutations are assessed as MEFV variants, this genetic change might be missed. Designing further studies to include the entire gene with its microenvironment would contribute to determining the actual role of MEFV in myeloid malignancies.

**Key words:** MEFV gene, 16p 13.3 location, deletion,  $\alpha$ -thalassemia myelodysplastic syndrome, malignant hematologic disorders.

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