doi: 10.3978/j.issn.2095-6959.2017.10.035
View this article at: http://dx.doi.org/10.3978/j.issn.2095-6959.2017.10.035

骨髓增生异常综合征中常见的基因突变及其临床意义

张阳[1]，刘铭[2] 综述 刘红星[1] 审校

(1. 河北燕达陆道培医院病理和检验医学科，河北 廊坊 065201；2. 青岛大学附属医院血液科，山东 青岛 266003)

[摘 要] 骨髓增生异常综合征(myelodysplastic syndrome，MDS)是一组在生物学上和临床上均表现出异质性的干细胞克隆性疾病。由于MDS在诊断、治疗、临床预后和疾病监测中缺乏特异性的标志物，经常为正确诊治带来困扰。随着分子生物学研究的进展，目前已鉴定与MDS发病相关的突变基因超过50种。这些基因突变的组合与MDS的发生、发展、药物治疗反应和预后密切相关，为MDS的诊治提供了重要的依据。

[关键词] 骨髓增生异常综合征；基因突变；突变组；精准医疗

Gene mutations and its clinical significance in myelodysplastic syndrome

ZHANG Yang[1], LIU Ming[2], LIU Hongxing[1]

(1. Division of Pathology & Laboratory Medicine, Hebei Yanda Lu Daopei Hospital, Langfang Hebei 065201;
2. Department of Hematology, Affiliated Hospital of Qingdao University, Qingdao Shandong 266003, China)

Abstract Myelodysplastic syndrome (MDS) is a group of stem cell clonal diseases that are biologically and clinically heterogeneous. Due to lack of specific markers in the diagnosis, treatment, clinical prognosis and disease monitoring of MDS, it often brings confusion for correct diagnosis and treatment. With advances in precision medicine and molecular biology, more than 50 kinds of mutant genes have been reported involved in the pathogenesis of MDS. Combination of these mutations is closely related to the occurrence and development of MDS, treatment response and prognosis, and provides an important basis for the diagnosis and treatment of MDS.

Keywords myelodysplastic syndrome; gene mutation; mutaome; precision medicine

骨髓增生异常综合征(myelodysplastic syndrome，MDS)是一组异质性的造血干细胞克隆性疾病，其特点为病态造血、无效造血致外周血细胞减少并具有向急性白血病转化的风险[1]。由于MDS在诊断、治疗、临床预后和疾病监测中缺乏特异性的标志物，经常为正确诊治带来困扰。“精准医疗”是伴随人类对疾病分子机制研究的深入而提出的新概念，最简单的定义是根据每个患者特异的临床表现和基因分子特征为其制定个体化的治疗方案[2]。近年来分子生物学研究的进展促进了MDS相关基因突变的发现和研究。现已报道有超过50种基因的突变与MDS的发生、发展、

收稿日期 (Date of reception)：2017–08–24
通信作者 (Corresponding author)：刘红星，Email: starliu@pku.edu.cn

治疗反应和预后密切相关，这些基因突变在MDS中的总阳性率可高达90%，为MDS的诊治提供了重要的依据[3-9]。

1 MDS 中常见突变基因及其致病机制

目前对MDS的病因和致病机制尚不明确，近年来随着人们对MDS的认识，其发病机制与基因突变、染色体异常、表观遗传学改变及免疫学异常相关[10]。基因突变在MDS发病中发挥关键的作用，包括原癌基因、抑癌基因、RNA剪切因子基因和表观遗传学调控相关的基因等。MDS中常见的基因突变按所属基因家族和功能可分为六大类：1)RNA剪切因子基因突变；2)表观遗传学调控基因突变；3)黏合素基因突变；4)转录因子基因突变；5)信号转导相关基因突变；6)DNA损伤修复相关基因突变。

RNA剪切因子基因，常见的有SF3B1，SRSF2，U2AF1和ZRSR2等，其突变率在MDS中高达60%[3,5,11]。其中SF3B1是最常累及的基因，其突变导致3’剪接位点的选择改变，导致与铁稳态相关基因的异常剪接，可能介导环形铁粒幼细胞表型[12]。该基因突变见于约80%的难治性贫血伴环形铁粒幼细胞增多(refractory anemia with ring sideroblast，RARS)和难治性血细胞减少伴多系发育异常和环形铁粒幼细胞(refractory cytopenia with multilineage dysplasia and ring sideroblast，RCMD-RS)患者[13-14]。不同剪接因子基因间的突变互斥，不同剪接因子基因突变可导致不同的异常剪接模式，并改变相应靶基因的丰度或功能[11,15-16]。

表观遗传学调控基因，也是MDS中较常见的突变，包括DNA甲基化调控基因TET2，DNMT3A和IDH1/2等，以及组蛋白修饰相关的基因ASXL1，EZH2，BCOR和EP300等[5]。TET2是MDS中最常见的突变之一，其突变与增强子序列中胞嘧啶高甲基化有关，可抑制对髓系分化有重要作用基因的表达[17]。组蛋白修饰相关基因ASXL1，EZH2和BCOR的突变都可导致几种重要造血谱系基因的调节异常[18-19]。

黏合素基因突变，包括STAG2，RAD21，SMC1A和SMC3等，这些基因突变分别在11%和17%的低危和高危MDS中发现，多数突变互斥[20-21]。黏合素蛋白可形成围绕DNA的环状蛋白复合体结构，有助于维持姐妹染色单体粘连，稳定DNA环以促进启动子和远端增强子之间的相互作用[22]。目前研究[23]认为：黏合素基因突变主要通过异常调节远程染色质相互作用导致基因表达水平改变来驱动MDS的发生，尚需进一步的研究证实。

转录因子基因突变，包括RUNX1，GATA2和ETV6等，这些基因既可以发生体细胞突变，也可以发生胚系突变，胚系突变常与髓系肿瘤易感相关。RUNX1参与调节多种造血相关的基因，RUNX1体细胞突变见于约10%的MDS患者，常与黏合素基因突变伴随出现[3,5,24]。GATA2基因编码的锌指转录因子高表达于HSCs，对于正常的造血分化至关重要，GATA2体细胞突变见于1%~2%的MDS患者[5,24]。

信号转导相关基因突变，包括JAK2，CBL，KIT，FLT3，MPL等基因，参与异常激活激酶等信号通路，与细胞增殖相关。与急性髓系白血病(acute myeloid leukamis，AML)、骨髓增殖性肿瘤(myeloproliferative neoplasms，MPN)相比，这些基因在MDS中的突变率相对较低(约10%)[3,5]，多见于MPN转变为MDS的患者或提示MDS向AML转变[25-28]。

DNA损伤修复相关基因突变，包括TP53和PPM1D等。TP53通过参与凋亡和细胞周期阻滞基因的表达来介导对细胞应激的反应，该途径通过磷酸酶PPM1D进行负性调节[29]。TP53是人类癌症中最常突变的抑癌基因，在MDS中也常见发生突变[30]，见于约5%的MDS患者，与低血小板和高原始细胞计数、复杂核型和化疗密切相关[6]。

2 基因突变对 MDS 精准诊断的影响

MDS的发病率随年龄增加，中位发病年龄约70岁，男性高于女性[31]。随着人口老龄化、肿瘤治疗相关MDS的增多及临床医生对MDS认知和诊断水平的提高，MDS的发病率和诊出率都有所提高[32]。诊断MDS主要有3个关键点：1)血细胞减少是MDS诊断的必要条件，在以前的分类中MDS的命名就是以全血细胞减少或特定类型的血细胞减少(例如“难治性贫血”)并排除其他血液或非血液系统引起血细胞减少的疾病。2)骨髓中发育异常血细胞比例>10%。3)通过骨髓细胞染色体核型分析、FISH、突变基因的检测发现克隆性造血[33]。

2016修订版世界卫生组织造血和淋巴组织肿瘤分类标准[1]中对MDS的分类进行了修订。与以往相比在命名上以“MDS伴相应异常”代替“难治性贫血伴相应异常”，并提出存在SF3B1基因突变时环形铁粒幼红细胞≥5%就可以归为MDS伴环形铁粒幼细胞(myelodysplastic syndrome with

ring sideroblast，MDS-RS)。SF3B1基因突变指标的增加，肯定了分子生物学在MDS诊断分型中的价值。MDS中的突变基因有50多种，超过90%的MDS患者可检测到一种以上基因突变，每种基因突变的发生率较低，发生率最高的SF3B1和TET2也仅为20%~25%[3-4]。

在正常外周血计数的健康老年个体中进行基因测序，也发现部分携带MDS相关的基因突变，而且发生率随年龄的增加而升高，常见的突变基因有TET2，SRSF2和ASXL1等。基因突变的检出提示克隆性造血的发生，这些突变携带者具有发展为造血系统恶性疾病的风险，但也有个体不会进展为MDS，因此被称为意义未明的克隆性造血(clonal hematopoiesis of indeterminate potential，CHIP)，此外，随着年龄的增加，意义未明的克隆性血细胞减少症(clonal cytopenias of undetermined significance，CCUS)也随之增加[34-36]。

基因突变的检出为MDS造血克隆性的判定提供了重要依据，也为诊断和鉴别诊断提供了重要的参考，但并非所有携带相关基因突变的病例都应该被诊断为MDS[36-37]。MDS的诊断仍应综合患者病史、体格检查、骨髓形态学、细胞遗传学、分子生物学进行全面评估。部分不典型患者需综合性、排除性诊断及长期观察随访来确诊MDS。

3 基因突变在 MDS 预后方面的影响

不同的MDS患者携带基因突变数量、种类和组合有很大不同，临床表现也存在差异性。MDS的异质性使不同个体的自然病程和预后存在很大的差异，对不同危险分层的患者选择不同治疗方案十分重要。国际上常用的MDS预后评分系统有国际预后评分系统(international prognostic scoring system，IPSS)、基于WHO分型的预后评分系统(WHO classification-based prognostic scoring system，WPSS)、修订的IPSS评分系统(revised IPSS，IPSS-R)。这些评分系统主要依据骨髓形态、细胞遗传学、血细胞减少程度等指标对患者进性危险度分层，目前还没有加入基因突变的指标。依据这些评分系统分层的相同危险度的患者，实际预后也会存在显著的差异[38]。

近年来许多研究[3,6,39]已表明突变基因的种类和突变的数目对MDS的预后有着不可替代的作用，甚至具有独立的预后价值，基因突变数目越多的MDS患者更易向AML转化，预后更差。在Papaemmanuil等[3]的报道中，只携带1种基因突变或细胞遗传学异常的MDS患者无白血病中位生存期为49个月，而携带2，3，4~5和≥6个突变的患者的中位生存期分别为42，27，18和4个月。

在单因素分析中，不同基因突变对MDS的预后也不同。TP53，EZH2，ETV6，RUNX1，ASXL1和SRSF2突变的MDS患者预后差，而SF3B1突变的患者通常预后较好[3,5]。Nazha等[40]报道将分子指标加入到IPSS-R评分系统中的研究，拟建立一种新的MDS预后模型。他们将508例确诊为MDS的患者分为两组，其中333例患者为训练集，另外175例患者验证新建的模型。他们的研究发现MDS患者重要的独立预后因素包括年龄，EZH2，SF3B1和TP53基因突变，将基因突变纳入到评价体系中可改善对MDS预后的预测能力。这些研究显示基因突变检测在MDS患者预后评价中具有很重要的价值，但由于突变基因的种类和组合繁多，每种基因突变及组合的临床意义还需更多研究[41]。

4 基因突变对 MDS 个体化治疗的影响

MDS的治疗包括一般支持治疗、促造血治疗、免疫调节和免疫抑制治疗、去甲基化药物治疗、联合化疗和造血干细胞移植(hematopoietic stem cell transplantation，HSCT)，一般根据患者不同的危险度分层并结合年龄、身体状况等制定治疗方案。但即使相同危险度分层的患者其治疗反应也存在很大差异，尤其是在使用去甲基化药物和异基因造血干细胞移植治疗时[42-43]。去甲基化药物地西他滨、阿扎胞苷作为治疗MDS的一线药物，可以提高外周血细胞和总体生存率[44-45]。但多项研究表明大约只有30%~40%的患者对去甲基化药物有反应[46-48]。Itzykson等[49]在82例MDS和AML患者的临床研究中，发现TET2突变的患者接受地西他滨治疗时的反应率可达82%，无TET2突变的患者反应率仅42%，并且TET2突变是地西他滨治疗反应的独立预测因素。Traina等[50]在92位接受地西他滨或阿扎胞苷治疗的MDS患者的研究中，也发现TET2，DNMT3A或IDH1/2基因突变患者的反应率是无这些基因突变患者的一倍。Welch等[51]在一项关于使用地西他滨治疗AML和MDS患者的研究中，发现TP53突变的患者临床有效性高于野生型TP53患者。

来那度胺作为5q-综合征患者的首选用药，对76%的患者治疗有效，使67%的患者减少输血依赖[52]。此外，约25%的不伴5q-的MDS患者同

样对来那度胺治疗有效[53]。提示除5q-外，还存在其他一些与来那度胺治疗有效性相关的分子机制。Negoro等[54]的研究发现：在5q-和非5q-队列中U2AF1突变均与治疗无效相关，在5q-队列中TP53突变与治疗无效相关，而在非5q-队列中DEAD盒蛋白家族RNA解旋酶基因突变(DDX41，DDX54和DHX29)患者对来那度胺有较好的反应性。来那度胺与去甲基化药物联用，因其作用机制不同可能存在协同作用，已在几项临床试验[55-56]中显现出潜在的益处。

HSCT是目前唯一可能治愈MDS的方法，越来越多的报道发现基因突变在HSCT后预后评估中也有重要意义。Bejar等[57]在对87例进行HSCT的MDS患者的研究中，发现TP53，TET2，DNMT3A突变的患者HSCT后总体生存率更低，尤其TP53突变的患者，HSCT后中位总生存率<6个月。Lindsley等[42]对1 514例MDS患者的研究显示TP53突变的患者生存期短且更易出现早期复发。

除上述治疗外，目前一些针对MDS的新药和靶向药物也正在临床试验中。如Luspatercept，是一种新型的融合蛋白，作用于转化生长因子β超家族，刺激晚期红细胞的分化与成熟，目前正在进行的II期临床试验结果表明SF3B1突变的患者具有更好的反应性[58-59]。此外，IDH1/2的靶向药物AG-120和AG-221在MDS和AML患者的I/II期临床试验中已取得较好效果。

5 结语

MDS中基因突变的检出率已超过90%，分子生物学的研究有力地促进了MDS诊断和治疗的进展。不同的基因突变组合是MDS发生发展的分子基础，并且是重要的预后影响因素[2]。在AML中，已有多种基因突变指标被纳入疾病分类和预后评价中，并且已经在临床推广应用[60-62]。在MDS中，逐步也有一些基因突变指标开始被列入疾病的分类和预后评价中，但不同于AML，MDS中的基因突变缺乏特异性，限制了以基因突变作为MDS分型指标的应用。另外MDS中突变的基因种类繁多，不同基因突变的组合更是多样，基因突变之间、基因突变和临床其他因素之间都会相互影响，每种基因突变及组合的临床意义还需更多研究。但随着相关医学数据和研究的积累，各种靶向药物的研发和应用，基因突变检测将为MDS的精准医疗提供越来越多的依据。

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本文引用： 张阳, 刘铭, 刘红星. 骨髓增生异常综合征中常见的基因突变及其临床意义[J]. 临床与病理杂志, 2017, 37(10): 2237-2242. doi: 10.3978/j.issn.2095-6959.2017.10.035

Cite this article as: ZHANG Yang, LIU Ming, LIU Hongxing. Gene mutations and its clinical significance in myelodysplastic syndrome[J]. Journal of Clinical and Pathological Research, 2017, 37(10): 2237-2242. doi: 10.3978/j.issn.2095-6959.2017.10.035