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MPN相关突变基因及JAK2抑制剂治疗

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摘　要

骨髓增殖性肿瘤(MPN)是一组由髓系细胞过度产生而引起的疾病，大多数MPN都有一个可识别的驱动突变，如JAK2V617F突变、MPL突变、CALR突变，此外还包括一些其他非驱动突变，如ASXL1、DNMT3A和TET2等。由JAK2V617F、MPL和CALR突变激活的JAK2信号通路已成为MPN患者靶向治疗开发的一个重点，JAK2抑制剂已成为治疗MPN不可或缺的一部分，本综述将讨论MPN相关突变基因的发病机制、JAK2抑制剂的相关治疗。

关键词

MPN，JAK2，CALR，MPL驱动突变，JAK2抑制剂

MPN-Related Mutations and JAK2 Inhibitor Therapy

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Abstract

Myeloid proliferative tumors (MPNS) are a group of diseases caused by overproduction of myeloid cells. Most MPNS have an identifiable driver mutation, such as JAK2V617F mutation, MPL mutation, CALR mutation, and some other non-driver mutations, such as ASXL1, DNMT3A, and TET2. JAK2 signaling pathways activated by JAK2V617F, MPL and CALR mutations have become a focus in the development of targeted therapies for patients with MPN. JAK2 inhibitors have become an integral part of the treatment of MPN. This review will discuss the pathogenesis of MPN-related mutations and the treatment of JAK2 inhibitors.

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Keywords

MPN, JAK2, CALR, MPL Drive Mutation, JAK2 Inhibitors

1. 前言

表型驱动突变，就是那些能够在 MPN 中驱动骨髓增殖表型的突变，发生在 JAK2、CALR 或 MPL 基因中。最初认为这些突变是相互排斥的，但在一部分病例中确实可以共存，这影响了我们诊断 MPN 的方式，因为除了典型的骨髓形态学发现外，我们越来越依赖遗传/基因组信息[1] [2] [3] [4]。根据 MPN 过去几年的广泛遗传特征，98%的 PV 患者以及 85%~90%的 ET 和 PMF 患者可通过常规遗传检测检测到驱动基因突变。JAK2、CALR 或 MPL 驱动突变的存在不是特异性的，但高度提示为 MPN，因此代表了支持诊断 PV、ET 或 PMF 比较有价值的工具。

2. 相关突变基因

2.1. JAK2V617F 突变

JAK2V617F 突变见于大多数 MPN 患者(包括所有三种亚型)，其中 95%的病例出现在 PV 患者中，50%~60%的病例出现在 ET 或 PMF 患者中[5]，还有一种突变类型为 JAK2 第 12 外显子的突变，大多数为框内的缺失或插入，这种突变仅出现在 1%~2%的 PV 患者中，大多数 JAK2V617F 突变是阴性的，在 ET 和 PMF 中不会出现[6] [7]。JAK2 和 JAK1、JAK3、TYK2 具有相似的结构，共有七个 JAK 同源性结构域(JH1-JH7) [8] [9]。JAK 蛋白的 4 个基因与 7 个 STAT 蛋白相互作用，介导转录控制的差异效应。JAK 蛋白与许多细胞表面相关受体、JAK/STAT 信号在许多代谢、免疫细胞功能和造血控制中被激活[10]。V617F 突变发生在 JH2 中，通过 JH1-JH2 构象的变化导致 JH2 失去正常的自我抑制功能，并导致 JAK2 活化。被激活的 JAK2 突变体概括了对细胞因子结合的生理反应。随后，细胞内信号的下游激活通过 STAT 蛋白、丝裂原活化蛋白激酶(MAPK)和磷酸肌醇-3-激酶(PI3K)发生[11]。对红细胞生成、巨核细胞生成和颗粒细胞生成的有效控制对于在整个生命过程中以及在生理应激或感染时应对生理需求的变化是至关重要的。Erythropoietin (促红细胞生成素)、Thrombopoietin (血小板生成素)和 Granulocyte Colony Stimulating Factor (粒细胞集落刺激因子)的激素信号通过各自的受体分别促进红细胞、血小板和粒细胞的生成，在这些受体激活后使得 JAK/STAT 途径以驱动增殖[12]。通常这些造血细胞因子受体与其配体的相互作用会导致受体二聚化，然后 JAK2 接受受体的自磷酸化和转磷酸化。被激活的 JAK2 受体复合体进而募集并磷酸化底物分子，包括 STAT 蛋白导致细胞核内靶基因转录[13]。

2.2. MPL 突变

由 12 个外显子组成了 MPL 基因，其中包括 2 个细胞因子受体结构域、1 个跨膜结构域和 1 个胞质结构域。最常见的突变是 W515L 及 W515K，W515 的 MPL 突变存在于 3%的 ET 病例和 5%的 PMF 病例中[14]。还有一种罕见的突变 MPLS505N 也被视为 ET 的遗传形式[15]。MPL 为 TPO 的细胞表面受体[16]，MPL 基因编码 TPOR (血小板生成素受体蛋白) [17]，TPO 与 MPL/TPOR 结合同时诱导受体同二聚化，随

后导致 STAT 磷酸化和 MAPK 信号传导[13]。MPL 表达还作为 TPO 水平的调节剂，成熟血小板通过去除与 MPL 受体结合的 TPO (TPOR)提供负反馈机制[18]。通过改变晚期巨核细胞和血小板中的 MPL 表达，TPO 不容易清除，从而导致驱动早期巨核细胞增殖的水平升高，进而导致随后的血小板增多，因为有缺陷的血小板不能提供正常的负反馈环[19]。

2.3. CALR 突变

CALR 基因位于第 19 号染色体 p13.13 位点，包括 9 个外显子，编码一种多功能蛋白产物，分别为 N-末端凝集素结构域、脯氨酸结构域和酸性羧基(C-)末端结构域，终止于 KDEL(赖氨酸、天冬氨酸、谷氨酸和亮氨酸)氨基序列[20]。CALR 突变是 MPN 患者中第二常见的突变，(仅次于 JAK2V617F)，有 20%~25%的病例出现在 ET 患者中，有 25%~30%的病例出现在 PMF 患者中[21] [22] [23] [24] [25]，很少有 CALR 突变出现在 PV 中[21] [26]。CALR 突变分为两种类型，第一种是 1 型(52-bp 插入)，并且 1 型突变导致所有带负电荷的氨基酸完全丧失。第二种是 2 型(5-bp 插入)，2 型突变消除了约 50%的氨基酸序列，且这些氨基酸序列都带有负电荷。其中 1 型突变在 PMF 中更为常见，并且预后好于其他形式的 PMF。2 型突变在 ET 中更为常见。然而，在 PMF 中，2 型突变赋具有与 JAK2V617F 阳性的 PMF 相似的表型，2 型突变表现出的脾肿大和血细胞减少较 1 型突变更为明显[27] [28]。近年来研究表明，突变型 CALR 可诱导 MPL 的细胞因子非依赖性激活。已描述了突变体 CALR 对 MPL 的相互作用和激活机制，其依赖于与未成熟天冬酰胺连接的聚糖的相互作用，与内质网中的未成熟 MPL 结合。突变体 CALR 和 MPL 之间形成的这种复合物然后被转运到细胞表面，诱导与 MPL 结合的下游激酶 JAK2 的组成型激活[29]。

2.4. 三阴性 MPN

JAK2、MPL 和 CALR 突变在 ET 和 PMF 病例中占 90%以上，但在 10%的 ET 和 5%~10%的 PMF 病例中，相关驱动突变不明，被称作三阴性 MPN [22]。MPN 患者中典型体细胞突变包括 JAK2 外显子 14、MPL 外显子 10 和 CALR 外显子 9，除了上述突变，还有约 10%的三阴性 ET 和 PMF 患者存在其他突变，这些突变可以是遗传性的，也可以是躯体获得性的[30] [31]。这些患者中的一些可能有其他可检测的克隆性遗传标记，或随后对驱动突变的检测呈阳性[32]。少数患者仍然具有典型的表型和形态学特征，并且没有可检测到的遗传异常[33]。随着对 MPN 分子基础认识的增加，驱动突变和非驱动突变在预后意义方面都具有相关性，MPN 伴有 CALR 突变尤其是 CALR1 型突变预后最好，而三阴性 MPN 预后最差[24] [25] [33]。

2.5. 其他相关突变

在上述提到的三种驱动突变不能完全阐明 MPN 的异质性。随着下一代测序技术的发展，超过三分之一的 MPN 患者中发现了多种突变[34]。这些突变并不局限于 MPN，也见于其他髓系恶性肿瘤，包括骨髓增生异常综合征(MDS)和急性髓系白血病(AML)。在 MPN 患者中，除了典型的骨髓特征外，这些突变还具有具体的诊断作用[2] [3] [4]。MPN 体细胞突变的发现使用全基因组分析暗示了显著高数量的突变。这种增加的遗传测序的可用性也在诊断环境中清除了 MPN 的遗传异质性[5] [35]。可以根据基因功能将这类突变分为三类。第一种为参与表观遗传调节的基因突变：TET2、DNMT3A、IDH1/2、EZH2 和 ASXL1。第二种为 RNA 剪接体机械成分的突变，包括 SF3B1、SRSF2、U2AF1 和 SRSR2。第三种为涉及转录因子和信号转导基因的突变，包括 TP53、RUNX1、NRAS、SH2B3、CBL、NF1 和 FLT3 [36]。

3. 相关治疗药物

3.1. JAK2 抑制剂

在 JAK2、CALR 和 MPL 突变以及三阴性 MPN 中，JAK2 信号的组成型激活为在 MPN 将 JAK2 抑

制作为一种治疗方法提供了合理的基础[37]。目前已获批准(芦可替尼，非德拉替尼)或正在临床开发中的JAK2 抑制剂(莫美洛替尼、帕西替尼等)。以活性构象接合 JAK2 的 ATP 结合位点，从而干扰 JAK2 催化活性，并且被称为类型 1 抑制剂[38]。除了治疗 MPN，JAK1/2 抑制剂在糖皮质激素难治性急性或慢性移植物抗宿主病的治疗中也显示出活性[39] [40]。

3.2. 芦可替尼

芦可替尼是继 COMFORT-I 和 COMFORT-II3 期临床试验结果之后出现的首个 JAK 靶向治疗药物。COMFORT-I 显示症状评分改善≥50%，41.9%的患者在第 24 周时脾体积减少≥35% (SVR)，COMFORT-II 显示 28%的患者在用药第 48 周时脾脏体积减少≥35% (SVR)，平均减少 56% [41] [42]。芦可替尼的使用范围不仅仅在 PMF 中，在 PV 和 ET 中也同样适用，尤其是应用羟基脲后出现耐药性或不能耐受的患者，在 PV 中，已经证明芦可替尼在对红细胞压积控制、脾脏缩小和完全血液学反映(CHR)方面优于最佳可行疗法(BAT) [43] [44] [45] [46]。另外，芦可替尼不能可靠地根除 MPN 中携带 JAK2V617F 或 CALR 突变，在 COMFORT-I 队列中只有 12%的患者 JAK2V617F 突变减少超过 50% [47]。

3.3. 非德拉替尼

非德拉替尼是一种 JAK2/FLT3 抑制剂，具有类似的 1 型 JAK2 结合模式，最近已被证实适用于 MPN 患者。相比于芦可替尼，非德拉替尼对 JAK2 具有更高的特异性[48]，是一种选择性 JAK2 抑制剂，对 JAK1、JAK3 或 TYK3 无显著抑制作用[49]。显示有疗效的主要研究是 JAKARTA-I 和 JAKARTA-II。JAKARTA-I 在 PMF 一线治疗中检查了非德拉替尼，结果显示与安慰剂相比，SVR ≥ 35%时有 36%的应答，总症状评分改善≥50%时也有 36%的应答[50]。

3.4. 莫美洛替尼

莫美洛替尼(CYT387)是一种 JAK1/2 抑制剂，现阶段正处于 3 期临床试验中，在此之前未应用过 JAK 抑制剂治疗的患者中，莫美洛替尼与芦可替尼疗效相差无几。莫美洛替尼的主要优势在于其使贫血的程度降低[51] [52]。在 SIMPLIFY (一项针对芦可替尼的 3 期非劣效性研究)中显示出对骨髓纤维化的疗效。在第 24 周时，与芦可替尼组 29%的患者相比，莫美洛替尼组有 26.5%的患者的 SVR ≥ 35%。但莫美洛替尼未能达到症状控制的非劣效性(≥50%的症状评分降低，莫美洛替尼为 28.4%，芦可替尼为 42.2%) [51]。随后 simple-II 未能证明优于最佳可行疗法，其中有 89%的患者服用芦可替尼[53]。

3.5. 帕西替尼

帕西替尼(SB1518)是一种对 JAK2、FLT3、白细胞介素受体相关激酶和集落刺激因子 1 受体(CSF1R)具有选择性的抑制剂[54]。在 PMF 患者中使用帕西替尼进行的 PERSIST-1 试验显示，19%的患者达到≥35%的 SVR，36%的患者总症状评分降低≥50%。在第 24 周时还测量了等位基因负荷的减少，与 BAT 的 7.9%相比，帕西替尼减少了 15.8% [55]。

3.6. JAK 抑制剂治疗的局限性

贫血、血小板减少和在较小程度上的免疫抑制是 JAK 抑制剂治疗的常见副作用，可能需要调整剂量[56] [57]。芦可替尼的 JAK1 抑制活性与免疫监测降低有关，与机会性感染(尤其是带状疱疹再激活)发生率升高有关，但也有肺结核、隐球菌脑菌膜脑炎、耶氏肺孢子虫病、乙型病毒性肝炎、弓形体病或巨细胞病毒视网膜炎再激活的报告，强调了提高警惕的重要性[58] [59] [60] [61] [62]。据推测，使用芦可替尼治疗的 MPN 患者可能具有更高的继发性癌症风险，并且在长时间的研究中发现非黑色素瘤皮肤癌的发生

率在逐年增加中[63]。由于复杂的发病机制，尽管采用了 JAK2 抑制剂治疗，但其他通路(如 MAPK 通路)仍显示出作为一个代偿过程而被激活，涉及 MEK 和 ERK 激酶。此外，靶向 MEK/ERK 激活途径似乎可提高 JAK 抑制剂的疗效[64]。

4. 总结

自从发现 JAK2V617F、CALR、MPL 驱动突变，再到 ASXL1、DNMT3A 和 TET2 等非驱动突变，对 MPN 相关分子病理发生的认识逐渐提高，对该疾病有了进一步的认识，尤其是对疾病的诊断和预后更加详细，对疾病的治疗有了更多的选择。从最开始的芦可替尼到一些新型的 JAK2 抑制剂，但是也仅仅是暂时改善患者症状，提高生活质量，无法使大多数患者根除疾病，而且还会带来相关的药物副作用和耐药性，另外 MPN 和 MDS 有着同样向急性髓系白血病转化的高风险，虽然可以通过行造血干细胞移植术可以治疗，但考虑到 MPN 患者多数年龄较大，移植风险较大，也不一定能找到合适的供者，所以需要在当前对疾病认识的基础上，进一步加强对相关分子病理的研究，尤其是对白血病相关突变基因的研究，研制出效果更佳的新型 JAK2 抑制剂和针对相关突变基因的靶向药物，在尽可能的减少药物副作用和耐药性的基础上，考虑把传统的化学治疗和这些药物联合起来达到更佳的治疗效果，如 JAK2 抑制剂联合去甲基化药物(如地西他滨、阿扎胞苷)或 Bcl-2 抑制剂(如维奈克拉)从而提高 MPN 患者的生存率。

参考文献

[1] Arber, D.A., Orazi, A., Hasserjian, R., *et al*. (2016) The 2016 Revision to the World Health Organization Classification of Myeloid Neoplasms and Acute Leukemia. *Blood*, **127**, 2391-2405. https://doi.org/10.1182/blood-2016-03-643544

[2] Stuckey, R. and Gómez-Casares, M.T. (2021) Recent Advances in the Use of Molecular Analyses to Inform the Diagnosis and Prognosis of Patients with Polycythaemia Vera. *International Journal of Molecular Sciences*, **22**, 5042. https://doi.org/10.3390/ijms22095042

[3] Jia, R. and Kralovics, R. (2020) Progress in Elucidation of Molecular Pathophysiology of Myeloproliferative Neoplasms and Its Application to Therapeutic Decisions. *International Journal of Hematology*, **111**, 182-191. https://doi.org/10.1007/s12185-019-02778-9

[4] Takenaka, K. (2020) Progress in Elucidation of Molecular Pathophysiology and Its Application in Therapeutic Decision-Making for Myeloproliferative Neoplasms. *International Journal of Hematology*, **111**, 180-181. https://doi.org/10.1007/s12185-019-02812-w

[5] Szybinski, J. and Meyer, S.C. (2021) Genetics of Myeloproliferative Neoplasms. *Hematology/Oncology Clinics of North America*, **35**, 217-236. https://doi.org/10.1016/j.hoc.2020.12.002

[6] Passamonti, F., Elena, C., Schnittger, S., *et al*. (2011) Molecular and Clinical Features of the Myeloproliferative Neoplasm Associated with JAK2 Exon 12 Mutations. *Blood*, **117**, 2813-2816. https://doi.org/10.1182/blood-2010-11-316810

[7] Scott, L.M., Tong, W., Levine, R.L., *et al*. (2007) JAK2 Exon 12 Mutations in Polycythemia Vera and Idiopathic Erythrocytosis. *The New England Journal of Medicine*, **356**, 459-468. https://doi.org/10.1056/NEJMoa065202

[8] McNally, R., Toms, A.V. and Eck, M.J. (2016) Crystal Structure of the FERM-SH2 Module of Human Jak2. *PLOS ONE*, **11**, e0156218. https://doi.org/10.1371/journal.pone.0156218

[9] Raivola, J., Haikarainen, T., Abraham, B.G. and Silvennoinen, O. (2021) Janus Kinases in Leukemia. *Cancers*, **13**, 800. https://doi.org/10.3390/cancers13040800

[10] Bharadwaj, U., Kasembeli, M.M., Robinson, P. and Tweardy, D.J. (2020) Targeting Janus Kinases and Signal Transducer and Activator of Transcription 3 to Treat Inflammation, Fbrosis, and Cancer: Rationale, Progress, and Caution. *Pharmacological Reviews*, **72**, 486-526. https://doi.org/10.1124/pr.119.018440

[11] Dusa, A., Mouton, C., Pecquet, C., *et al*. (2010) JAK2 V617F Constitutive Activation Requires JH2 Residue F595: A Pseudokinase Domain Target for Specific Inhibitors. *PLOS ONE*, **5**, e11157. https://doi.org/10.1371/journal.pone.0011157

[12] Wingelhofer, B., Neubauer, H.A., Valent, P., *et al*. (2018) Implications of STAT3 and STAT5 Signaling on Gene Regulation and Chromatin Remodeling in Hematopoietic Cancer. *Leukemia*, **32**, 1713-1726. https://doi.org/10.1038/s41375-018-0117-x

[13] Vainchenker, W. and Kralovics, R. (2017) Genetic Basis and Molecular Pathophysiology of Classical Myeloproliferative Neoplasms. *Blood*, **129**, 667-679. https://doi.org/10.1182/blood-2016-10-695940

[14] (2020) Online Mendelian Iinheritance in Man: An Online Catalog of Human Genes and Genetic Disorders. Johns Hopkins University, Baltimore.

[15] Ding, J., Komatsu, H., Wakita, A., *et al*. (2004) Familial Essential Thrombocythemia Associated with a Dominant-Positive Activating Mutation of the c-MPL Gene, Which Encodes for the Receptor for Thrombopoietin. *Blood*, **103**, 4198-4200. https://doi.org/10.1182/blood-2003-10-3471

[16] Staerk, J., Lacout, C., Sato, T., *et al*. (2006) An Amphipathic Motif at the Transmembrane-Cytoplasmic Junction Prevents Autonomous Activation of the Thrombopoietin Receptor. *Blood*, **107**, 1864-1871. https://doi.org/10.1182/blood-2005-06-2600

[17] Mead, A.J. and Mullally, A. (2017) Myeloproliferative Neoplasm Stem Cells. *Blood*, **129**, 1607-1616. https://doi.org/10.1182/blood-2016-10-696005

[18] Tiedt, R., Coers, J., Ziegler, S., Wiestner, A., Hao-Shen, H., Bornmann, C., Schenkel, J., Karakhanova, S., De Sauvage, F.J., Jackson, C.W., *et al*. (2009) Pronounced Thrombocytosis in Transgenic Mice Expressing Reduced Levels of Mpl in Platelets and Terminally Differentiated Megakaryocytes. *Blood*, **113**, 1768-1777. https://doi.org/10.1182/blood-2008-03-146084

[19] Lannutti, B.J., Epp, A., Roy, J., Chen, J. and Josephson, N.C. (2009) Incomplete Restoration of Mpl Expression in the mpl/Mouse Produces Partial Correction of the Stem Cell-Repopulating Defect and Paradoxical Thrombocytosis. *Blood*, **113**, 1778-1785. https://doi.org/10.1182/blood-2007-11-124859

[20] Prins, D., Arias, C.G., Klampflfl, T., Grinfeld, J. and Green, A.R. (2020) Mutant Calreticulin in the Myeloproliferative Neoplasms. *HemaSphere*, **4**, e333. https://doi.org/10.1097/HS9.0000000000000333

[21] Klampfl, T., Gisslinger, H., Harutyunyan, A.S., *et al*. (2013) Somatic Mutations of Calreticulin in Myeloproliferative Neoplasms. *The New England Journal of Medicine*, **369**, 2379-2390. https://doi.org/10.1056/NEJMoa1311347

[22] Rumi, E. and Cazzola, M. (2017) Diagnosis, Risk Stratification, and Response Evaluation in Classical Myeloproliferative Neoplasms. *Blood*, **129**, 680-692. https://doi.org/10.1182/blood-2016-10-695957

[23] Rumi, E., Pietra, D., Ferretti, V., *et al*. (2014) JAK2 or CALR Mutation Status Defines Subtypes of Essential Thrombocythemia with Substantially Different Clinical Course and Outcomes. *Blood*, **123**, 1544-1551. https://doi.org/10.1182/blood-2013-11-539098

[24] Rumi, E., Pietra, D., Pascutto, C., *et al*. (2014) Clinical Effect of Driver Mutations of JAK2, CALR, or MPL in Primary Myelofibrosis. *Blood*, **124**, 1062-1069. https://doi.org/10.1182/blood-2014-05-578435

[25] Tefferi, A., Lasho, T.L., Finke, C.M., *et al*. (2014) CALR vs JAK2 vs MPL-Mutated or Triple-Negative Myelofibrosis: Clinical, Cytogenetic and Molecular Comparisons. *Leukemia*, **28**, 1472-1477. https://doi.org/10.1038/leu.2014.3

[26] Nangalia, J., Massie, C.E., Baxter, E.J., *et al*. (2013) Somatic CALR Mutations in Myeloproliferative Neoplasm with Nonmutated JAK2. *The New England Journal of Medicine*, **369**, 2391-2405. https://doi.org/10.1056/NEJMoa1312542

[27] How, J., Hobbs, G.S. and Mullally, A. (2019) Mutant Calreticulin in Myeloproliferative Neoplasms. *Blood*, **134**, 2242-2248. https://doi.org/10.1182/blood.2019000622

[28] Pietra, D., Rumi, E., Ferretti, V.V., Di Buduo, C.A., Milanesi, C., Cavalloni, C., Sant'Antonio, E., Abbonante, V., Moccia, F., Casetti, I.C., *et al*. (2016) Faculty Opinions Recommendation of Differential Clinical Effects of Different Mutation Subtypes in CALR-Mutant Myeloproliferative Neoplasms. *Leukemia*, **30**, 431-438. https://doi.org/10.1038/leu.2015.277

[29] Masubuchi, N., Araki, M., Yang, Y., Hayashi, E., Imai, M., Edahiro, Y., Hironaka, Y., Mizukami, Y., Kihara, Y., Takei, H., *et al*. (2020) Mutant Calreticulin Interacts with MPL in the Secretion Pathway for Activation on the Cell Surface. *Leukemia*, **34**, 499-509. https://doi.org/10.1038/s41375-019-0564-z

[30] Cabagnols, X., Favale, F., Pasquier, F., *et al*. (2016) Presence of Atypical Thrombopoietin Receptor (MPL) Mutations in Triple-Negative Essential Thrombocythemia Patients. *Blood*, **127**, 333-342. https://doi.org/10.1182/blood-2015-07-661983

[31] Milosevic Feenstra, J.D., Nivarthi, H., Gisslinger, H., *et al*. (2016) Whole-Exome Sequencing Identifies Novel MPL and JAK2 Mutations in Triple-Negative Myeloproliferative Neoplasms. *Blood*, **127**, 325-332. https://doi.org/10.1182/blood-2015-07-661835

[32] Michail, O., McCallion, P., McGimpsey, J., *et al*. (2020) Mutational Profling in Suspected Triple-Negative Essential Thrombocythaemia Using Targeted Next-Generation Sequencing in a Real-World Cohort. *Journal of Clinical Pathology*, **74**, 808-811. https://doi.org/10.1136/jclinpath-2020-206570

[33] Tefferi, A., Lasho, T.L., Finke, C., Belachew, A.A., Wassie, E.A., Ketterling, R.P., Hanson, C.A. and Pardani, A. (2014) Type 1 vs. Type 2 Calreticulin Mutations in Primary Myelofibrosis: Differences in Phenotype and Prognostic

Impact. *Leukemia*, **28**, 1568-1570. https://doi.org/10.1038/leu.2014.83

[34] Lee, J., Godfrey, A.L. and Nangalia, J. (2020) Genomic Heterogeneity in Myeloproliferative Neoplasms and Applications to Clinical Practice. *Blood Reviews*, **42**, Article ID: 100708. https://doi.org/10.1016/j.blre.2020.100708

[35] Marneth, A.E. and Mullally, A. (2020) The Molecular Genetics of Myeloproliferative Neoplasms. *Cold Spring Harbor Perspectives in Medicine*, **10**, a034876. https://doi.org/10.1101/cshperspect.a034876

[36] Morsia, E., Torre, E., Poloni, A., Olivieri, A. and Rupoli, S. (2022) Molecular Pathogenesis of Myeloproliferative Neoplasms: From Molecular Landscape to Therapeutic Implications. *International Journal of Molecular Sciences*, **23**, 4573. https://doi.org/10.3390/ijms23094573

[37] Chachoua, I., Pecquet, C., El-Khoury, M., Nivarthi, H., Albu, R.I., Marty, C., Gryshkova, V., Defour, J.P., Vertenoeil, G., Ngo, A., *et al*. (2016) Thrombopoietin Receptor Activation by Myeloproliferative Neoplasm Associated Calreticulin Mutants. *Blood*, **127**, 1325-1335. https://doi.org/10.1182/blood-2015-11-681932

[38] Brkic, S. and Meyer, S.C. (2021) Challenges and Perspectives for Therapeutic Targeting of Myeloproliferative Neoplasms. *Hemasphere*, **5**, e516. https://doi.org/10.1097/HS9.0000000000000516

[39] Zeiser, R., von Bubnoff, N., Butler, J., Mohty, M., Niederwieser, D., Or, R., Szer, J., Wagner, E.M., Zuckerman, T., Mahuzier, B., *et al*. (2020) Ruxolitinib for Glucocorticoid-Refractory Acute Graft-versus-Host Disease. *The New England Journal of Medicine*, **382**, 1800-1810. https://doi.org/10.1056/NEJMoa1917635

[40] Zeiser, R., Polverelli, N., Ram, R., Hashmi, S.K., Chakraverty, R., Middeke, J.M., Musso, M., Giebel, S., Uzay, A., Langmuir, P., *et al*. (2021) Ruxolitinib for Glucocorticoid-Refractory Chronic Graft-versus-Host Disease. *The New England Journal of Medicine*, **385**, 228-238. https://doi.org/10.1056/NEJMoa2033122

[41] Harrison, C., Kiladjian, J., Al-Ali, H., Gisslinger, H., Waltzman, R., Stalbovskaya, V., McQuitty, M., Hunter, D.S., Levy, R., Knoops, L., *et al*. (2012) JAK Inhibition with Ruxolitinib versus Best Available Therapy for Myelofibrosis. *The New England Journal of Medicine*, **366**, 787-798. https://doi.org/10.1056/NEJMoa1110556

[42] Verstovsek, S., Mesa, R.A., Gotlib, J., Levy, R.S., Gupta, V., DiPersio, J.F., Catalano, J.V., Deininger, M., Miller, C., Silver, R.T., *et al*. (2012) A Double-Blind, Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis. *The New England Journal of Medicine*, **366**, 799-807. https://doi.org/10.1056/NEJMoa1110557

[43] Vannucchi, A.M., Kiladjian, J., Griesshammer, M., Masszi, T., Durrant, S., Passamonti, F., Harrison, C.N., Pane, F., Zachee, P., Mesa, R., *et al*. (2015) Ruxolitinib versus Standard Therapy for the Treatment of Polycythemia Vera. *The New England Journal of Medicine*, **372**, 426-435. https://doi.org/10.1056/NEJMoa1409002

[44] Verstovsek, S., Vannucchi, A.M., Griesshammer, M., Masszi, T., Durrant, S., Passamonti, F., Harrison, C.N., Pane, F., Zachee, P., Kirito, K., *et al*. (2016) Ruxolitinib versus Best Available Therapy in Patients with Polycythemia Vera: 80-Week Follow-Up from the RESPONSE Trial. *Haematologica*, **101**, 821-829. https://doi.org/10.3324/haematol.2016.143644

[45] Passamonti, F., Griesshammer, M., Palandri, F., Egyed, M., Benevolo, G., Devos, T., Callum, J., Vannucchi, A.M., Sivgin, S., Bensasson, C., *et al*. (2017) Ruxolitinib for the Treatment of Inadequately Controlled Polycythaemia Vera without Splenomegaly (RESPONSE-2): A Randomised, Open-Label, Phase 3b Study. *The Lancet Oncology*, **18**, 88-99. https://doi.org/10.1016/S1470-2045(16)30558-7

[46] Griesshammer, M., Saydam, G., Palandri, F., Benevolo, G., Egyed, M., Callum, J., Devos, T., Sivgin, S., Guglielmelli, P., Bensasson, C., *et al*. (2018) Ruxolitinib for the Treatment of Inadequately Controlled Polycythemia Vera without Splenomegaly: 80-Week Follow-Up from the RESPONSE-2 Trial. *Annals of Hematology*, **97**, 1591-1600. https://doi.org/10.1007/s00277-018-3365-y

[47] Deininger, M., Radich, J., Burn, T.C., Huber, R., Paranagama, D. and Verstovsek, S. (2015) The Effect of Long-Term Ruxolitinib Treatment on JAK2p.V617F Allele Burden in Patients with Myelofibrosis. *Blood*, **126**, 1551-1554. https://doi.org/10.1182/blood-2015-03-635235

[48] Talpaz, M. and Kiladjian, J.-J. (2021) Fedratinib, a Newly Approved Treatment for Patients with Myeloproliferative Neoplasm-Associated Myelofibrosis. *Leukemia*, **35**, 1-17. https://doi.org/10.1038/s41375-020-0954-2

[49] Mullally, A., Hood, J., Harrison, C. and Mesa, R. (2020) Fedratinib in Myelofibrosis. *Blood Advances*, **4**, 1792-1800. https://doi.org/10.1182/bloodadvances.2019000954

[50] Schönberg, K., Rudolph, J., Vonnahme, M., Yajnanarayana, S.P., Cornez, I., Hejazi, M., Manser, A.R., Uhrberg, M., Verbeek, W., Koschmieder, S., *et al*. (2015) JAK Inhibition Impairs NK Cell Function in Myeloproliferative Neoplasms. *Cancer Research*, **75**, 2187-2199. https://doi.org/10.1158/0008-5472.CAN-14-3198

[51] Mesa, R.A., Kiladjian, J.-J., Catalano, J.V., Devos, T., Egyed, M., Hellmann, A., McLornan, D., Shimoda, K., Winton, E.F., Deng, W., *et al*. (2017) SIMPLIFY-1: A Phase III Randomized Trial of Momelotinib versus Ruxolitinib in Janus Kinase Inhibitor-Naïve Patients with Myelofibrosis. *Journal of Clinical Oncology*, **35**, 3844-3850. https://doi.org/10.1200/JCO.2017.73.4418

[52] Patel, A.A. and Odenike, O. (2020) The Next Generation of JAK Inhibitors: An Update on Fedratinib, Momelotonib,

and Pacritinib. *Current Hematologic Malignancy Reports*, **15**, 409-418. https://doi.org/10.1007/s11899-020-00596-z

[53] Harrison, C., Vannucchi, A.M., Platzbecker, U., Cervantes, F., Gupta, V., Lavie, D., Passamonti, F., Winton, E.F., Dong, H., Kawashima, J., *et al*. (2018) Momelotinib versus Best Available Therapy in Patients with Myelofibrosis Previously Treated with Ruxolitinib (SIMPLIFY 2): A Randomised, Open-Label, Phase 3 Trial. *The Lancet Haematology*, **5**, e73-e81. https://doi.org/10.1016/S2352-3026(17)30237-5

[54] Singer, J.W., Al-Fayoumi, S., Ma, H., Komrokji, R.S., Mesa, R. and Verstovsek, S. (2016) Comprehensive Kinase Profile of Pacritinib, a Nonmyelosuppressive Janus Kinase 2 Inhibitor. *Journal of Experimental Pharmacology*, **8**, 11-19. https://doi.org/10.2147/JEP.S110702

[55] Mesa, R.A., Vannucchi, A.M., Mead, A.J., Egyed, M., Szoke, A., Suvorov, A., Jakucs, J., Perkins, A., Prasad, R., Mayer, J., *et al*. (2017) Pacritinib versus Best Available Therapy for the Treatment of Myelofibrosis Irrespective of Baseline Cytopenias (PERSIST-1): An International, Randomised, Phase 3 Trial. *The Lancet Haematology*, **4**, e225-e236. https://doi.org/10.1016/S2352-3026(17)30027-3

[56] Harrison, C.N., Vannucchi, A.M., Kiladjian, J.J., Al-Ali, H.K., Gisslinger, H., Knoops, L., Cervantes, F., Jones, M.M., Sun, K., McQuitty, M., *et al*. (2016) Long-Term Findings from COMFORT-II, a Phase 3 Study of Ruxolitinib vs Best Available Therapy for Myelofibrosis. *Leukemia*, **30**, 1701-1707. https://doi.org/10.1038/leu.2016.148

[57] Kiladjian, J.J., Zachee, P., Hino, M., Pane, F., Masszi, T., Harrison, C.N., Mesa, R., Miller, C.B., Passamonti, F., Durrant, S., *et al*. (2020) Long-Term Efficacy and Safety of Ruxolitinib versus Best Available Therapy in Polycythaemia Vera (RESPONSE): 5-Year Follow up of a Phase 3 Study. *The Lancet Haematology*, **7**, e226-e237. https://doi.org/10.1016/S2352-3026(19)30207-8

[58] Luo, Q., Xiao, Z. and Peng, L. (2021) Effects of Ruxolitinib on Infection in Patients with Myeloproliferative Neoplasm: A Meta-Analysis. *Hematology*, **26**, 663-669. https://doi.org/10.1080/16078454.2021.1967256

[59] Sadjadian, P., Wille, K., Griesshammer, M., Sadjadian, P., Wille, K. and Griesshammer, M. (2020) Ruxolitinib-Associated Infections in Polycythemia Vera: Review of the Literature, Clinical Significance, and Recommendations. *Cancers*, **12**, 3132. https://doi.org/10.3390/cancers12113132

[60] Khalid, F., Damlaj, M., Al Zahrani, M., Abuelgasim, K.A. and Gmati, G.E. (2021) Reactivation of Tuberculosis Following Ruxolitinib Therapy for Primary Myelofibrosis: Case Series and Literature Review. *Hematology/Oncology and Stem Cell Therapy*, **14**, 252-256. https://doi.org/10.1016/j.hemonc.2020.02.003

[61] Duan, M.-H., Cao, X.-X., Chang, L. and Zhou, D.-B. (2021) Risk of Hepatitis B Virus Reactivation Following Ruxolitinib Treatment in Patients with Myeloproliferative Neoplasms. *Hematology*, **26**, 460-464. https://doi.org/10.1080/16078454.2021.1945234

[62] Devos, T., Selleslag, D., Granacher, N., Havelange, V. and Benghiat, F.S. (2022) Updated Recommendations on the Use of Ruxolitinib for the Treatment of Myelofibrosis. *Hematology*, **27**, 23-31. https://doi.org/10.1080/16078454.2021.2009645

[63] Barraco, F., Greil, R., Herbrecht, R., Schmidt, B., Reiter, A., Willenbacher, W., Raymakers, R., Liersch, R., Wroclawska, M., Pack, R., *et al*. (2020) Real-World Non-Interventional Long-Term Post-Authorisation Safety Study of Ruxolitinib in Myelofibrosis. *British Journal of Haematology*, **191**, 764-774. https://doi.org/10.1111/bjh.16729

[64] Truong, B., Zhang, Y., Fahl, S., Cai, K.Q., Martinez, E., Al-Saleem, E.D., Gong, Y., Liebermann, D., Soboloff, J., Dunbrack, R., *et al*. (2021) ERK2 Substrate Binding Domains Perform Opposing Roles in Pathogenesis of a JAK2V617F-Driven Myeloproliferative Neoplasm. *Blood*, **138**, 2547. https://doi.org/10.1182/blood-2021-152063