Gene Mutations in Systemic Mastocytosis

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Systemic mastocytosis (SM) is a rare hematologic disease characterized by an abnormal expansion and accumulation of pathological mast cells (MCs) in skin and/or other several extracutaneous tissues such as bone marrow (BM) and the gastro-intestinal tract. Currently, SM is divided into five different diagnostic subtypes according to the World Health Organization (WHO) 2016 classification. These include indolent SM (ISM), smouldering SM (SSM), aggressive SM (ASM), SM with associated haematological neoplasms (SM-AHN) and MC leukaemia (MCL). Additionally, the inclusion of two new subtypes of SM into the classification of the disease is currently under consideration: a variant of ISM known as BM mastocytosis (BMM), which is characterized by a low BM MC burden in the absence of skin lesions, and a very rare (<5%) variant of mastocytosis, which shows tumour mast cells (MCs) with a well-differentiated morphology together with a $CD25^{-}$ $CD2^{-}$ immunophenotype and unique clinical, biological and molecular features, termed well-differentiated SM (WDSM). From a prognostic point of view, all these diagnostic subtypes of SM can be grouped into (i) non-advanced forms of SM (Non-AdvSM), which include BMM, ISM and SSM, typically characterized by a more stable and indolent course of the disease and a life expectancy similar or close to that of a sex- and age-matched population; and (ii) advanced SM (AdvSM) including ASM, SM-AHN and MCL, which typically display an adverse prognosis associated with a significantly shortened life expectancy requiring cytoreductive therapy. Despite this, some ISM patients (<5%) can eventually evolve to SSM and AdvSM. Conversely, a small proportion of AdvSM patients may also show a relatively stable disease course over years or even decades.

Keywords: systemic mastocytosis ; prognostic ; mutations ; KIT ; D816V ; ASXL1 ; DNMT3A

1. *KIT* Mutations in Systemic Mastocytosis

The *KIT* gene is a proto-oncogene encoding for a trans-membrane receptor (mast/stem cell growth factor receptor (KIT)) with tyrosine kinase (TK) activity located on the long arm of human chromosome 4 [1]. When the KIT ligand—stem cell growth factor (SCF)—binds to KIT, conformational changes occur that lead to dimerization of the receptor and its activation by autophosphorylation [2]. Of note, intracellular signalling triggered upon activation of the KIT receptor is key to the normal development of haematopoiesis and the survival of haematopoietic stem cells (HSC) [3]. Except for MCs and some natural killer (NK) cells, *KIT* is no longer expressed by other mature myeloid and lymphoid haematopoietic cells [4]. In mast cells (MCs), *KIT* expression remains at high levels throughout maturation [5][6], playing a critical role in MC proliferation, differentiation and survival [2][7]. Therefore, the acquisition of mutations that could impair the normal function of KIT (e.g., activating *KIT* mutations) has pro-oncogenic effects associated with inhibition of apoptosis and increased MC proliferation and survival [8][9].

1.1. *KIT* D816V Mutation

The D816V mutation of *KIT* is located at exon 17 within the tyrosine kinase (TK) 2 domain of the *KIT* gene. This mutation causes constitutive activation of the KIT receptor in the absence of SCF binding and represents the most frequent genetic alteration in SM (>90% of adult SM patients) [2][10]. In fact, constitutive activation of KIT causes preferential differentiation of HSC toward cell lines regulated by *KIT* expression and signalling (mainly MCs and to a large extent also other myeloid lineages). The fact that MCs are the only haematopoietic cells that express *KIT* throughout their maturation [5][6] would explain why this *KIT*-activating mutation induces the expansion and accumulation of pathological MCs in different organs and tissues, as typically observed in SM and other *KIT*-mutated MC diseases [11]. Of note, the prevalence of the *KIT* D816V mutation is very similar among adult patients diagnosed with Non-AdvSM and AdvSM [10]. Therefore, the *KIT* D816V mutation is considered as a (specific) diagnostic marker of SM, regardless of the subtype of the disease, its presence being one of the four minor criteria required by WHO for the diagnosis of SM [12][13][14]. However, the presence of this mutation cannot explain by itself the wide spectrum of disease behaviour observed among SM patients, ranging from stable and even pauci-symptomatic to progressive and even highly-aggressive disease [15].

1.2. Other *KIT* Mutations

Overall, *KIT* mutations other than *KIT* D816V can be found in up to 4–5% adults and one third of children with mastocytosis [10]. In adults, these mutations are mostly located at codons 814–822 within exon 17 [10][16][17][18][19][20][21], including several mutant variants at codon 816 [10][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36]. *KIT* mutations located outside exon 17 include rare mutations that mostly affect exons 2 [19], 5 [30], 7–11 [19][22][30][36][37][38][39][40][41][42][43][44][45][46][47][48], 13 [19][49] and 18 [19]. Of note, most mutations other than *KIT* D816V correspond to isolated cases of SM-AHN, MCL or WDSM. Interestingly, MCL patients with *KIT* mutations other than D816V often lack additional somatic high-risk mutations [36]. Although the vast majority of *KIT* mutations defined above are acquired (somatic) genetic variants, a few mutations typically located in exons 8 to 10 of *KIT* (e.g., delD419 [50], S451C [51], K509I [52][53] or F522C [44]) correspond to germinal mutations that frequently show a familial aggregation pattern.

From a clinical point of view, the exact location of the mutations in the *KIT* gene is of great relevance, since those mutations that occur within the transmembrane or juxtamembrane domains of the *KIT* gene (exons 9–11) induce spontaneous receptor dimerization, making pathological MCs sensitive to conventional TK inhibitor therapies (e.g., imatinib) [42][43][44][45][52][54], while *KIT* mutations involving the catalytic domain (exons 13–18) cause a conformational change of the protein, which confers intrinsic resistance to imatinib and other TK inhibitors commonly used to treat other human tumours [55][56].

2. Clonal Haematopoiesis in Systemic Mastocytosis

SM is considered a clonal HSC disease characterized by the expansion and accumulation of neoplastic MCs [57][58][59]. As a neoplasm involving the HSC compartment, the *KIT* D816V (and other *KIT*) mutations can be found in both neoplastic MCs and $CD34^+$ BM HSC, as well as in other myeloids (e.g., neutrophils [10][60][61][62], monocytes [10][58][60][61][62], basophils [58][60][62] and/or eosinophils [10][62]) and/or lymphoid (e.g., T and B lymphocytes [10][58][61][62]) cells. In such cases presenting multilineage involvement of haematopoiesis, clonal myeloid (MM) or myeloid plus lymphoid (MML) cells are found, which derive from the expansion and differentiation of D816V-mutated HSCs to different myeloid and/or lymphoid cell lineages [15][63]. Moreover, *KIT* D816V-mutated BM mesenchymal stem cells (MSCs) are also frequently detected in MML-mutated cases [26][64][65]. Overall, multilineage involvement of haematopoiesis by the *KIT* D816V mutation is found in virtually all ASM and SSM patients, in around one third of ISM cases and in a small proportion (≤10%) of BMM patients [10][66]. In SM-AHN, the frequency of patients that show a multilineage *KIT* D816V mutation may vary significantly [26] depending on the specific subtypes of SM and AHN [10]. Thus, *KIT* D816V-mutated AHN cells have been found in 89% of SM associated with chronic myelomonocytic leukaemia (SM-CMML), while this would only occur in 20% of SM associated with myeloproliferative neoplasms (MPN) and 30% of SM associated with acute myeloblastic leukaemia (AML); in turn, the *KIT* mutation is almost systematically restricted to the MC compartment in patients with SM associated with lymphoid neoplasms [26].

3. Mutations in Genes Other Than *KIT*

Emergence of the *KIT* D816V mutation in an HSC during the development of haematopoietic cells would potentially lead to multilineage involvement of haematopoiesis [65]. This would favour the expansion of neoplastic MCs and an increasing tumour burden; in addition, it might also lead to an increased genomic instability that may facilitate acquisition and accumulation of additional genetic alterations and Table S1) in the *KIT*-mutated or unmutated HSC and contribute to the malignant transformation of the disease via distinct molecular mechanisms, e.g., activation/repression of anti-/pro-apoptotic mechanisms [67].

In line with this hypothesis, mutations in genes which are also frequently mutated in other myeloid malignancies are also present at relatively high frequencies in AdvSM patients [68][69][70][71][72][73]. In this regard, it has been recently described that certain DNA methylation patterns may be relevant in the pathogenesis of systemic diseases associated with MC activation [74]. Moreover, a significant number of somatic mutations has been identified in a broad number of genes involved in epigenetic regulatory mechanisms, which have been associated, at least in part, with the pathogenesis, clinical behaviour and evolution of different myeloid neoplasms, including SM [75][76]. Thus, around 30–40% of AdvSM present with an associated myeloid haematological neoplasm already at diagnosis [57], suggesting a close relationship between both malignancies. In line with this, next generation sequencing (NGS) studies have confirmed the presence of recurrent mutations in genes involved in post-transcriptional mRNA processing, epigenetic modification of DNA and transcription and signal transduction factors, in both SM and other myeloid neoplasms [41][68][69][77][78]. Among others, mutations have been recurrently reported in AdvSM in the *ASXL1*, *CBL*, *DNMT3A*, *NRAS*, *RUNX1*, *SRSF2* and *TET2* genes in AdvSM [19]

[22][36][40][41][68][70][77][78][79][80][81][82][83]. In contrast, the presence of these additional mutations is a relatively infrequent finding in BMM and ISM patients [19][41][68][78][81].

3.1. Mutations Affecting Transcription Factors and Signalling Pathways

The correct function and development of the human organism strongly relies on the precise regulation and appropriate production of specific sets of proteins. Gene expression is largely regulated by transcription factors and the activation of processes involved in various intracellular signalling pathways. In this regard, alterations in genes involved in these processes, such as the *CBL*, *JAK2*, *K/NRAS* and/or *RUNX1* genes [84], have been associated with several haematological malignancies. To date, mutations in a total of 11 genes related to transcription factors and signalling pathways have been described in patients with different subtypes of SM; of note, while some of these genes have been sporadically reported to be mutated in SM (*EPHA7* [70][79], *FLT3* [19], *IKZF1* [70], *PIK3CD* [70][79], *ROS1* [70][79] and *TP53* [19]) (Tables S1 and S2), others (e.g., *CBL*, *JAK2*, *K/NRAS* and *RUNX1*) are recurrently found to be altered in SM, particularly among SM-AHN patients.

The *CBL* (Casitas B-lineage lymphoma proto-oncogene) gene is located on chromosome 11 and encodes for a protein involved in the functional regulation (via competitive blockade) of tyrosine kinase (TK) receptors; in addition, the CBL product also acts in ubiquitination-mediated protein degradation in the proteasome [85][86]. Overall, mutations affecting the *CBL* gene in myeloid malignancies show a predominance of deletions involving the exon 8 of this gene [87] at frequencies that vary from 15% of patients diagnosed with juvenile myelomonocytic leukaemia, to 13% of CMML (mostly the *CBL* Y371 mutation) [88][89], 10% of AML and 8% of atypical chronic myeloid leukaemia cases [89][90][91]. Similarly, *CBL* mutations are found in a variable percentage of SM patients [19][36][68][69][77][80][81], where they are predominantly located at exon 8 (frequently also at codon Y371), their frequency ranging from <1% in Non-AdvSM patients to >10% of AdvSM cases [19][68][71][77][81], including >25% of SM-AHN patients in some cohorts [68][71] (average of 15%). In contrast to other myeloid neoplasms in which the impact of *CBL* mutations remains unclear [86][89][90][92], their presence in SM has been associated with poorer outcomes [71].

The *JAK2* (Janus Kinase 2) gene is located on human chromosome 9 and encodes a protein that acts as an intracellular (non-receptor) TK that is associated with various cell surface receptors for transducing activating signals through relevant pathways such as the mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription (STATs) pathways [93][94][95]. The most common *JAK2* activating mutation, the *JAK2* V617F mutation, has been reported in several diagnostic subtypes of MPN [96], which can explain its high incidence (about 11%) in SM-AHN patients [19][40][41][77][97] as compared to other diagnostic subtypes of SM [19][41][68][79][97]. A recent study in SM-AHN patients showed that *KIT* D816V and *JAK2* V617F mutations probably arise in two independent clones in most patients, in which the presence of *JAK2* mutations appears to have a low prognostic impact [98].

The *KRAS* (Kirsten Rat Sarcoma Viral Oncogene Homolog) and *NRAS* (Neuroblastoma RAS Viral Oncogene Homolog) genes are both located on chromosome 12, and they encode proteins involved in signalling pathways associated with growth factor membrane receptors through their interaction with membrane GTPases. A large number of somatic mutations involving the *KRAS/NRAS* genes have been identified, mostly associated with solid tumours such as lung cancer, pancreatic cancer and colorectal cancer, among other prevalent tumours [99][100]; in some of these tumours such as metastatic colorectal cancer, *KRAS* and *NRAS* mutations have also been associated with a poorer prognosis [101]. In myeloid neoplasms, *NRAS* mutations have been associated with the development of AML (7–13%) secondary to different subtypes of MPN; however, it remains unclear whether these mutations directly promote progression to leukaemia [91]. With regards to SM, *KRAS* and/or *NRAS* mutations have been sporadically reported in ISM [79][83] and MCL cases [19][68], while they are more frequently found among SM-AHN patients, particularly in cases associated with poor-prognosis myeloid neoplasms (i.e., AML) [19][36][40][41][68][80][102]; in this setting, some researchers have suggested that these mutations might have an adverse prognostic impact [103].

RUNX1 (Runt-Related Transcription Factor 1) is a gene located on human chromosome 21 that encodes a functional protein that acts as a transcription factor involved in the development of HSC [104]. The most frequent *RUNX1* mutations have been associated with progression from MPN to AML [105], which could explain the high frequency of these mutations (up to 37%) among patients with secondary AML [85][91]. In line with these findings, the presence of *RUNX1* mutations in patients with MDS is associated with resistance to specific chemotherapeutic drugs and shortened survival [106][107]. In SM, *RUNX1* mutations are preferentially located at exons 4 and 5 of the gene [19][22][68][69][70][79][80][83][108], with a frequency that ranges from <1% of Non-AdvSM patients to up to 18% of AdvSM cases, the highest frequency being detected in SM-AHN patients [68][70]. From a prognostic point of view, *RUNX1*-mutated cases have been associated with an adverse outcome, both among Non-AdvSM and AdvSM patients [69][70][79][83][109].

3.2. Mutations in Genes Involved in Epigenetic Regulatory Mechanisms

Although the specific role of each individual epigenetic alteration detected in SM remains unknown [110][111][112][113], recurrent mutations in genes involved in epigenetic modifications of DNA (i.e., *ASXL1*, *CILK1*, *DNMT3A*, *EZH2*, *IDH1*, *IDH2*, *KAT6B*, *NPM1*, *SETBP1* and *TET2* genes) have been recurrently identified; among these, mutations involving the *ASXL1*, *DNMT3A*, *EZH2* and *TET2* genes are the most commonly reported ones.

The *ASXL1* (ASXL transcriptional regulator 1) gene encodes for a protein that interacts with the retinoic acid receptor involved in chromatin remodelling, although its precise function remains largely unknown [114]. The most frequent *ASXL1* mutations found in myeloid neoplasms are located at exon 12 [115], with an overall incidence that ranges from <7% of patients with essential thrombocytopenia (ET) or polycythaemia vera (PV), to almost 40% of primary myelofibrosis cases [116]. *ASXL1* is also the second most frequently mutated gene in MDS and CMML, and it is altered in up to 30% of AML patients [115][117]. Most reported *ASXL1* mutations in SM are also located at exon 12 [19][22][70][77][79][81] with a highly variable frequency that ranges from 1% of BMM cases to >20% of AdvSM patients, particularly of SM-AHN cases. Similarly to other myeloid neoplasms [107][116][118], *ASXL1* mutations have been also (recurrently) associated with a worse prognosis in SM [19][69][77][80][81][119].

The *DNMT3A* (DNA Methyltransferase 3 Alpha) gene located on chromosome 2, encodes for an enzyme responsible for the methylation of CpG islands, which is critical in various physiological processes during embryogenesis and/or in the inactivation of the X chromosome [120]. The most frequently described mutation in the *DNMT3A* gene occurs at codon R882 [121], being present in 8–13% of MDS, 26% of AML secondary to MDS and 2% of CMML patients [121][122]. In general, the presence of *DNMT3A* mutations in patients with myeloid malignancies has been associated with a higher number of blasts in BM and greater leukocyte counts in blood [107][117] in the absence of a clear prognostic impact [117][121][122][123]. Although *DNMT3A* mutations have been described at relatively similarly low frequencies in Non-AdvSM and AdvSM (4% vs. 6%, respectively), their presence has been associated with a significantly poorer prognosis in some patient cohorts [79][81].

The *EZH2* (Enhancer of Zeste 2 polycomb repressive complex 2 subunit) gene encodes a protein of the PRC2 complex involved in proliferation, differentiation, ageing and maintenance of the chromatin structure through methylation, acting as both a tumour suppressor gene and an oncogene [85]. The *EZH2* gene is coded in chromosome 7, and its mutations have been described in both myeloid and lymphoid malignancies, as well as in solid tumours, where they have been recurrently associated with more advanced tumour stages and metastatic disease [124]. In myeloid neoplasms, *EZH2* mutations have been described in patients with PV (3%), myelofibrosis (13%), CMML (6%), AML (6%) and MDS (10%) [85][117][123][125][126]; in MDS they have been associated with a worse prognosis [107][126]. In SM, *EZH2* mutations have been reported almost exclusively within AdvSM patients [19][22][68][70][119], particularly among ASM and SM-AHN cases.

The *TET2* (Ten–eleven translocation methylcytosine dioxygenase 2) gene is located on chromosome 4 and encodes for a protein that catalyses the conversion of 5-methylcytosine (5-mc) to 5-hydroxymethylcytosine (5-hmc) in the DNA [127]. It is believed that 5-hmc may initiate DNA demethylation by preventing binding to the CpG islands of DNA methyltransferases characteristic of these sequences [128]. To date, *TET2* mutations have been described in every exon of the gene, and sometimes mutations involving both alleles coexist in the same cell [70][129]. *TET2* mutations are considered to be early events in the development of haematological malignancies such as MPN, MDS, CMML and different subtypes of leukaemia and lymphoma, as well as in SM [129]. Overall, *TET2* mutations have been described in about 14% of MPN, 23% of MDS (in which they usually occur together with mutations in *SF3B1*, *U2AF1*, *ASXL1*, *SRSF2* and/or *DNMT3A* and also a normal karyotype [107]) and 30% of CMML patients (often associated with mutations in the *SRSF2* and *U2AF1* genes) [68][72][107][117][130]. In SM, *TET2* is the most frequently mutated gene other than *KIT*. In these later patients, *TET2* mutations have been reported along the entire gene sequence but more frequently at exons 3, 9 and 11. As found also in MDS, the coexistence of *TET2* and *SRSF2* gene mutations has also been reported in SM [68][119]. Of note, in vitro studies suggest that in a significant proportion of patients with SM-AHN, *TET2* mutations may precede the *KIT* D816V mutation [119], similarly to what would also occur with *ASXL1* and *SRSF2* mutations. However, despite *TET2* mutations being significantly more frequently detected in AdvSM vs. Non-AdvSM patients (39% vs. 3% of the cases, respectively) [22][40][41][68][70][71][77][79][80][81][97][119], and their being associated with the presence of C-findings [41], they do not seem to have any prognostic impact in SM [19][68][69][70][77][79][80][81][83][123].

3.3. Mutations in Genes Involved in Alternative mRNA Splicing

The presence of mutations in genes associated with the spliceosome, responsible for alternative RNA processing, has been linked to different diagnostic subtypes of haematopoietic malignancies (e.g., MDS) and some solid tumours (e.g., ocular uveal melanoma or pulmonary fibrosis) [131][132]. These include mutations in the *SF3B1*, *SRSF2* and *U2AF1* genes,

from which mutations in the former two genes have been described in SM at relatively high frequencies in SM and/or (i.e., *SRSF2*) in association with poorer outcomes [69][82].

The *SRSF2* (serine and arginine rich splicing factor 2) gene encodes for a protein that is critical for alternative mRNA processing at the post-transcriptional level [133], which also acts as an important regulator of DNA stability, being a key player in the DNA acetylation/phosphorylation network [134]. The most frequent somatic mutations of *SRSF2* found in SM patients are located at codon P95 [22][68][70][78][79]. Among patients with other myeloid haematological neoplasms, *SRSF2* mutations are particularly frequent (28–30%) among CMML cases [135] and, to a less extent, MDS (11%) and AML (6%) patients [107][117][135]. Recent studies in SM patients show the presence of *SRSF2* mutations in a variable percentage of cases ranging from <1% of Non-AdvSM cases to around one third of AdvSM patients, being one of the most frequently mutated genes in SM, particularly in SM-AHN cases [19][22][36][40][68][69][70][78][79][80][81][83]. In contrast to other haematological neoplasms [117][136][137][138], the presence of *SRSF2* mutations has been consistently associated with an adverse prognosis in patients with SM [70][83], particularly among AdvSM cases [36][69][80].

The *SF3B1* (splicing factor 3b subunit 1) gene is located in chromosome 2, and it encodes for the largest subunit of the SF3B complex, a core component of the U2 small nuclear ribonucleoprotein of the U2-dependent spliceosome [139]. *SF3B1* is the most commonly mutated splicing factor gene in MDS patients [140], in whom it is associated with a more favourable outcome [141]. In contrast to *SRSF2*, *SF3B1* mutations have been less frequently described in SM [19][22][70][79][131][142], with only the K666 codon found to be mutated in more than two patient series. Actually, *SF3B1* mutations are detected in <7% of AdvSM patients (most frequently in SM-MDS cases [70][80][119]) (Table S3), while they are rarely found in Non-AdvSM patients [19][68][79][80]. Likewise, *U2AF1* mutations are also relatively rare in SM, with a higher incidence in AdvSM [19][40][68] vs. Non-AdvSM cases (6% vs. 1%, respectively) (Table S2); these mutations are mostly located at codons S34 [19][143][144] and Q157 [19] of the *U2AF1* gene.

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