FIP1L1/PDGFR α -Associated Systemic Mastocytosis

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Key Words

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Abstract

Since the identification of the *FIP1L1/PDGFR α* fusion gene as a pathogenic cause of the hypereosinophilic syndrome (HES), the importance of the molecular classification of HES leading to the diagnosis of chronic eosinophilic leukemia (CEL) has been recognized. As a result, a new category, 'myeloid and lymphoid neoplasm with eosinophilia and abnormalities in PDGFRA, PDGFRB or FGFR1', has recently been added to the new WHO criteria for myeloid neoplasms. FIP1L1/PDGFR α -positive disorders are characterized by clonal hypereosinophilia, multiple organ dysfunctions due to eosinophil infiltration, systemic mastocytosis (SM) and a dramatic response to treatment with imatinib mesylate. A murine HES/CEL model by the introduction of FIP1L1/PDGFR α and IL-5 overexpression also shows SM, representing patients with FIP1L1/PDGFR α -positive HES/CEL/SM. The murine model and the in vitro development system of FIP1L1/PDGFR α -positive mast cells revealed the interaction between FIP1L1/PDGFR α , IL-5 and stem cell factor in the devel-

opment of HES/CEL/SM. Current findings of FIP1L1/PDGFR α -positive HES/CEL are reviewed focusing on aberrant mast cell development leading to SM.

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Introduction

The importance of the molecular classification of the hypereosinophilic syndrome (HES) has been increasingly recognized. The fusion gene *FIP1L1/PDGFR α* was identified in a large number of patients initially diagnosed as having a myeloproliferative variant of HES or chronic eosinophilic leukemia (CEL) [1]. Subsequently, other variant PDGFRA fusion genes as well as those involving PDGFRB or FGFR1 have also been described in myeloproliferative neoplasms with eosinophilia in the last years [2–4]. As a result, a new category of myeloid neoplasms, 'myeloid and lymphoid neoplasm with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1', has recently been added to the new WHO criteria [5]. FIP1L1/PDGFR α fusion-positive disorders are characterized by clonal myeloproliferation resulting in hypereosinophilia, multiple organ dysfunctions due to eosinophil infiltration, a dramatic response to treatment with

imatinib mesylate and systemic mastocytosis (SM) [6]. Murine models of FIP1L1/PDGFR α -induced diseases have been reported recently [7, 8]. Interestingly, these models demonstrated severe SM representing patients with FIP1L1/PDGFR α fusion-positive diseases [9]. In this review, the clinical manifestation of FIP1L1/PDGFR α fusion-associated disorders are summarized, focusing on mastocytosis induced by FIP1L1/PDGFR α expression, and the mechanisms of mastocytosis in FIP1L1/PDGFR α -positive HES/CEL are discussed.

Eosinophilia in SM Patients

Peripheral blood eosinophilia has been reported in 15–28% of SM patients [10–12]. This is no big surprise since crosstalk between eosinophils and mast cells is well known, especially in allergic inflammation. For instance, mast cell activation by major basic protein, an eosinophil granule protein, elicits the generation of lipid mediators and cytokines. Eosinophils also produce cytokines associated with mast cell activation such as stem cell factor (SCF), granulocyte/macrophage colony-stimulating factor and nerve growth factor [13]. The D816V mutation in the *KIT* gene resulting in constitutive activation of the receptor tyrosine kinase has been shown in the majority of patients as a cause of SM [14]. D816V-kit mutation-positive SM with eosinophilia has been clinically distinguished from that without eosinophilia. D816V-kit mutation-positive SM patients with eosinophilia present hepatosplenomegaly, lymphadenopathy, anemia and monocytosis more frequently as well as higher levels of circulating tryptase, whereas anaphylaxis is seen with a low frequency in these patients, in comparison to patients without eosinophilia [10].

Clinical Manifestations of Mastocytosis Associated with FIP1L1/PDGFR α

A recent report has shown that FIP1L1/PDGFR α -associated SM is a clinically distinguishable disease from D816V mutation SM with eosinophilia [10]. FIP1L1/PDGFR α -associated SM shows lower tryptase levels in the circulation, less aggregation of bone marrow mast cells, more severe eosinophilia, higher serum vitamin B12 levels and more frequent pulmonary and cardiac involvement than D816V SM with associated eosinophilia. The clinical difference is important since it would justify the differential diagnosis between these two entities,

based on the analysis of the expression of the FIP1L1/PDGFR α fusion gene. More recently, Klion [15] proposed a scoring system to approach FIP1L1/PDGFR α fusion-positive HES/CEL therapy appropriately.

SM in Murine Models of FIP1L1/PDGFR α -Positive Disorders

First, Cools et al. [7] reported that the introduction of the *FIP1L1/PDGFR α* fusion gene into bone marrow hematopoietic stem cells and progenitors (HSC/P) induces a murine model of a myeloproliferative disorder (MPD) similar to that found in p210-BCR/ABL-induced chronic myelogenous leukemia-like disease (F/P-MPD). Subsequently, an HES/CEL murine model was developed by the introduction of the *FIP1L1/PDGFR α* fusion gene into bone marrow HSC/Ps in the presence of T-cell overexpression of IL-5 (F/P-HES/CEL) [8]. More recently, these two murine models were also shown to develop tissue mast cell infiltration and increased circulating mast cell protease 1 (MMCP-1) levels, which is a systemic assay of mast cell content and degranulation in the mouse resembling serum tryptase determination in SM patients [9]. Similar to the patients with *FIP1L1/PDGFR α* fusion gene, tissue mast cell infiltration of hematopoietic organs, skin and intestine, where mast cell morphology is aberrant, is present in F/P-HES/CEL mice. Tissue mast cell shape is irregular with frequent cytoplasmic extensions reminiscent of the 'spindle shape' found in clinical SM. In addition, serum levels of MMCP-1 are extremely elevated in F/P-HES/CEL mice.

A possible interaction of IL-5 with the SM phenotype was analyzed in F/P-HES/CEL mice. F/P-HES/CEL and F/P-MPD mice showed significantly greater mast cell infiltration in their skin and intestine, and higher levels of MMCP-1 compared to both controls with and without IL-5 overexpression. Interestingly, intestinal mast cell infiltration and serum MMCP-1 levels in F/P-HES/CEL mice were significantly higher compared to F/P-MPD, suggesting that FIP1L1/PDGFR α in conjunction with IL-5 exacerbates mastocytosis in murine F/P-HES/CEL [9].

Mechanism of FIP1L1/PDGFR α -Promoted Mast Cell Development

Since the c-kit signaling pathway is pivotal for normal mast cell development and function, the question of whether FIP1L1/PDGFR α -associated SM is still c-kit de-

Fig. 1. Intracellular signaling of FIP1L1/PDGFR α + (F/P) cells. FIP1L1/PDGFR α + (F/P) primary mouse eosinophils express up-regulated IL-5R α and FIP1L1/PDGFR α activates the JAK2/STAT5 pathway. The CCR3/ERK1/2 signaling pathway may be amplified by FIP1L1/PDGFR α expression [25]. Up-regulated expressions of α_4 integrin and Siglec-F were observed in FIP1L1/PDGFR α + murine eosinophils [8]. FIP1L1/PDGFR α synergizes with SCF stimulation via c-kit to activate Akt signaling in mouse mast cells. Eosinophils and mast cells also express c-kit and IL-5R α , respectively.

pendent arises. In fact, following blockade of the the c-kit signaling pathway using anti-c-kit antibody, tissue mast cells and circulating levels of MMCP-1 were significantly decreased, suggesting that tissue infiltration of FIP1L1/PDGFR α fusion-positive mast cells are associated with SCF/c-kit signaling. The ex vivo cytokine-dependent mast cell differentiation of FIP1L1/PDGFR α -expressing HSC/Ps was largely dependent on the use of SCF in the culture conditions. Moreover, FIP1L1/PDGFR α fusion-positive mast cells showed prolonged survival and enhanced migration toward SCF. Specific synergistic stimulation of the Akt signaling pathway by FIP1L1/PDGFR α and SCF indicated collaboration of two tyrosine kinase activities in their downstream signaling pathways. Taken together, FIP1L1/PDGFR α synergizes with the SCF/c-kit pathway to promote mast cell development, activation and survival both in vivo and in vitro [9].

Fig. 2. FIP1L1/PDGFR α in conjunction with SCF and IL-5 promote leukemic hematopoiesis and eosinophil and mast cell (MC) development. FIP1L1/PDGFR α may occur in hematopoietic stem cells or early progenitor cells resulting in the expression of FIP1L1/PDGFR α in most hematopoietic cells. Progenitors including earlier and mature eosinophils and MCs express c-kit. In contrast, IL-5R α expression has been observed on eosinophil progenitor (EoP), MC progenitor (MCP) and mature eosinophils and MCs. FIP1L1/PDGFR α enhances SCF/c-kit signaling by sharing downstream signaling and up-regulates IL-5R α expression facilitating its intracellular signaling. There is significant crosstalk between eosinophils and MCs. These findings imply that FIP1L1/PDGFR α in collaboration with SCF may affect leukemic myeloproliferation, and synergistically with IL-5 expand and activate MC and eosinophil lineages. ST-HSC = Short-term HSC; CMP = common myeloid progenitor; GMP = granulocyte-macrophage progenitor.

Pathogenesis of FIP1L1/PDGFR α -Positive HES/CEL/SM Associated with SCF and IL-5

Previously, we reported that the induction of murine HES/CEL by FIP1L1/PDGFR α requires a second event that is associated with IL-5 overexpression [8]. In addition, the level of expression of IL-5R α was exclusively up-regulated in FIP1L1/PDGFR α -positive splenocytes and FIP1L1/PDGFR α fusion protein shares the downstream JAK2/STAT5 pathway with IL-5 signaling (fig. 1) [16]. Interestingly, polymorphisms of the human *IL-5RA* gene have been found linked to the constitutional *IL-5RA* genotype and the severity of FIP1L1/PDGFR α -positive CEL [17]. These findings suggest that amplification of IL-5 signaling by FIP1L1/PDGFR α triggers a CEL-like disease. Interestingly, IL-5R α is expressed on eosinophil and mast cell progenitors [18, 19] as well as mature eosinophils [20]

and mast cells [21], whereas c-kit expression is not only found on progenitors but also on mature eosinophils and mast cells [14, 18, 19]. Importantly, expression of the *FIP1L1/PDGFR* fusion gene or deletion of the surrogate marker *CHIC2* have been detected in non-eosinophilic cells, including neutrophils, monocytes, mast cells, lymphoid lineage cells and bone marrow CD34-positive cells in part of the patients, suggesting that the fusion of the *FIP1L1/PDGFR* genes may occur in HSCs or early progenitors [22–24]. Taken together, these findings imply that *FIP1L1/PDGFR* in collaboration with SCF may affect leukemic myeloproliferation and synergistically with IL-5 expand and activate mast cell and eosinophil lineages (fig. 2).

Conclusion

HES/CEL has attracted a lot of attention since the patients were successfully treated with imatinib mesylate, and subsequently the target, *FIP1L1/PDGFR*, was discovered in a large number of patients initially diagnosed as myeloproliferative variant of HES. To our knowledge, there is little doubt that *FIP1L1/PDGFR* preferentially affects eosinophil and mast cell proliferation, survival, differentiation and tissue infiltration, and leukemogen-

esis is induced combined with systemic or local extrinsic factors, as demonstrated by crucial roles of IL-5 and SCF in the pathogenesis of *FIP1L1/PDGFR*-initiated HES/CEL/SM. This disease, an example of the crosstalk between oncogenesis and inflammation, represents an excellent model to study cellular integration of biochemical signals in cancer, being responsible for crucial aspects of cancer biology, e.g. cell proliferation, survival, tissue invasion and communication with the specific tissue microenvironment.

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Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the content of this article.

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