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Genetic and molecular diagnosis of severe congenital neutropenia

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Abstract

Purpose of review: Severe congenital neutropenia has been a well-known haematological condition for over 50 years. Over this long period of time, the variable genetic etiology and associated sequelae of the disease have been ascertained, and successful treatment strategies developed. Over the last 2 years, however, new studies have added greatly to our understanding of the molecular basis of the disease, details of which are presented in this review.

Recent findings: Recent studies have elucidated a role for the unfolded protein response in mediating the pathogenic effects of *ELA2* mutations, the most common mutation in SCN as well as cyclic neutropenia. Genetic lesions in *HAX1* have also been identified in the original Kostmann pedigree representing the autosomal recessive form of SCN. An emerging theme is the convergence of these and other genetic lesions underlying SCN in enhancing neutrophil apoptosis. Other studies have revealed the importance of multiple independent mutations in these and other genes in SCN. Finally, the key role for STAT5 in mediating the effects of G-CSFR truncation mutations in the development of MDS/AML following SCN has been elucidated.

Summary: As the full spectrum of molecular mutations causing neutropenia emerges it is becoming possible to differentiate patients into sub-types with different prognoses, for whom tailored therapies are indicated.

Keywords

Severe congenital neutropenia; ELA2; CSF3R; HAX1; GFI1; WASp; neutrophil elastase; G-CSF receptor

INTRODUCTION

Severe congenital neutropenia (SCN) represents a heterogeneous disease, with autosomal recessive, autosomal dominant, sporadic and X-linked forms. The majority of patients present with life-threatening infections during the first 6 months of life, due to extremely low numbers of circulating neutrophils [1]. Treatment with pharmacological doses of granulocyte colony-stimulating factor (G-CSF) has proven to be effective in restoring the neutrophil count in the majority of SCN patients, with a concomitant reduction in infection-related events [2,3]. However, some SCN patients remain unresponsive [3]. Moreover, surviving SCN patients remain at high risk of developing myelodysplastic syndrome (MDS) and/or acute myeloid leukemia (AML) [4,5*,6**].

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REVIEW TEXT

Neutropenias represent a series of potentially life-threatening disorders characterised by a reduction in circulating neutrophils. Since neutrophils play a major role in host defense against bacteria, neutropenia patients suffer from frequent episodes of opportunistic bacterial infections [7**]. Severe congenital neutropenia (SCN) is a heterogeneous group of disorders characterized by a severe decrease in the number of blood neutrophils ($<0.5\times10^9$/l), and a maturation arrest of bone marrow progenitor cells mainly at the promyelocyte/myeloid stage [5*,7**]. Although SCN was originally described as an autosomal recessive disorder in Swedish families, this form is now recognized as a separate syndrome, Kostmann's neutropenia, which produces even lower neutrophil counts ($<0.2\times10^9$/l) [8*]. More commonly, SCN occurs as a sporadic and autosomal dominant disorder, and as a feature of several other inherited disorders. Most SCN patients are successfully treated by G-CSF therapy, although around 10% are unresponsive. However, a major clinical concern for SCN patients remains their increased risk of developing myelodysplastic syndrome (MDS) and/or acute myeloid leukemia (AML) with poor prognosis for survival [5*,6**].

Previous studies have shown that constitutive mutations in the *ELA2* gene (encoding neutrophil elastase) are found in the majority of SCN patients [9,10*] and cause neutropenia [11]. Other important observations are the finding of acquired mutations in the *CSF3R* gene (encoding the G-CSF receptor, G-CSFR) in the majority of patients transforming to MDS/AML [12**], and constitutive (alternate) mutations in the same gene leading to poor responsiveness to G-CSF [13**]. This review describes recent studies that have furthered our understanding of each of these mutations, as well as other mutations responsible for other variants of this disease.

Molecular basis of disease

A number of genes have now been identified that appear to contribute to the etiology of SCN or its associated sequelae (Figure 1).

Neutrophil elastase (NE)—Neutrophil elastase, encoded by the *ELA2* gene, is serine protease produced at the promyelocyte stage of neutrophilic differentiation and stored within the primary granules of mature neutrophils [14]. Over 50 mutations in *ELA2* have been found in patients with autosomal dominant and sporadic forms of SCN, as well as in cyclic neutropenia [10*]. While it has been hypothesized that defective enzyme activity or inappropriate localization may represent the mechanism of pathogenesis for the various mutations [10*], more recent studies argue that NE mutations elicit the unfolded protein response (UPR), which increases the transcription of chaperone-encoding, endoplasmic reticulum-associated protein degradation (ERAD), and pro-apoptotic genes, which ultimately leads to apoptosis [15,16*].

Granulocyte colony-stimulating factor receptor (G-CSFR)—The G-CSF-R, encoded by the *CSF3R* gene, plays a crucial role in the production and function of neutrophilic granulocytes, being able to stimulate the proliferation, differentiation and survival of cells along the neutrophilic lineage, activate the functions of mature neutrophils, as well as mobilize various precursor cells [17*]. Two classes of *CSF3R* mutations have been associated with SCN, with quite different roles [5*,13**].

Acquired mutations in the *CSF3R* gene have been identified in around 20-30% of SCN [17*, 18]. These mutations produce C-terminally truncated hyper-responsive forms of the receptor ($G\text{-}CSFR^{hyper}$), which act in a dominant-negative manner to enhance proliferation at the expense of maturation [13**,19]. The role of $G\text{-}CSFR^{hyper}$ mutations in neutropenia appears to be relatively modest [5*,13**]. However, SCN patients carrying $G\text{-}CSFR^{hyper}$ mutations show a strong predisposition to both MDS and AML, where they appear to represent an early

step in leukemogenesis [5*,12**]. Recent studies suggest that the pathogenic properties of G-CSFR^{hyper} mutation are largely due to the enhanced Stat5 activation they elicit [20,21**], which appears to provide a selective advantage HSCs expressing this mutation [21**,22*].

Constitutive mutations in the *CSF3R* gene, leading to hypo-responsive forms of the receptor (G-CSFR^{hypo}), have been reported in several SCN patients who were unable to respond to normal G-CSF therapy [23]. Again, these mutations – which perturb the extracellular domain – act in a dominant manner over wild-type receptors, probably by disrupting normal ligand binding [13**]. While G-CSFR^{hypo} mutations have not formally been shown to cause SCN, this remains likely, but such mutations are certainly responsible for refractoriness to G-CSF treatment observed in these cases.

HAX1—HAX1 is a ubiquitously-expressed mitochondrial protein, which functions as an anti-apoptotic protein, in a manner similar to bcl-2 with which it has weak homology [24**]. Mutations in HAX1 have been reported in cases of autosomal-recessive SCN (as described in the original Kostmann pedigree) [24**], with some mutations also producing neurological disorders [25*,26*]. In each case, the genetic lesions serve to inactivate the HAX1 protein, leading to a loss of mitochondrial membrane potential, release of proapoptotic proteins and subsequent apoptosis of neutrophils [24**].

Wiskott-Aldrich syndrome protein (WASp)—WASp is exclusively expressed in hematopoietic cell, where it plays a regulatory key role actin polymerization involved in cell signaling, cell-cell interactions and cell motility. Patients with X-linked SCN have been reported with activating mutations in WASp leading to a constitutively-active form of the protein, and unregulated actin polymerization [27,28]. Concomitant defects in mitosis and cytokinesis lead to decreased proliferation and increased apoptosis in myeloid progenitors [29**].

Growth factor-independent protein 1 (GFI1)—GFI1 is a zinc finger protein which appears to function as a transcriptional repressor [30]. Inactivating mutations in this protein have been reported in a small number of SCN patients [31]. Two distinct mechanisms have been proposed for its action, based on the two genes identified to be up-regulated once the repressive effects of GFI1 have been alleviated by mutation: (i) upregulation of NE [31] leading to induction of the unfolded protein response and hence apoptosis [7**]; (ii) upregulation of C/EBPε leading to induction of CSF-1 expression and lineage switching to the macrophage lineage [32].

Other proteins—Many cases of SCN exist for which no underlying molecular cause have been identified, although several of the above candidates have been excluded, making it likely that other mutations also contribute to neutropenia. In one such case, CD40 ligand deficiency has been suggested as a possible cause [33*]. Moreover, there are several disorders which exhibit neutropenia as part of a broader spectrum of disease spectrum, the molecular basis of which have been determined. These include mutations in the Rab27 protein, a small GTPase, in Griscelli syndrome type 2 [34], the MAPBPIP scaffolding protein in so-called ‘p14 deficiency’ [35], the AP3B1 adapter protein in Hermansky-Pudlak syndrome type 2 [36] and the CHS1/LYST protein in Chediak-Higashi syndrome [37*].

Key themes

Emerging from the most recent studies are some consistent themes, which serve as a framework for future work.

Convergence of mutations at the biological level—Many neutropenia-associated mutations converge to disrupt the delicate developmental pathway required to form these protease-packed cells [38*]. Defects in protein trafficking [10*], as well as the molecular defects underpinning p14 deficiency [35], Griscelli syndrome type 2 [34], Hermansky-Pudlak syndrome type 2 [36] and Chediak-Higashi syndrome [37*] appear to cause a similar outocme. Recently, the unfolded protein response has both associated with mutations in both NE [15, 16*] and GFI1 [7**]. Several of the SCN-related mutations result in increased apoptosis, including those in NE [15,16*], WASp [29**], G-CSFR^{hypo} [39], HAX1 [24**], and potentially GFI1 [7**], suggesting that mistakes in trafficking and the unfolded protein response are trigger events for initiating premature cell death. This hypothesis has a number of implications for therapy. Firstly, such a scenario would imply that the key role of G-CSF therapy in SCN is as a survival factor for neutrophils, rather than simply stimulating the production of neutrophils (as is its role in the treatment of other forms of neutropenia). Secondly, it is possible that other agents that enhance neutrophil survival might be effective therapeutic agents. Thirdly, the expansion of acquired G-CSFR^{hyper} mutant clones might be due to enhanced clonal survival rather than exclusively an enhanced proliferative advantage.

Co-operation between mutations—Another common theme from recent studies is the presence of combinations of the above mentioned mutations in neutropenia. For example, one of the original Kostman family possessed an NE mutation and another member had an acquired G-CSFR^{hyper} mutation, presumably on the background of an HAX1 mutation [40]. Similarly, combinations of NE and acquired G-CSFR^{hyper} mutations have been reported [5*], while we recently reported a patient with constitutive NE and G-CSFR^{hypo} mutations, who acquired sequential G-CSFR^{hyper} mutations [41*]. Other cases have been reported with multiple G-CSFR^{hyper} mutations [5*], as well as with multiple NE mutations [42*]. In the case of constitutive mutations, such combinations are presumably the result of chance, although there remains a possibility that the mutations synergise in some way, particularly those that converge at a similar biological level. In the case of the acquired G-CSFR^{hyper} mutations, it is possible that the presence of an altered myeloid compartment and G-CSF therapy in neutropenic patients creates an millieau favourable for the expansion of clones possessing such a mutation [13**]. Indeed, such acquired G-CSFR^{hyper} mutations may partially rescue neutropenia caused by NE and/or G-CSFR^{hypo} mutations [41*,43].

Treatment strategies—Treatment with G-CSF is effective in the majority of SCN [3]. However, alternative therapies are needed, particularly for patients who are refractory to G-CSF treatment, and those acquiring truncating G-CSFR^{hyper} mutations on G-CSF treatment due to concerns about possible contribution of G-CSF to progression to MDS/AML. One approach would be to improve the reduced neutrophil survival common in neutropenia. While there are several strategies for doing this, including the inhibition of NE, one key therapeutic target is STAT5 that we and others have shown to be a key mediator of survival in neutrophilic granulocyte [41*,44*]. Various strategies can be brought to bear to target this molecule [45*]. Indeed, we have successfully used corticosteroids to enhance Stat5 activation and survival *in vitro* with successful application in the treatment of neutropenia [39], and more recently showed that constitutively-active Stat5 could improve survival in a cell model of granulopoiesis [41*]. Undoubtedly, other aspects of the cell survival machinery could also be targeted.

CONCLUSIONS

Recent studies have elucidated several genetic and molecular perturbations leading to severe congenital neutropenia. They provide important new insights into both normal and pathogenic myelopoiesis. Diagnosis and classification based of this new genetic, molecular and cellular

information affords the opportunity to develop tailored, and potentially new, therapeutic strategies, and much improved care for SCN patients.

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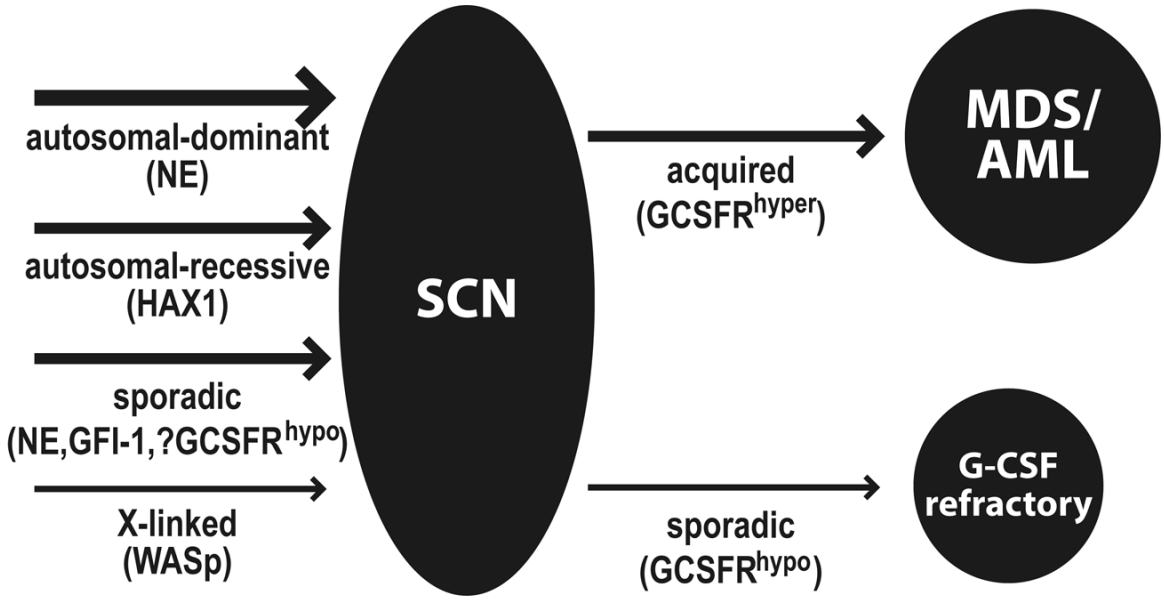

Figure 1. Mutations in severe congenital neutropenia

Model for the involvement of mutations in severe congenital neutropenia (SCN). Mutations underlying the different forms of SCN are indicated on the left hand side, while mutations associated with predisposition of these patients to MDS/AML, or refractoriness to G-CSF treatment are shown on the right hand side.