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Large granular lymphocyte cells and immune dysregulation diseases – the chicken or the egg?

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In less than 1% of patients suffering from rheumatoid arthritis (RA), a condition known as Felty syndrome (FS) can develop.[1,2] FS, first described by the American physician Augustus Roi Felty in 1924, is characterized by the triad of RA, (unexplained) neutropenia, and splenomegaly, and is more common in people aged 50 years and over. In spite of the clear association with RA, the common underlying cause of all three characteristic symptoms remains largely elusive. It is known that FS shows an overlap with a rare type of T-cell leukemia, called T-cell large granular lymphocyte (T-LGL) leukemia, which also typically presents in elderly individuals with a median age of 60 years. In fact, T-LGL leukemia patients can show all the features that FS patients have, albeit at varying frequencies, thus making the differential diagnosis between LGL leukemia and FS problematic at times.[3] An additional complication to that of the overlapping clinical features is the fact that both conditions share the presence of LGL cells.

Based on the overlapping features, Savola and colleagues explored a potential common pathogenic mechanism between FS and LGL leukemia. In this issue of *Haematologica* they report on a cohort of 14 FS patients, which were evaluated by next-generation sequencing (NGS) technology for the occurrence of somatic mutations in the *STAT3* and *STAT5B* genes.[4] Both of these genes have been notably implicated in a subset of the $CD8^+$ $TCR\alpha\beta^+$ T-cell type of LGL leukemia, and the occurrence of *STAT3* mutations in LGL leukemia is strongly associated with RA and neutropenia.[5-7] Indeed, in >40% of FS cases somatic *STAT3* hotspot mutations were found, which is at a rate comparable to LGL leukemia cases. The fact that the *STAT3* variant allele frequencies were lower in FS can be explained by the smaller T-cell clone sizes in FS patients. Nevertheless, LGL cell proportions were increased in FS patients, and in two cases the LGL cell numbers additionally fulfilled the criteria for LGL lymphocytosis. Taken together, these observations firmly support the idea that FS and LGL leukemia are part of a disease spectrum with a common pathogenesis, in

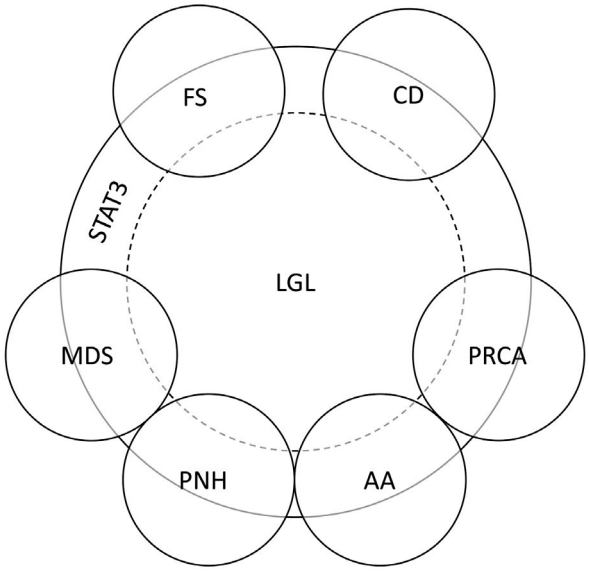

Figure 1. Overlap between LGL leukemia / proliferation and immune dysregulation diseases and conditions that show an increase of LGL cells and/or the presence of *STAT3* mutated cells. AA: aplastic anemia; CD: celiac disease; FS: Felty syndrome; MDS: myelodysplastic syndrome; PNH: paroxysmal nocturnal hemoglobinuria; PRCA: pure red cell aplasia; LGL: large granular lymphocyte.

which LGL leukemia ranges from poly/oligoclonal to monoclonal.[8] The concept of a disease continuum is further strengthened by the observation that IL-15RA and CXCL10 levels are also increased in both conditions.

Hitherto, the occurrence of LGL cells and clones were associated with bone marrow failure syndromes such as aplastic anemia (AA) and (hypoplastic) myelodysplastic syndrome (MDS), both of which are believed to reflect an autoimmune pathogenesis.[9,10] However, in conditions such as pure red cell aplasia (PRCA), characterized by the killing of red cell precursors, and paroxysmal nocturnal hemoglobinuria (PNH), characterized by the complement-mediated destruction of red blood cells, LGL proliferations have also been reported.[11,12] It is of interest that in many of these conditions *STAT3* mutations have been documented. The current description of high LGL counts and *STAT3* mutations in FS thus extends the spectrum of immune dysregulation disease conditions in which LGL cells are prominently associated (Figure 1). Notably, in their series, Savola *et al.* found four FS cases that also showed celiac disease (CD),[4] which confirms earlier suggestions of links between LGL cells, *STAT3* mutations, and CD.[13,14]

The presumed common pathogenesis of LGL leukemia and immune dysregulations such as FS, CD, and bone marrow failure and related conditions (AA, hypoplastic MDS, PNH) would pave the way for more sophisticated treatment strategies than the current general immune suppressive modalities which are frequently applied.[15] Such targeted strategies would have to exploit common molecular aberrations, one of the most promising approaches being STAT3 inhibition in JAK/STAT hyperactive LGL cells. This is of special interest as constitutive STAT activation is observed in almost all LGL proliferations regardless of the presence of mutations in the *STAT3* gene.[16] In addition, specific inhibition of JAK family kinases with the AG-490 tyrosine kinase inhibitor has been demonstrated to induce apoptosis of LGL leukemia cells *in vitro* and antisense oligonucleotide therapy to inhibit STAT3 activation, which has been shown to restore FAS sensitivity in LGL leukemia cells.[17] However, further investigation into other common molecular aberrations might reveal distinct molecular mechanisms or pathways in subgroups of these diseases, which could be targeted by yet different molecule-centered treatment strategies. This would require deep sequencing approaches in larger cohorts, and might have to go beyond genomics by studying the transcriptome, the epigenome, and perhaps also small non-coding RNAs.

In all the associations between LGL leukemia / proliferations and immune dysregulations, however, one central question remains to be addressed more definitely; "the chicken or the egg" question. In other words, in scientific parlance, are LGL cells truly causing the immune dysregulation, or is their presence more likely to be an epiphenomenon as a consequence of chronic (auto)antigen stimulation in these conditions? Based on existing literature, it is tempting to speculate that LGL cells have an authentic causative role, nevertheless, before definite conclusions can be drawn further research is required. This should undoubtedly include studies that aim to eradicate the LGL clones in patients through targeted treatment, and which could categorically disclose the presumed causative role of LGL cells.

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