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Commentary

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Defects in DNA replication hit NK cells and neutrophils

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Patients who present with unique immunological phenotypes provide an opportunity to better understand defect-driving mutations. In this issue of the JCI, Cottineau and colleagues characterize 5 individuals who exhibited growth restriction, facial deformities, and a history of bacterial and viral infection. Further characterization revealed that these patients were neutropenic and NK cell deficient. These phenotypes were unexpectedly linked to mutations in the gene encoding a subunit of the Go-Ichi-Ni-San (GINS) complex, which is essential for DNA replication prior to cell division. Together, the results of this study lay the groundwork for future studies to explore the role of DNA replication in immune cell generation and function.

Unexpected cause of NK cell deficiency and neutropenia

In this issue, Cottineau and colleagues (1) report the characterization of 5 patients with previously unidentified mutations in the 5' UTR of the gene encoding Go-Ichi-Ni-San (GINS) complex subunit 1 (GINS1). GINS1 is a required component of the GINS complex, which plays an essential role in DNA replication preceding cell division (2, 3). As expected for such a fundamental defect, the patients experienced a wide range of conditions, including intrauterine and postnatal growth retardation, facial deformities, and immunological defects. Unexpectedly, these patients also completely lacked natural killer (NK) cells and suffered from neutropenia. These immune defects resulted in viral and bacterial infections, osteosarcoma, protein-losing enteropathy, hypothyroidism, premature aging, and autoimmune hemolytic anemia.

The GINS complex is a heterodimer composed of GINS1, GINS2, GINS3, and GINS4. At the G₁-to-S phase transition, the GINS complex is recruited to the origins of replication. The mutations identified by Cottineau and colleagues in the 5' UTR mutant of *GINS1* resulted in reduced expression and deletions in exon 2. However, in these patients, about 5% to 10% of WT GINS1

was still transcribed. This residual WT GINS expression may explain the phenotype of these patients, as global *Gins1* deletion in mice results in embryonic lethality (4).

Cottineau et al. determined that the amount of GINS1 expressed in patient-derived cells ranges from 29% to 53% of the level of GINS1 generated by cells from healthy controls (1). This reduced expression apparently leads to decreased expression of GINS3 and GINS4, resulting in defective GINS complex assembly. Consistent with these findings, fewer patient-derived fibroblasts were found to be in G₁, and they were more likely to be in G₂/M, resulting in slower proliferation and signs of senescence. The slow replication was caused by fewer replication clusters and fewer bidirectional replication forks per cell, defects that were partially compensated by an increase in replication speed compared with control-derived fibroblasts.

Why are neutrophils and NK cells so severely affected by the *GINS1* mutations? It could be argued that neutrophil precursors must divide a lot to supply the billions of neutrophils that are needed each day. Thus, neutrophil precursors might be severely affected by a DNA replication defect. NK cell precursors on the other hand would not be expected to divide as much, because NK cells are a

longer-lived population, and, therefore, fewer precursors are needed each day to replenish the pool. Unfortunately, at this time there is not really a unifying hypothesis explaining the phenotypes of the patients.

Treatment efforts in these patients may provide a clue as to how GINS1 deficiency affects NK cell and neutrophil populations. In one of these patients, the neutropenia was rescued by granulocyte colony-stimulating factor (G-CSF), a cytokine that speeds up neutrophil maturation. However, the addition of IL-2 or IL-15 to patient PBMCs did not rescue the NK cell defect. It seems reasonable that NK cells may be particularly susceptible to elimination if replication is defective or imprecise. Such a notion would make biological sense, because aberrant NK cells could be very dangerous to the host. However, it is unclear what the elimination mechanism might be, and how replication defects would be detected.

Concluding remarks

Overall, this is an exciting and provocative article from Cottineau and colleagues. Like any new discovery, it raises more questions than it answers. More work will be required to determine the mechanism by which GINS1 defects affect neutrophils and NK cells and why these mutations do not seem to affect T or B lymphocytes or monocytes. It may be useful to generate a hypomorphic *Gins1* mutant mouse by gene targeting and homologous recombination or by CRISPR to better address how GINS1 deficiency influences different cell populations. Such a mouse line might produce live litters in which expected neutrophil and NK cell defects could be studied.

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