Congenital dyserythropoietic anemias: III’s a charm

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Comment on Liljeholm et al, page 4791

In this issue of Blood, Liljeholm et al show that congenital dyserythropoietic anemia (CDA) type III is caused by a missense mutation in KIF23, which encodes a ubiquitous protein that regulates daughter cell separation during mitosis.1

CDA III patients exhibit increased risk for multiple myeloma, a potential oncogenic consequence of failed cytokinesis.3 Liljeholm et al used time-lapse microscopy to show that this is precisely what occurs in HeLa cells when MKLP1 P916R replaces the normal protein.

The current study is interesting and satisfying because it provides a direct mechanistic link between the extensively studied biology of mitosis and the multinuclearity of CDA. More generally, this work illustrates how modern genetics can rapidly and efficiently identify human disease causing mutations. Of course, many questions remain. For example, if MKLP1 is an essential component for mitosis in all cells, why does the P916R mutation produce a phenotype that is largely (though not completely) erythroid-restricted? This situation is similar to Diamond Blackfan anemia in which haploinsufficiency of ribosomal proteins affects tissue development selectively. These clinical observations indicate that redundant biochemical pathways exist for fundamental cellular processes and that different tissues exhibit unique thresholds for pathology when these processes are perturbed. It is also possible that tissue-specific forms of MKLP1 exert unique functions, perhaps 1 of which is to facilitate the specialized cell divisions that occur during erythroid maturation. Indeed, MKLP1 is expressed at particularly high levels in red blood cell precursors where KIF23 is bound by the essential erythroid transcription factors GATA1 and TAL1 (http://biogps.org/goto?genereport&id=9493; http://genome.ucsc.edu). Additionally, Liljeholm et al identified a novel MKLP1 alternative splice isoform that is enriched in hematopoietic tissues including peripheral blood, bone marrow, and spleen. However, the consequences of MKLP1 P916R may not be entirely erythroid-specific, because CDA III patients exhibit increased risk for multiple myeloma, a potential oncogenic consequence of failed cytokinesis.9,10

It is also of interest to better understand how the P916R mutation impairs MKLP1 function. Is this simply haploinsufficiency for MKLP1 or does this particular mutation have a specific dominant negative effect? This mutation occurs at the carboxyl terminus of the protein, a region that participates in several important protein interactions, some of which are regulated by phosphorylation (see B in figure). Future studies should ascertain how the P916R mutation affects these...
phosphorylation events, the assembly of the centralspindlin complex, and/or its recruitment of partner proteins to the central spindle and midbody.

Finally, this study may provide a toehold for understanding how other disorders cause erythroid multinuclearity. For example, it is possible that the CDA-associated transcription factors GATA1 or KLF1 regulate MKLP1 expression during erythroid maturation. Likewise, SEC23B and/or codanin 1 may function in pathways that regulate MKLP1 or associated proteins. Myelodysplastic syndromes and erythroleukemias also exhibit erythroblast multinuclearity, perhaps by altering processes that occur at the central spindle and midbody. It is possible that polyploidy associated with these acquired disorders contributes to their malignant transformation. In these ways, the study by Liljeholm et al raises interesting possibilities as to how a variety of diverse inherited and acquired anemias may converge on a common pathway to cause erythroid multinuclearity.

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REFERENCES


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