effect, suggesting that CK2 binding to JAK2 is required for maximal ligand activation of JAK2. However, the degree of JAK2 inhibition is significantly less than the inhibition of Stat signaling, raising the possibility that CK2 may have additional effects on Stat signaling.

Based on these findings, Zheng and colleagues hypothesize that CK2 inhibitors will be potent inhibitors of constitutively activated JAK2 V617F and pathways downstream of JAK2 V617F. They find in cells from PV patients and in cultured human erythroid leukemia (HEL) cells, both of which express endogenous JAK2 V617F, that indeed, JAK2 binds CK2 and that CK2 inhibitors significantly depress the amount of active JAK2, Stat3, Stat5, and ERK. More importantly, CK2 inhibitors decrease proliferation and induce apoptosis in cells expressing JAK2 V617F, assessed by proliferation assays, cell-cycle analysis, increased levels of annexin V and decreased levels of pro-caspase 8, pro-caspase 3, and/or Bcl-xL.

These studies raise a number of interesting questions related to both basic and clinical science realms. How does CK2 bind to JAK2 and is it regulated in any way that could be manipulated? Given the large number of CK2 substrates, manipulation of the JAK2/CK2 interaction would provide a more precise therapeutic intervention than simply inhibiting JAK2 or CK2. What sites in JAK2 does CK2 phosphorylate and what are the ramifications of those phosphorylations on JAK2 activity and binding partners? Is the effect of CK2 direct on JAK2 or on some other JAK2 binding partner? Interestingly, Zheng et al find CK2 also binds to JAK1, and that CK2 inhibitors decrease oncostatin M-induced JAK1 activation to a much greater extent than oncostatin M-induced JAK2 activation. Is it possible that CK2 acts primarily on JAK1 in the context of oncostatin M signaling? Finally, might CK2 inhibitors provide an additional therapeutic intervention for myeloproliferative neoplasms associated with constitutively activated JAK2 or for the variety of other diseases that are associated with elevated JAK–Stat signaling, such as solid tumors (eg, androgen-independent prostate cancer) and rheumatologic diseases?

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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pathway, either in the early Golgi or ER, providing evidence that the 2 newly synthesized proteins traffic together to the membrane. In contrast, no intracellular interaction of RhAG and Rh was detected. However, the 2 polypeptides could be coimmunoprecipitated from plasma membranes of basophilic erythroblasts, signifying that they link within the membrane after their individual incorporation. In addition, knockdown of RhAG during early erythropoiesis resulted in decreased expression of Rh polypeptides, indicating that the stability of Rh in the membrane requires the presence of RhAG. Together these findings establish for the first time that major, core components of the band 3 macrocomplex have assembled in early-stage erythroblasts.

These data generate a host of intriguing questions of significance to both erythroid biology and clinical medicine. In particular, what are the anion, NH₃ and CO₂ transport capabilities of partially assembled complexes compared with fully assembled complexes? And in a related issue, at what point during differentiation do these ion and gas transport apparatuses need to be functional for the health of the cell? Another question is at what stage of differentiation do the membrane complexes associate with the cell cytoskeleton? In erythrocytes, vertical interactions between the lipid bilayer and the cytoskeleton created by these multiprotein complexes are crucial for maintaining membrane cohesion and protecting cells from surface area loss. One might postulate that when exuberant endocytosis of iron is required for hemoglobin synthesis, a less cohesive membrane might be advantageous to facilitate endocytosis. Thus future studies may show that lipid bilayer/cytoskeleton linkages mediated by the band 3 macrocomplex form at a late stage of differentiation. A third issue to consider has therapeutic implications for patients with HS. In HS, a mutation in a gene encoding one component of the band 3 complex (ankyrin, band 3 or protein 4.2), leads to a decrease in the other components of the complex in mature erythrocytes. One mechanism known to generate these deficiencies is their loss during the process of erythroblast protein partitioning to the reticulocyte membrane at the time of enucleation. However it is also possible that the band 3 complex does not assemble normally during erythropoiesis, leading to ineffective erythropoiesis. This would be a novel and as yet unexplored mechanism contributing to the anemia of HS, which until now has been considered solely because of hemolysis. If ineffective erythropoiesis is, indeed, an important contributor to the anemia in some cases of HS, it would have therapeutic implications, because splenectomy might not successfully ameliorate the severity of anemia.

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