CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Inhibition of Casein Kinase 1 Alpha in Acute Myeloid Leukemia

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Acute myeloid leukemia (AML) is a genetically heterogeneous cancer that arises in hematopoietic stem cells. For the past 40 years, standard treatment for AML has consisted of a combination of two chemotherapeutic agents, cytarabine and an anthracycline. This regimen results in high rates of remission but, in the majority of cases, fails to eradicate the residual leukemic stem cells that are the reason for relapse and poor outcomes in patients with AML. The comprehensive genetic analysis of AML in the past 10 years has revealed recurrent, somatically mutated genes, leading to the development of new targeted therapies including inhibitors of fms-like tyrosine kinase 3 (FLT3) and isocitrate dehydrogenase 1 and 2. However, monotherapy with these drugs does not result in durable responses, and combination with chemotherapy has only modestly improved outcomes; thus, new drug targets in patients with AML are needed.

In their current work, Minzel et al.[1] synthesized highly potent inhibitors of casein kinase 1 alpha (CK1α) and tested them for activity in AML. CK1α is a serine–threonine kinase that negatively regulates β-catenin and TP53 signaling.[2] The finding that CK1α suppresses TP53 activity has led to efforts to develop an inhibitor that, in theory, should activate TP53 and induce apoptosis. Indeed, genetic inactivation of *Csnk1a* (which encodes CK1α) in mice induces rapid apoptosis in normal and leukemic hematopoietic cells that can be suppressed by inactivation of *Tp53*.[3] In another preclinical study, AML cells were shown to be more sensitive to pharmacologic CK1α inhibition than are normal hematopoietic cells.[4] CK1α has recently been identified as the critical downstream target of lenalidomide in the myelodysplastic syndrome with deletion of chromosome 5q (del[5q]). Lenalidomide induces degradation of CK1α through ubiquitination — a process that targets proteins to the proteasome, which degrades them. Activation of TP53 and apoptosis ensue. The therapeutic effect arises from synthetic lethality: the myelodysplastic syndrome with del(5q) is particularly sensitive to lenalidomide because of the haploinsufficiency of *CSNK1A1*, which is located on chromosome 5q.[5]

In AML, lenalidomide as a single agent or in combination with chemotherapy or demethylating agents failed to show sustained antileukemic effects in clinical trials. This implies that the therapeutic window for lenalidomide is too narrow between leukemic cells containing two copies of *CSNK1A1* and normal hematopoietic cells. In persons with AML with del(5q), lenalidomide is not active, probably because these persons usually harbor inactivating *TP53* variants. In aggregate, these findings suggest that degradation of CK1α by lenalidomide is not sufficient to kill AML cells. One possible reason for this may be that CK1α activates pro-oncogenic Wnt/β-catenin signaling and MDM2, which antagonizes TP53.

Minzel et al. found that the most active compounds in their series inhibit not only CK1α but also cyclin-dependent kinase 7 (CDK7) and CDK9, which are catalytic subunits of transcription factors (transcription factor IIH [TFIIH] and transcription elongation factor b [P-TEFb], respectively). In AML cells, inhibition of CDK7 and CDK9 resulted in transcriptional down-regulation of several key oncogenes. Thus, inactivation of CDK7 and CDK9 counteracted some of the pro-oncogenic effects of CK1α inhibition. Combined inhibition of CK1α, CDK7, and CDK9 was highly synergistic in activating TP53 and inducing apoptosis in AML cells (Fig. 1). Even short-term exposure with CK1α/CDK7/CDK9 inhibitors for several minutes induced protracted transcriptional down-regulation of the oncogenes *MYC*, *MCL1*, and *MDM2*. Oral administration of the inhibitors delayed the onset of AML and eradicated leukemic stem cells, resulting in long-term survival in several mouse models of aggressive AML and in mice with AML xenografts. The compounds were

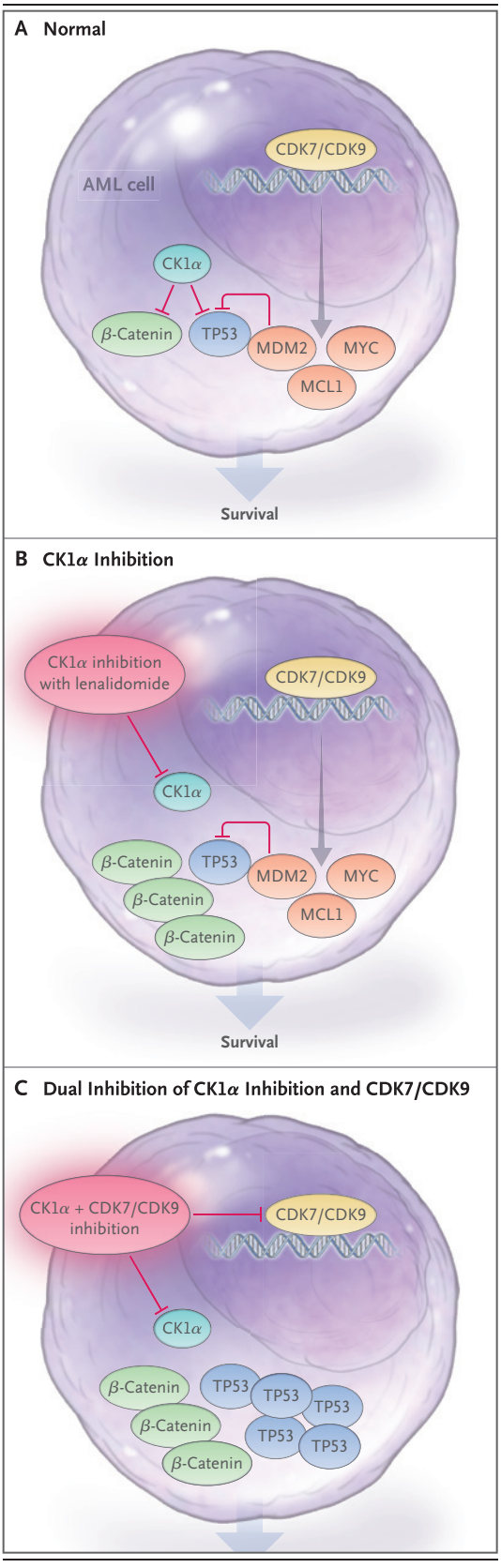

Figure 1. Casein Kinase 1 Alpha (CK1α) — A Negative Regulator of TP53 and β-Catenin.

Cyclin-dependent kinase 7 (CDK7) and CDK9 are subunits of transcription factors that regulate expression of several important oncogenes in acute myeloid leukemia (AML) including *MDM2*, *MYC*, and *MCL1*. Minzel et al.[1] recently reported that co-targeting of CK1α and CDK7/CDK9 results in decreased transcription of *MDM2*, *MCL1*, and *MYC* and strong activation of TP53 and apoptosis in AML cells.

more active than cytarabine and the FLT3 inhibitor midostaurin. Most drugs with antileukemic activity, including both conventional chemotherapy and targeted therapies, also affect normal hematopoiesis, which is a major reason why these drugs fail in clinical trials. When administered at concentrations sufficient to kill AML cells, the CK1α/CDK7/CDK9 inhibitors impaired normal hematopoiesis only moderately. Furthermore, the compounds had no severe toxic effects in mice, rats, or dogs. A potential disadvantage of CK1α/CDK7/CDK9 inhibition is that this mechanism depends on an intact TP53 pathway and thus is predicted to be inactive in AML with inactivating *TP53* mutations that can be found in approximately 8% of patients with AML. On the flip side, this therapeutic approach has the potential to counter forms of cancer other than AML that have an intact TP53 pathway.

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