(DNMT) depletion. They further demonstrate that replacement of miR 29b oligonucleotides results in both re-expression of the methylated tumor suppressor genes PTEN and ESR1 (to an extent comparable to that using the DNMT inhibitor decitabine) and differentiation in AML cell lines. The putative hypomethylating agents, 5-azacytidine and decitabine, are the first agents to have had a significant impact on prognosis for patients with high-risk myelodysplastic syndrome and have shown promising efficacy in elderly patients with AML. These agents are incorporated into DNA forming adducts with and inactivating DNMTs 1, 3A, and 3B which are responsible for maintenance and de novo methylation, respectively. Both aberrant DNA hypermethylation of tumor suppressor genes and overexpression of DNMT isoforms have been demonstrated in a variety of malignancies including AML. Although controversy remains with regard to the mechanism of action of these drugs, there is considerable circumstantial evidence that tumor suppressor gene re-expression plays an important role in their efficacy.

The demonstration of a potentially pharmacologically active miRNA provides a unique opportunity for further insight into the activity of 5-azacytidine and decitabine. Debate continues over the mechanism of action of these so-called hypomethylating agents. However, no definitive evidence shows that methylation reversal is responsible for their clinical efficacy. In fact, if these agents exert their effects via hypomethylation of tumor suppressor genes (and resultant gene re-expression), their activity should be mimicked in vitro and in vivo models by expression of exogenous miR 29b. While miRs could conceivably replace or augment the azanucleosides therapeutically, as with all genetically driven therapies, effective delivery to the tissue of interest will be a challenge. Ultimately, even if these agents do not prove to be useful pharmaceuticals, they should provide an opportunity to finally understand whether demethylation is central to the benefit seen with 5-azacytidine and decitabine.

**REFERENCES**


**Comment on Yost et al, page 6419**

**Babies born without safety NET**

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In this issue of Blood, Yost and colleagues demonstrate that neutrophils from newborn infants lack the ability to produce so-called extracellular traps and exhibit impaired extracellular killing of bacteria. Newborn babies present with various immaturities of their humoral and cellular immune system, particularly during the first days of life. This has important and deleterious consequences. Bacterial infection is a major cause of death and long-term morbidity in preterm newborn infants. Therefore, despite the origin of the word (from innatus, existing at the time of birth), the innate immune responses against microbial invasion are apparently impaired in neonates. Defective antibacterial function of neutrophils of neonates has thus been noted for some time, and circumstantial evidence for an immaturity of granulopoiesis—which might explain the frequent development of neutropenia in neonates in response to bacterial sepsis—has also been documented. However, the syndrome of neonatal neutrophil deficiency remains incompletely understood.

Neutrophils are essential effector cells of the innate immune system and play a crucial role in the killing of microorganisms. Neutrophils kill pathogens through reactive oxygen species (ROS)—dependent and independent mechanisms. The former pathway is associated with activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase at the phagosomal membrane. Patients suffering from chronic
Neutrophils from newborn babies. Yost et al examine NET formation by scanning electron microscopy following stimulation of isolated neutrophils with bacterial lipopolysaccharide (LPS). LPS-stimulated neutrophils from an adult donor were found to generate extensive extracellular lattices (left panels). In contrast, NET formation could not be detected when control or LPS-stimulated neonatal neutrophils were examined (middle panels: term; right panels: preterm). The net result of this novel defect was shown to be impaired extracellular killing of bacteria. See the complete figure in the article beginning on page 6419.

No NET formation in neutrophils from newborn babies. Yost et al examine NET formation by scanning electron microscopy following stimulation of isolated neutrophils with bacterial lipopolysaccharide (LPS). LPS-stimulated neutrophils from an adult donor were found to generate extensive extracellular lattices (left panels). In contrast, NET formation could not be detected when control or LPS-stimulated neonatal neutrophils were examined (middle panels: term; right panels: preterm). The net result of this novel defect was shown to be impaired extracellular killing of bacteria. See the complete figure in the article beginning on page 6419.
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