Comment on Bot et al, page 1147

Hematopoiesis: yet another milestone for RNAi

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Bot and colleagues demonstrate shRNA-derived long-term silencing and consequent loss of functionality both in vitro and in vivo. Their work represents a frontline study constructing hematopoietic knock-downs using RNAi.

Cellular effects of double-stranded RNA (dsRNA) have been studied extensively for almost 4 decades. The interferon induction, a typical response against long dsRNA molecules, was investigated in numerous studies at the end of the 1960s, as reviewed by Merigan.1 The earliest observations that dsRNA plays a role in protein expression came in 1971 when Ehrenfeld and Hunt demonstrated, in their sophisticated work, poliovirus dsRNA inhibition of protein synthesis in reticulocyte lysates.2 According to their study, most of the silencing was caused by small fragments of genomic RNA, concluding that “various double-stranded RNAs with different specificities can shut off cellular protein synthesis.”2 Ever since, the field nowadays known as RNA interference (RNAi) has evolved with the addition of outstanding studies, including the recently published works of Fire et al,3 which received an excited response from the scientific community, and of Carmell et al4 and Tiscornia et al,5 both of which showed successful production of transgenic short hairpin RNA (shRNA) mouse models.

Despite unparalleled recent progress in resolving the intricacies of RNAi, in vivo applications of this approach have been limited by the same challenge well known from numerous gene therapy studies: transfer of genetic material into the primary cells and tissues. In this sense, RNAi may be an even more difficult approach than gene therapy since it requires close to 100% transfer efficiency to target cells or tissues to reach measurable or therapeutic biologic effect. This technical requirement is particularly challenging with the transfer of genetic material into hematopoietic stem cells; the method must not only yield a high transfer efficiency but also the conditions used must allow delivery in the shortest possible time to prevent differentiation of these cells in vitro.

In this issue of Blood, Bot and colleagues report lentivirus shRNA-mediated silencing of CC-chemokine receptor 2 (Ccr2), which is known to have a critical role in inflammation and early atherogenesis. The authors show a functional knock-down of the target gene with a high 90% retrovirus marking level in peripheral blood cells as determined by green fluorescent protein (GFP) flow analysis. The decreased messenger RNA and protein expression of the target protein as well as loss of functionality were shown both in vitro in HEK 293 cells and in vivo in a mouse model after transplanting lentivirus shRNA-transduced hematopoietic stem cells into irradiated recipients. Transplantation resulted in a long-lasting 6- to 7-week silencing effect, providing a cutting edge model to study in vivo the effects of targeted Ccr2 silencing in hematopoietic cells and delineating yet another milestone in the rising field of RNAi.

REFERENCES

Comment on Tassone et al, page 1341

A “not so micro” model for a “macro” problem

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Tassone and colleagues present a new mouse model for the study of Waldenström macroglobulinemia.

A major impediment to the understanding of Waldenström macroglobulinemia is the lack of adequate in vivo and in vitro models for the study of this indolent lymphoproliferative disorder. The bulk of studies describing disease biology and genetics have been descriptive because of the limited proliferative potential of the tumor cells.1 In this issue of Blood,

![Engraftment of primary patient WM cells in SCID-hu mice.](image)

See the complete figure in the article beginning on page 1341.
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