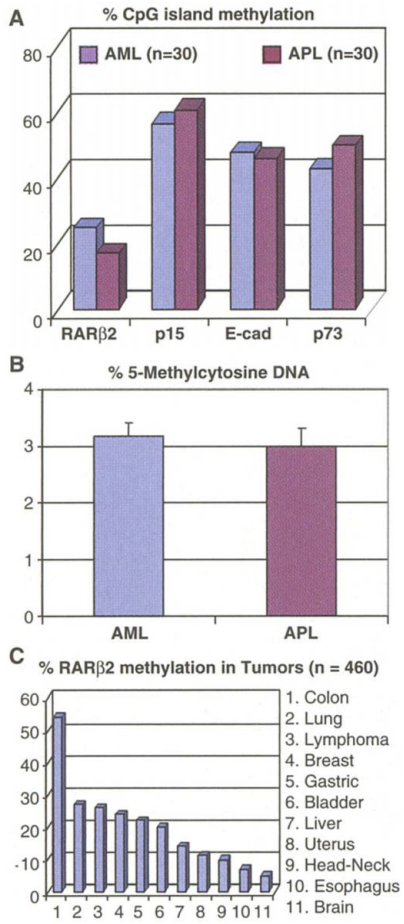
some light on this subject ("Methyltransferase recruitment and DNA hypermethylation of target promoters by an oncogenic transcription factor," Reports, 8 Feb., p. 1079). They report that the leukemia-promoting PML-RAR fusion protein may be an important cause of this epigenetic aberration. However, several lines of evidence suggest that this experimental model does not explain the accumulating data concerning promoter region methylation.



(A) Frequency of CpG island hypermethylation of the *RARβ2*, $p15^{INK4b}$ E-cadherin, and p73 genes in AML versus APL. (B) Global genomic methylation content in AML versus APL. (C) Frequency of RARβ2 promoter hypermethylation in human cancer.

In this experimental model, expression of the PML-RAR transcript with an exogenous construct leads to recruitment of DNMT1 and DNMT3a and increased methylation of a RARβ-Luc fusion construct or the endogenous promoter. Consistent with this, seven of nine primary acute promyelocytic leukemias (APLs) had methylation of the 5′ region of the endogenous *RARβ2* gene. Our own analysis suggests that the frequency of methylation of *RARβ2* is the same in APLs that have the PML-RAR translocation as it is in other subtypes of acute myelogenous leukemia (AML) that do not have this alteration (see figure). This suggests that the presence of the PML-RAR translocation is neither necessary nor sufficient to induce *RARβ2* methylation. In fact, many other malignancies have *RARβ2* methylation without this translocation (see figure), in some cases more commonly than APL. We have also observed that APL patients with the PML-RAR translocations have the same frequency of CpG island hypermethylation of $p15^{INK4b}$, CDH1, and p73 (all of them with potential RAR elements in their promoters) and global genomic methylation as other AML subtypes without the translocation (see figure). These observations prompt us to caution the extension of the experimental studies described into the more complex genetic and epigenetic alterations observed in primary human malignancies.

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Response

WE RECENTLY DEMONSTRATED THAT, IN APLS, PML-RAR promotes specific methylation of its target gene *RARβ2* by recruiting DNA methyltransferases (DNMTs) to the promoter region. On the basis of these findings, we have proposed a general mechanism for the specificity of DNA methylation in cancer cells, e.g., aberrant recruitment of DNMTs by oncogenic transcription factors to specific regulative loci. Esteller *et al.* now report that the frequency of *RARβ2* methylation (and other RA-target genes) is similar for APLs, which express PML-RAR, and other subtypes of AMLs, which do not express this fusion protein, and they question the importance of the role of PML-RAR in *RARβ2* methylation.

The mechanism(s) responsible for *RARβ2* methylation in AMLs is presently unknown. On the basis of our proposed model, *RARβ2* methylation in AMLs might be triggered by AML-specific fusion proteins. Indeed, one of the two components of each fusion protein is generally a transcription factor, so that AML-associated fusion proteins function as aberrant transcriptional regulators (similar to PML-RAR in APLs). We have recently shown that transcriptional repression of RA signaling is a common feature of AMLs. In particular, we have shown that *AML1-ETO*, the most common AML-associated fusion protein, is an HDAC-dependent repressor of RA signaling, thereby suggesting that RA target genes (such as *RARβ2* and potentially the $p15^{INK4b}$, CDH1, and p73 genes mentioned by Esteller *et al.*) are deregulated by AML-fusion proteins (*1*). Thus, the data reported by Esteller *et al.* do not contradict our model. Rather, they suggest that methylation of RA target genes is a frequent event in leukemias. Further investigation is required to decipher the mechanistic roles of AML-associated fusion proteins in establishing specific DNA methylation in AMLs.

A similar scenario (aberrant recruitment of DNMTs by oncogenic transcription factors) can be envisioned for *RARβ2* methylation in other cancers. Indeed, we are currently investigating the interactions between DNMTs and general transcription factors, both in normal and transformed cells. However, we cannot rule out the possibility that, in some tumors, *RARβ2* methylation is caused by secondary mechanism(s).

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Consequences of Siberian Traps Volcanism

M. K. REICHOW *ET AL.* ("$^{40}Ar/^{39}Ar$ DATES from the West Siberian Basin: Siberian flood basalt province doubled," Reports, 7 June, p. 1846) report that the areal extent and volume of the Siberian Traps volcanism of 250 million years ago were much greater than previously thought. Traps volcanism was already known to be the largest eruptive sequence of the past 540 million years and was synchronous with (*1*) and likely linked to the great end-Permian biotic crisis, when 90 to 95% of then-existing species perished.

The vastly greater Traps magmatism may have had biological consequences well beyond the "climate change [caused] by the injection of volatiles and aerosols into the atmosphere," suggested by Reichow *et al.* These more important consequences would have resulted from the erupted basalts being extruded into and onto permafrost regions of Siberia (then at about the same high northern latitude as today) (*2*) and the adjacent underwater continental margin (*3*) in the West Siberian Basin.

This direct heating would have produced

three important effects. First, the substantial quantities of methane hydrates in the permafrost and in the West Siberian Basin sediments would have dissociated, and methane would have been immediately released into the surrounding water and atmosphere. This methane, a greenhouse gas (GHG) some 20 times more powerful than carbon dioxide, would itself have quickly (within 10 years) oxidized to the GHGs carbon dioxide and water vapor, warming the atmosphere and drawing down marine and atmospheric oxygen in the process.

Together with the carbon dioxide released by Traps volcanism and augmented by water evaporated from the West Siberian Basin (a second effect of direct heating), these GHGs would have rapidly overcome an initial atmospheric cooling triggered by Traps-generated sulfates and initiated a major warming of the North polar region and the Paleo-Arctic Ocean, into which the West Siberian Basin's water emptied (*3*).

As today (*4*), the Arctic Ocean of the Permian would have been a driving force of the world ocean's thermohaline circulation, sending frigid Paleo-Arctic Deep Water (PADW) into the great ocean of the time, Panthalassa, which extended over more than half of Earth's surface. The melting of the polar ice and the replacement of PADW by Traps-heated polar seawater from the Paleo-Arctic Ocean (the third effect) would have rapidly initiated a complete reorganization of global thermohaline circulation and triggered the release of vast quantities of additional methane from Pangea's continental margins.

We see the signature of this methane in the highly depleted carbon isotopes of the end-Permian boundary, when $\delta^{13}C$ shifted downward by about 6 per mil (‰) (*5*, *6*), an effect attributable overwhelmingly to ~60‰ methane hydrate–derived carbon (*7*). A similar methane hydrate release has been linked to the Late Paleocene Thermal Maximum and the end-Paleocene biotic turnover (*8*) and other Phanerozoic biotic crises, in a sort of "Little Gaia Cycle," where hydrate release and global warming typically extend over 10,000 to 20,000 years and recovery takes 100,000 to 200,000 years (*9*).

Hammered by the three blows of (i) sulfate and carbon dioxide–derived acid rain, (ii) abrupt and substantial global warming, and (iii) widespread marine anoxia (*10*), dysoxia, hypermethia and possible hypercapnia (*11*), and diminished atmospheric oxygen caused by methane oxidation, Earth's Permian biota was plunged into the greatest crisis in the history of life (*12*).

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Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted by e-mail (science_letters@aaas.org), the Web (www.letter2science.org), or regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

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