What should we conclude from these studies? First, CNN-LOH occurring in a CP MPD indicates the presence of genomic instability, probably due to constitutive tyrosine kinase signaling, which promotes apoptosis resistance, augmented homologous recombination, a mutator phenotype, and loss of the tumor suppressor mechanism, heterochromatin gene silencing. These abnormalities may not only explain spontaneous AL in the MPD, particularly in PMF with its large clonal burden, they also are conducive to t-AL. Second, if the data are confirmed, SNP arrays may be a useful guide for MPD prognosis.

Third, with respect to MPD t-AL, HU can now be securely added to the list of agents that are leukemogenic in the MPD because HU is not different from them or even drugs like azathioprine that also impede DNA repair and cause t-AL. This is not to suggest that HU should not be used in the MPD but rather that its use be judicious. In all studies to date, HU has failed to prevent arterial or venous thrombosis or myofibrosis and has prevented transient ischemic attacks only because it is a nitric oxide donor.

Finally, what about JAK2\textsuperscript{V617F}-negative AL arising in a JAK2\textsuperscript{V617F}-positive MPD? It is apparent that JAK2\textsuperscript{V617F} is not the initiating lesion in the MPD, and, because JAK2\textsuperscript{V617F}-positive cells are more sensitive to HU than JAK2\textsuperscript{V617F}-negative cells, we may only be transforming or selecting for a more resistant but less robust primitive ancestral clone by targeting the more sensitive one (see figure), suggesting that nonspecific therapy such as pegylated interferon may be more appropriate for MPD than targeted therapies.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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Comment on Wang et al, page 2971

HDAC5: going with the flow

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In this issue of Blood, Wang and colleagues uncover a novel mechanism by which fluid shear stress regulates expression of endothelial genes through effects on HDAC5 phosphorylation. The endothelium of blood vessels serves important functions in normal physiology including regulation of vascular tone, endothelial cell survival, smooth muscle cell proliferation, leukocyte recruitment, and thrombosis.

Abnormalities in endothelial function are critically important to atherosclerosis, as the endothelium is thought to integrate the effects of multiple cardiovascular risk factors on the vessel wall. Endothelial dysfunction can be quantitated in patients by fluid-mediated dilation, in which the degree of vasodilation of the brachial artery is measured during reperfusion after a period of vascular occlusion. Endothelial response to flow is very important, but the mechanisms by which fluid shear stress causes changes in endothelial function are not well understood.

Now, Wang et al show that fluid shear stress stimulates phosphorylation of HDAC5, which affects its interactions with MEK2 transcription factor, with subsequent effects on KLF2 activity and endothelial nitric oxide synthase expression. This work represents an important advance in the field of vascular biology for several reasons. First, although HDAC5 is known to serve as a negative regulator of MEF2 and KLF2 promoters in response to flow, this paper demonstrates that increased activity of both KLF2 and MEK2 in response to flow. Interestingly, HDAC5 effects on KLF2 transcription factor activity in response to cytokines involve p65 and NF-κB, while HDAC5 effects in response to flow involve its phosphorylation. Thus, different physiological signals mediate changes through different but overlapping effector mechanisms.

Third, this study shows that these effects are relevant to processes known to be important to atherogenesis. The functional importance is demonstrated by effects on monocye...
adhesion to endothelial cells. eNOS transcription and expression are increased by these flow–dependent changes in HDAC5 phosphorylation, MEF2 activity, and KLF2 activity.

Endothelial dysfunction is an important potential pharmacologic target that has not been fully investigated for the treatment and prevention of atherosclerotic cardiovascular disease.3,7 So far, providing exogenous NO by pharmacologic donors and gene transfer of NOS isoforms have not been effective. In part, this may be because NO needs to be generated in the proper subcellular location with the proper kinetics, which cannot be replicated by nonselective NO donors or gene therapy. One specific abnormality associated with endothelial dysfunction is eNOS phosphorylation at S1176, and restoration of normal phosphorylation is one potential approach to correcting endothelial dysfunction.8,9 Another potential approach raised by this study is correcting the defective eNOS gene expression regulation by flow. In this respect, cardiovascular diseases may well soon join cancer as a potential application for pharmacologic agents that target HDAC activity.

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