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, heterochromatinc 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 azathiprine 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 myelofibrosis and has prevented transient ischemic attacks only because it is a nitric oxide donor.4,8

Finally, what about JAK2V617F-negative AL arising in a JAK2V617F-positive MPD? It is apparent that JAK2V617F is not the initiating lesion in the MPD, and, because JAK2V617F-positive cells are more sensitive to HU than JAK2V617F-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.10

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.1,2

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.3 Endothelial dysfunction can be quantitated in patients by flow-mediated dilation, in which the degree of vaso-dilation 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 MEF2 transcription factor, with subsequent effects on KLF2 activity and endothelial nitric oxide synthase (eNOS) gene expression.4 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 activity in cardiovascular cells, this is the first demonstration that HDAC5 activity can be affected by fluid shear stress in endothelial cells. shear stress induces HDAC5 phosphorylation, which stimulates its nuclear export and interferes with its interactions with MEF2. As a result, the tonic repression of MEF2 activity by HDAC5 is released. Pharmacologic inhibitors establish that flow-induced phosphorylation of HDAC5 is mediated by Ca2+ and calmodulin, but does not involve CaM kinase II or protein kinase D (which is involved in VEGF effects on HDAC5).

Second, this study provides further insight into the flow-induced regulation of KLF2 activity. KLF2, a zinc finger transcription factor, regulates leukocyte–endothelial cell interactions, endothelial cell proliferation and migration, and endothelial gene expression including eNOS expression. KLF2 is known to be responsive to flow,1 and MEF2 is known to be a key transcription factor in its expression. In addition to the MEK/ERK pathway, this paper shows that KLF2 expression can be modulated by effects of flow on HDAC5. Using an unphosphorylatable serine–to–alanine mutant of HDAC5, the authors have elegantly demonstrated that increased activity of both MEF2 and KLF2 promoters in response to flow requires HDAC5 phosphorylation. Interestingly, HDAC5 effects on MEF2 transcription factor activity in response to cytokines involve p65 and NF-κB, while HDAC5 effects in response to flow involve its phosphorylation.5 Thus, different physiologic 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 atherosclerosis. The functional importance is demonstrated by effects on monocyte...
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. 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. 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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