

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

REFERENCES

1. Annunziata CM, Hernandez L, Davis RE, et al. A mechanistic rationale for MEK inhibitor therapy in myeloma based on blockade of MAF oncogene expression. *Blood*. 2011;117(8):2396-2404.
2. Zhan F, Huang Y, Colla S, et al. The molecular classification of multiple myeloma. *Blood*. 2006;108(6):2020-2028.
3. Hurt EM, Wiestner A, Rosenwald A, et al. Overexpression of c-maf is a frequent oncogenic event in multiple myeloma that promotes proliferation and pathological interactions with bone marrow stroma. *Cancer Cell*. 2004;5(2):191-199.
4. Martínez-García E, Popovic R, Min DJ, et al. The MMSET histone methyl transferase switches global histone methylation and alters gene expression in t(4;14) multiple myeloma cells. *Blood*. 2011;117(1):211-220.
5. Brito JL, Walker B, Jenner M, et al. MMSET deregulation affects cell cycle progression and adhesion regulons in t(4;14) myeloma plasma cells. *Haematologica*. 2009;94(1):78-86.
6. Lauring J, Abukhdeir AM, Konishi H, et al. The multiple myeloma associated MMSET gene contributes to cellular adhesion, clonogenic growth, and tumorigenicity. *Blood*. 2008;111(2):856-864.
7. Solit DB, Garraway LA, Pratilas CA, et al. BRAF mutation predicts sensitivity to MEK inhibition. *Nature*. 2006;439(7074):358-362.
8. Tai YT, Fulciniti M, Hideshima T, et al. Targeting MEK induces myeloma-cell cytotoxicity and inhibits osteoclastogenesis. *Blood*. 2007;110(5):1656-1663.
9. Bergsagel PL. Impressions of the myeloma landscape. *Blood*. 2010;116(14):2403-2404.

● ● ● THROMBOSIS & HEMOSTASIS

Comment on Acharya et al, page 2484

Unraveling hemophilic arthropathy

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In this issue of *Blood*, Acharya and colleagues provide evidence for the role of angiogenesis in the pathophysiology of hemophilic joint disease.¹ Is this the linchpin that unravels this important clinical condition or merely a cog in a not so stepwise process?

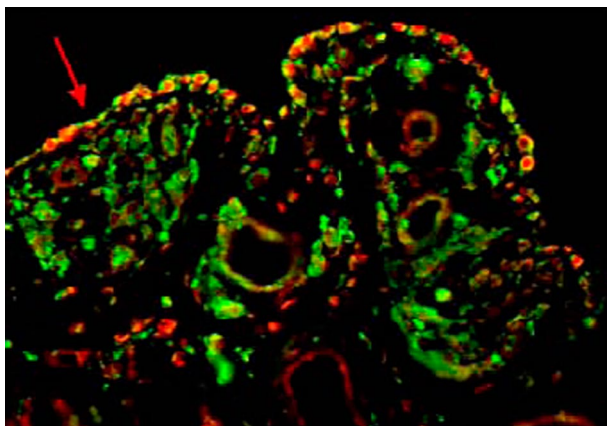
Joint disease has always been the hallmark of severe hemophilia, but recent practice of regular infusions of intravenous factor VIII or IX (prophylaxis) from an early age has lessened its impact. Prophylaxis has now become the standard of care for children with hemophilia,² but for those born in the prophylaxis era or who demonstrate bleeding despite the regular infusion of factor concentrates, the treatment of established joint disease must include (alone or in combination) ongoing

infusions of factor concentrate, radionuclide, or surgical synovectomy,³ or for those with end-stage arthropathy, chronic anti-inflammatory and pain management and/or joint replacement. Interestingly, it is well recognized that not all subjects with severe hemophilia will have joint bleeding and not all with joint bleeding demonstrate progressive joint disease. This paradox speaks to the role of factors other than the factor VIII/IX level and/or clinical bleeding as important to this process.

The hallmarks of hemophilic arthropathy involve joint bleeding, inflammation, synovial hypertrophy/villous formation, and cartilage/bony destruction; in essence, inflammation and cellular proliferation (angiogenesis). Iron deposition from joint bleeding, deep in synovial tissue, appears to be a key culprit. Iron has also correlated with increased c-myc expression,⁴ as well as overexpression of mdm2.⁵ The increased inflammatory response is a result of monocytes/macrophages recruited to the area along with accompanying inflammatory cytokines (interleukin-6 [IL-6], IL-1 β , tumor necrosis factor α).⁶ The actual mediators of cellular proliferation and synovial hypertrophy are unknown, but evidence has partially implicated the previously mentioned cytokines and c-myc and mdm2 expression. In this issue of *Blood*, Acharya and colleagues provide evidence for the role of key angiogenic factors (vascular endothelial growth factor [VEGF], matrix metalloproteinase-9) in cellular proliferation.¹

Several key experiments were performed to support the authors' hypothesis that angiogenesis plays a major role in the pathogenesis of hemophilic arthropathy. First, proangiogenic growth factors (previously mentioned) and monocytes/macrophages (CD68⁺, CD11b⁺) were both significantly elevated in synovium and peripheral blood of hemophilic patients with joint disease compared with controls. Second, sera and peripheral blood monocytes from subjects with hemophilia caused endothelial cell and synovial cell proliferation, and these proliferative responses were down-regulated by blocking the effect of VEGF. Finally, the potential role of hypoxia in this angiogenic process was suggested by expression of hypoxia-inducible factor 1 α from human synovial cells when incubated with sera from subjects with hemophilic arthropathy. The figure is illustrative of the pivotal role of monocytes and key angiogenic factors in synovial hypertrophy (see figure). It demonstrates (red arrow) by immunofluorescent staining, CD68⁺ cells coexpressing VEGF in the synovium of a subject with hemophilic arthropathy.

It is not surprising that angiogenesis plays a key role in hemophilic arthropathy



CD68⁺ cells coexpressing VEGF within the hemophilic synovium.

because neovascularization is crucial to tumor growth and rheumatoid arthritis progression. Could elevated levels of angiogenic markers such VEGF be a marker of hemophilic arthropathy? Nonetheless, despite the promise of this investigation, the exact mechanism underlying hemophilic joint disease remains unknown and although the contributions of iron deposition, inflammatory cell recruitment, and cytokine/growth factor production to hemophilic joint disease have individually been demonstrated, no linchpin for this process has been demonstrated. Collection of cytokine and growth factor samples from subjects on prophylaxis and with joint disease should be considered as a first step to more clearly define the etiology of hemophilic arthropathy. Until more data are obtained, VEGF and other angiogenic mediators remain a cog in this complicated pathway.

● ● ● VASCULAR BIOLOGY

Comment on Yao et al, page 2538

Cocaine and the blood-brain-barrier

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Cocaine is one of the most abused street drugs; according to the National Survey on Drug Abuse, 15% of Americans have used cocaine at least once in their lifetime. Cocaine has been shown to alter behavior and mood, causing feelings of euphoria. One of the most damaging effects of cocaine abuse is that it compromises judgment capacity leading to risky sexual behavior, thereby increasing chances of contracting HIV infection.

In this issue of *Blood*, Yao et al present evidence that cocaine alters blood-brain-barrier (BBB) permeability via a mediator: platelet-derived growth factor (PDGF).¹ Previously, it has been reported that cocaine as well as HIV can down-regulate tight junction proteins.²⁻⁴ It is well established that blood microvascular endothelial cells structurally and functionally control the BBB; this report now shows that cocaine—via binding to its cognate σ receptors—elicits a signaling cascade, leading to the induction of PDGF-B chain which is a key mediator of increased endothelial permeability. Yao and colleagues show that the activation of mitogen-activated protein kinase and transcription factor (Egr1) pathways lead to an activation of increased

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REFERENCES

1. Acharya SS, Kaplan RN, Macdonald D, Fabyi OT, DiMichele D, and Lyden D. Neoangiogenesis contributes to the development of hemophilic synovitis. *Blood*. 2011;117(8):2484-2493.
2. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med*. 2007; 357(6):535-544.
3. Dunn AL, Busch MT, Wyly JB, et al. Arthroscopic synovectomy for hemophilic joint disease in a pediatric population. *J Pediatr Orthop*. 2004;24(4):414-426.
4. Wen FQ, Jabbar AA, Chen YX, et al. c-myc proto-oncogene expression in hemophilic synovitis: in vitro studies of the effects of iron and ceramide. *Blood*. 2002; 100(3):912-916.
5. Hakobyan N, Kazarian T, Jabbar AA, et al. Pathobiology of hemophilic synovitis I: overexpression of mdm2 oncogene. *Blood*. 2004;104(7):2060-2064.
6. Roosendaal G, Vianen ME, Wenting MJ, et al. Iron deposits and catabolic properties of synovial tissue from patients with haemophilia. *J Bone Joint Surg Br*. 1998; 80(3):540-545.

expression of PDGF-BB. Earlier studies have also shown that the Egr-1 pathway is involved in neuronal plasticity and may possibly be involved in regulating apoptosis via the phosphatase and tensin homolog pathway.^{5,6} The findings in the present report were further validated in mice pretreated with anti-PDGF-BB neutralizing antibodies. This treatment led to abrogation of subsequent possible cocaine-mediated induction of permeability.

The findings in this report have significant implications for our understanding of molecular mechanisms leading to leaky vessels in the brain. A synergistic action of cocaine and HIV-1, as shown by Yao et al, will go a long way to explaining an accelerated

neuroprogression of HIV-1 infection among cocaine abusers. Moreover, these findings are important in opening newer avenues in our understanding of cocaine-mediated functions in the central nervous system. Despite combined anti-retroviral therapy, HIV-associated neurocognitive disorders (HAND) continue to afflict approximately 60% HIV-infected individuals, most likely because of partial or complete inability of antiretroviral drugs to go across the BBB. The findings in this report may lead to initiatives seeking alternatives to treat HAND and the development of novel interventions, as well as continuation of the search for methods of reversing cocaine-mediated increased permeability. It will also be of great interest to investigate whether cocaine-induced increased permeability can be reversed by stopping cocaine addiction. Moreover, recent reports suggest that gold nanoparticles can inhibit microvascular endothelial growth factor-induced vascular permeability in retinal endothelial cells.⁷ Although the mode of action of gold nanoparticles in retinal endothelial cells may follow a different pathway, such studies need to be carried out if similar phenomenon can occur in the brain microvasculature.

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REFERENCES

1. Yao H, Duan M, Buch S. Cocaine-mediated induction of platelet-derived growth factor: implication for increased vascular permeability. *Blood*. 2011;117(8):2538-2547.
2. Toborek M, Lee YW, Flora G, et al. Mechanisms of the blood-brain-barrier disruption in HIV-1 infection. *Cell Mol Neurobiol*. 2005;25(1):181-199.
3. Kanmogne GD, Primeaux C, Grammas P. HIV-1 GP120 protein alters tight junction protein expression and brain endothelial cell permeability: implication for the pathogenesis of HIV-associated dementia. *J Neuropathol Exp Neurol*. 2005;64(6):498-505.
4. Dhillon NK, Peng F, Bokhari S, et al. Cocaine-mediated alterations in tight junction protein expression and modulation of CCL2/CCR2 axis across the blood-brain-barrier: implications for HIV-dementia. *J Neuroimmune Pharmacol*. 2008;3(1):52-56.
5. Knapska E, Kaczmarek L. A gene for neuronal plasticity in the mammalian brain: Zif268/Egr-1/NGF1-A/Krox-24/TIS8/ZENK? *Prog Neurobiol*. 2004;74(4):183-211.
6. Virolle T, Adamson ED, Baron V, et al. The Egr-1 transcription factor directly activates PTEN during irradiation-induced signaling. *Nat Cell Biol*. 2001;3(12): 1124-1128.
7. Kalishwaralal K, Sheikpranbabu S, Barathanikanth S, Haribalaganes R, Ramkumarpanidiam S, Gurunathan S. Gold nanoparticles inhibit vascular endothelial growth factor-induced angiogenesis and vascular permeability via Src dependent pathway in retinal endothelial cells [published online ahead of print November 9, 2010]. *Angiogenesis*. doi:10.1007/s10456-010-9193-x.