EBioMedicine 2 (2015) 1574–1575

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Bromodomain Blockade for Intimal Hyperplasia — A Good BET?

Allison C. Ostriker, Kathleen A. Martin *

[a] Department of Cardiovascular Medicine, Cardiovascular Research Center, Vascular Biology and Therapeutics, Yale University School of Medicine, United States
[b] Department of Pharmacology, Yale University School of Medicine, United States

Atherosclerosis contributes to heart attack, stroke, and peripheral vascular disease and remains the leading cause of death in the U.S. (Tabas et al., 2015). Atherosclerotic plaques can be treated by revascularization procedures, including angioplasty, stenting, or bypass surgery, but microtrauma to the blood vessel during these procedures can lead to a complication called intimal hyperplasia, a hyperproliferation of cells in the vascular lumen (Katz et al., 2015). Smooth muscle cells (SMC), which comprise the muscular layer of arteries, retain the remarkable ability to dedifferentiate in response to injury and assume a repair phenotype. These SMC downregulate expression of their characteristic contractile proteins and migrate from the vessel wall into the lumen where they proliferate and secrete matrix proteins, forming a fibrotic scar (Liu et al., 2015). While local drug delivery with drug-eluting stents has been effective in reducing intimal hyperplasia in coronary arteries, intimal hyperplasia remains a major challenge in diabetic patients and in peripheral blood vessels (Katz et al., 2015). In this issue, Wang et al. present exciting findings that targeting epigenetic "reader" proteins is a promising therapeutic strategy for preventing intimal hyperplasia.

Our understanding of the smooth muscle phenotypic switching that underlies the intimal hyperplastic response has been largely at the transcriptional level, but recent studies revealed roles for epigenetic regulation, including DNA methylation and modifications of the histone proteins that organize DNA into chromatin. Collectively, these epigenetic modifications, made by proteins referred to as "writers" and "erasers", govern chromatin accessibility to transcription factors (Liu et al. 2015). The bromodomain and extraterminal domain (BET) family of reader proteins serve as critical adaptors, recognizing histone acetylated lysine residues and recruiting additional proteins to promote transcription elongation (Shi and Vakoc, 2014). Wang et al. demonstrate that BET proteins play an important role in intimal hyperplasia. The authors found that the BET protein BRD4 was expressed at low levels in normal rat carotid artery but was highly induced in SMC following balloon angioplasty. BRD4 was also present in human vein and artery graft intimal hyperplastic lesions but not in normal vessels. The most exciting finding was that a BET-specific bromodomain inhibitor, JQ1, reduced intimal hyperplasia by 75% when applied to the vessel prior to angioplasty. Mechanistically, JQ1 treatment inhibited proliferation and migration in cultured aortic SMC in response to PDGF-BB, a growth factor that mediates much of the intimal hyperplastic response. While this inhibitor targets multiple BET proteins, knockdown experiments implicated BRD4, but not BRD2 or BRD3, in SMC proliferation. Their data support a model where BRD4 expression is induced by PDGF-BB, but also potentiates the signaling of its cognate receptor, PDGFRβ. An interesting finding was that PDGFRα was dramatically upregulated in the luminal hyperplastic SMC following angioplasty and its expression depended on BET protein function in cultured SMC. The role of PDGFRα and its ligands PDGF-AA or –CC in intimal hyperplasia is not well understood, but this work suggests that further investigation in this area is warranted. Other questions raised by this work include whether there may be roles for BRD2 or BRD3 (also inhibited by JQ1) in SMC biology, identifying the key target genes regulated by BRD4 in intimal hyperplasia, and determining the mechanisms that confer the specific interaction of BRD4 with target genes.

A concern for many potential inhibitors of restenosis is that their anti-proliferative effects are not specific to SMC and can therefore also inhibit proliferation of endothelial cells (EC) that line the lumen. Delayed re-endothelialization of the treated area creates a thrombogenic surface for platelet adhesion, which can cause an acute severe occlusion of the vessel leading to myocardial infarction, stroke, or peripheral tissue ischemia (Katz et al., 2015). Importantly, the BET inhibitor JQ1 did not appear to promote thrombosis in vivo, and even exerted protective effects on EC in culture, preventing apoptosis and migration defects in response to inflammatory cytokines (Wang et al., 2015). The profile of BET domains expressed in EC and their roles in endothelial function are not yet well characterized, but these preliminary experiments suggest that BET inhibitors may be endothelium-sparing.

While this is the first study to implicate epigenetic reader proteins in intimal hyperplasia, several recent studies have also identified roles for BRD4 in other diseases of SMC remodeling. BRD4 was also upregulated in human pulmonary arterial hypertension (PAH), and JQ1 treatment reversed PAH in a rat model. Mechanistically, microRNA-204 targeted BRD4, and BRD4 regulated cell cycle and survival genes (Meloche et al., 2015). BRD4 was also implicated in TGFβ responses in airway SMC from asthmatic patients, regulating chemokine and cytokine expression (Perry et al., 2015). Intriguingly, BET proteins may hold promise for treating systemic atherosclerosis, as BET inhibitors (RVX-208)

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2015.09.045.
* Corresponding author at: Yale Cardiovascular Research Center, 300 George Street, Room 759, New Haven, CT 06510, USA.
E-mail address: kathleen.martin@yale.edu (K.A. Martin).

http://dx.doi.org/10.1016/j.ebiom.2015.11.007

have been found to increase expression of the HDL particle protein ApoA-I, and to induce cholesterol efflux in mice, non-human primates, and human patients. A recent Phase 2b trial (ASSURE) of RVX-208, however, did not demonstrate significant differences in HDL, LDL, CRP, or atheroma volume (Nicholls et al., 2015). Whether other parameters such as SMC-mediated plaque stability are beneficially affected is not known. BET inhibitors are also in clinical trials for multiple types of malignancies, targeting *MYC*, *BCL2*, and other oncogenes (Shi and Vakoc, 2014). Collectively, emerging studies suggest a common theme for BRD4 in SMC proliferative responses. As BET inhibitors have shown safety and promise in clinical trials, further studies are warranted to understand the target genes, mechanisms of action, and therapeutic potential.

The authors declare no conflicts of interest.

References

Katz, G., Harchandani, B., Shah, B., 2015. Drug-eluting stents: the past, present, and future. Curr. Atheroscler. Rep. 17 (3), 485.

Liu, R., Leslie, K.L., Martin, K.A., 2015. Epigenetic regulation of smooth muscle cell plasticity. Biochim. Biophys. Acta 1849 (4), 448–453.

Meloche, J., Potus, F., Vaillancourt, M., Bourgeois, A., Johnson, I., Deschamps, L., Chabot, S., Ruffenach, G., Henry, S., Breuils-Bonnet, S., Tremblay, È., Nadeau, V., Lambert, C., Paradis, R., Provencher, S., Bonnet, S., 2015. Bromodomain-containing protein 4: the epigenetic origin of pulmonary arterial hypertension. Circ. Res. 117 (6), 525–535 (2015).

Nicholls, S.J., Puri, R., Wolski, K., Ballantyne, C.M., Barter, P.J., Brewer, H.B., Kastelein, J.J., Hu, B., Uno, K., Kataoka, Y., Herrman, J.R., Merkely, B., Borgman, M., Nissen, S.E., 2015. Effect of the BET protein inhibitor, RVX-208, on progression of coronary atherosclerosis: results of the phase 2b, randomized, double-blind, multicenter, ASSURE trial. Am. J. Cardiovasc. Drugs (2015 Sep 18. [Epub ahead of print]).

Perry, M.M., Durham, A.L., Austin, P.J., Adcock, I.M., Chung, K.F., 2015. BET bromodomains regulate transforming growth factor-β-induced proliferation and cytokine release in asthmatic airway smooth muscle. J. Biol. Chem. 290 (14), 9111–9121.

Shi, J., Vakoc, C.R., 2014. The mechanisms behind the therapeutic activity of BET bromodomain inhibition. Mol. Cell 54 (5), 728–736.

Tabas, I., García-Cardeña, G., Owens, G.K., 2015. Recent insights into the cellular biology of atherosclerosis. J. Cell Biol. 209 (1), 13–22.

Wang, B., Zhang, M., Takayama, T., Shi, X., Roenneburg, D.A., Kent, K.C., Guo, L.-W., 2015. BET bromodomain blockade mitigates intimal hyperplasia in rat carotid arteries. EBioMed. http://dx.doi.org/10.1016/j.ebiom.2015.09.045.