Apabetalone (RVX-208) inhibits key drivers of vascular inflammation, calcification, and plaque vulnerability through a BET-dependent epigenetic mechanism

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Apabetalone (RVX-208) is an orally available small molecule bromodomain & extraterminal (BET) protein inhibitor that targets the second bromodomain (BD2) of BET proteins. Apabetalone returns dysregulated BET-dependent transcription toward normal physiological levels. In phase 2 trials, apabetalone treatment reduced the incidence of major adverse cardiac events by 44% in CVD patients and by 57% in diabetic CVD patients. Previous studies have highlighted apabetalone’s positive impact on vascular calcification (VC) and inflammation (VI) marker expression in vitro, as well as its ability to lower serum alkaline phosphatase (ALP) levels, and improve atherosclerotic plaque stability parameters in treated patients. In CVD, elevated inflammatory mediators and cell surface adhesion molecules drive VI, resulting in leukocyte adhesion, infiltration, uptake of oxLDL, and ultimately plaque formation. Here we show in vitro that THP-1 monocyte adhesion to human aortic endothelial cells (HAECs) increases with TNFa stimulation and is attenuated by apabetalone treatment, with fewer monocytes attaching to HAECs under flow conditions. This functional outcome is attributed to apabetalone’s reduction of key endothelial adhesion genes, VCAM-1 (50%, p = 0.0001) and SELE (37%, p = 9 x 10^-5). Apabetalone also prevents TNFa induction of endothelial recruitment genes (MCP-1; 75%, p = 0.0002) and genes involved in plaque rupture (IL8; 24%, p = 2 x 10^-5). Basal HAEC ALP expression, a potential contributor to endothelial dysfunction and VC, also decreases with apabetalone treatment (70%, p = 0.005). Induction of VI genes by TNFa is BET-dependent as degradation of BET proteins by MZ-1 prevents an increase in transcripts in response to TNFa treatment. Ingenuity® Pathway Analysis (IPA®), GSEA, and GO analysis of HAEC gene expression data predicts apabetalone inhibition of pro-atherogenic pathways, gene sets, and upstream regulators induced by TNFa. These include cytokine and chemokine, Toll-Like Receptor (TLR), Nfkβ, Interferon and TNFa signaling. In addition, IPA® disease and biological function analysis predicts inhibition of immune cell activation and recruitment by apabetalone. Plasma proteomics (SOMAscan®) and IPA® analysis from apabetalone-treated CVD patients in ASSERT and ASSURE phase 2 trials indicate that apabetalone inhibits pro-atherogenic upstream regulators (IL-6 and IFNy), canonical pathways, and diseases and functions. Serum ALP also decreases dose dependently with apabetalone treatment (ASSERT). Epigenetic inhibition of VI and VC driven atherogenesis likely contributes to the reduction in MACE observed in phase 2 apabetalone treated patients. The ongoing phase 3 post-acute coronary syndrome (ACS) clinical trial in T2DM patients, BETonMACE, is currently testing this hypothesis.