MedicalXpress

Super enhancers in the inflamed endothelium

September 25 2014

Normally, the lining of blood vessels, or endothelium, when at rest, acts like Teflon, ignoring the many cells and other factors rushing by in the bloodstream. In response to inflammatory signals, as well as other stimuli, endothelial cells change suddenly and dramatically—sending out beacons to attract inflammatory cells, changing their surface so those cells can stick and enter tissues, and initiating a complex cascade of responses essential to fighting infection and dealing with injury. Unfortunately, these same endothelial responses also promote atherosclerosis, the build-up of plaque in arteries that cause heart attacks, strokes and other inflammatory diseases.

Now, a study led by researchers at Brigham and Women's Hospital (BWH) and Dana-Farber Cancer Institute is the first to demonstrate that BET bromodomain-containing proteins help execute this global inflammatory program in the endothelium while BET bromodomain inhibition can significantly decrease atherosclerosis in vivo.

The study is published online September 25, 2014 in *Molecular Cell*.

"By using tools that interrogate the entire genome, it has been exciting to uncover how inflammatory signals known to promote atherosclerosis employ BET bromodomain-containing proteins as an epigenetic means of directing entire programs of endothelial gene expression," said Jorge Plutzky, MD, director, BWH Preventive Cardiology, co-corresponding senior author. "BET bromodomain-containing proteins have been studied in cancer for some time, where they are in therapeutic trials, but now we have mechanistic evidence for how BETs and their inhibition can impact

endothelial inflammation and atherosclerosis."

Looking at the epigenome of endothelial cells, researchers sought to get a better understanding of the inflammatory response responsible for the initiation of atherosclerosis by characterizing the dynamics, structure and function of the elements responsible for regulating inflammatory response. This work involved harnessing the expertise of different research teams. James E. Bradner, MD, Dana-Farber Cancer Institute, developed one of the first BET inhibitors and has been a leader in this field.

"This research demonstrates how environmental influences lead to dynamic changes in genome structure leading to disease states, here the inflammation associated with heart disease," said Bradner. "Further, we have identified a set of compounds we developed initially for cancer that halt the progression of coronary disease. These unexpected findings exemplify the very best outcome of open, interdisciplinary science."

To stimulate transcription of genes that carry out the inflammatory program, researchers demonstrated how activation of NF-kB, a canonical mediator of inflammation, leads to a complex between BET bromomdomain-containing proteins and p65, a key NF-kB protein, at specific DNA regulatory regions. These spots are known as super enhancers or stretch enhancers. Super enhancers have been implicated in oncologic processes by Bradner and others but not in endothelial biology or atherosclerosis, at least up until now.

In pre-clinical models, the researchers found that activating NF-kB rapidly re-distributed the BET protein known as BRD4 to chromosomal sites where super enhancers driving expression of nearby inflammatory genes are located. Bromodomains are amino acid regions that bind to specifically modified sites on histones, the proteins around which DNA is coiled. By binding to these amino acid regions, BET bromodomain

inhibitors block the assembly of protein complexes that drive expression of certain genes. In these studies, inhibiting BET bromodomains turned off an inflammatory program in human endothelial cells, decreased white blood cells adhering to endothelial cells, and decreased atherosclerosis in mice.

"By offering new perspectives on transcriptional programs in inflammation and atherosclerosis and how to identify previously unrecognized players in those responses, these studies can offer new therapeutic approaches for atherosclerosis and other inflammatory conditions," said Plutzky. "It also shows what collaborative teams thinking about completely different disease states can uncover by working together."

Provided by Brigham and Women's Hospital