PRC2 Regulates Heart Development (p 406)

He et al reveal the importance of keeping chromatin quiet during the development of the heart.

Congenital malformations of the heart are among the most common major birth defects. Although it is well known that normal heart development involves a variety of transcription regulators and chromatin remodeling proteins, few studies have pursued the role of chromatin silencing factors. A key chromatin silencer is the highly-conserved polycomb repressive complex (PRC). At particular regions of the genome, PRC methylates histone proteins, which renders the chromatin—and the genes within—inaccessible. He et al investigated the role of PRC in heart development by inactivating Ezh2, a subunit of PRC, in mouse cardiac progenitor cells. This inactivation upregulated a number of normally silenced genes, including cell proliferation inhibitors, Ink4a and b. It also resulted in lethal heart abnormalities in the embryo, such as ventricular and septal defects and a thinner myocardium. Interestingly, inactivating Ezh2 later in development caused no such problems, suggesting that Ezh2 has a critical window of functionality during heart development. The results will be important in understanding not only very early changes in chromatin but also their influence on heart formation and the development of congenital defects, say the authors.

NR4A1 and Atherosclerosis (p 416)

Nur77 prevents atherosclerotic lesion formation by discouraging monocytes from becoming pro-inflammatory macrophages, say Hanna et al.

Nur77 belongs to a small family of orphan nuclear receptors. It is expressed in and drives the differentiation of a subset of monocytes called Ly6C−. Although these cells can give rise to both classical pro-inflammatory (M1) macrophages, and alternative anti-inflammatory (M2) cells, they tend to favor the latter. Mice lacking Nur77 also lack Ly6C− cells, leaving Hanna et al to wonder how this monocyte imbalance might affect the outcome of inflammatory disorders. Because Nur77 is known to be expressed in atherosclerotic lesions, they focused their study specifically on atherosclerosis. In two different mouse models of the disease, they found that the absence of Nur77 exacerbated symptoms—the size, macrophage content, and lipid content of plaques. Consistent with these results, macrophages in Nur77-lacking mice were preferentially pro-inflammatory, expressing inflammatory factors such as TNF-α and nitric oxide. The authors also found that a newly-identified subset of human monocytes thought to be equivalent to Ly6C− cells expressed Nur77 as well. Together these findings suggest that boosting Nur77 in humans might be an effective means to suppress atherosclerosis.

Nur77 Reduces Atherosclerosis (p 428)

Like Hanna et al, Hamers et al find that Nur77 dampens the fire of atherosclerosis.

In an independent research study, a group from the Netherlands also investigated the effect of Nur77 deletion on inflammation. Their focus, however, was more specifically centered on the question of macrophage phenotype. They found that in addition to an increase in inflammatory factors such as nitric oxide, cells lacking Nur77 had increased expression of the chemokine stromal cell–derived factor 1 (SDF1). In vitro, SDF1α promoted macrophage migration, while in vivo, Nur77−/− mice exhibited increased inflammatory cell migration towards a site of irritation when compared with wild-type mice. The team also found that in a mouse model of atherosclerosis, animals transplanted with Nur77−/− bone marrow cells had larger lesions containing a greater number of macrophages, T cells, and smooth muscle cells than those given wild-type bone marrow cells. Plaques in the animals with Nur77−/− bone marrow cells also had high levels of SDF1α expression. The team concluded that deletion of Nur77, by increasing in SDF1α, attracted inflammatory cells to plaques. Thus both Nur77 and SDF1α may be good targets for atherosclerosis therapies.
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