Journal Scan

C/EBP transcription factors mediate epicardial activation during heart development and injury

The epicardium which encapsulates the heart and functions as a source of multipotent progenitor cells and paracrine factors is essential for cardiac development and repair. Cells of the adult epicardium are typically quiescent but are rapidly activated in response to cardiac injury, promoting cell cycle reentry and embryonic gene expression. The authors established a mouse embryonic heart organ culture and gene expression system that facilitated the identification of epicardial enhancers activated during heart development and injury. Epicardial activation of these enhancers depends on a combinatorial transcriptional code centered on CCAAT/enhancer binding protein (C/EBP) transcription factors. Disruption of C/EBP signaling in the adult epicardium reduced injury-induced neutrophil infiltration and improved cardiac function. The authors report the transcriptional mechanisms underlying epicardial activation during cardiac development and repair, and a functional link between the adult epicardium and cardiac remodeling following ischemic injury.

Comment

The present work highlights the role of the epicardium in regulation of the inflammatory response and neutrophil infiltration after injury. In this regard, manipulations that inhibit neutrophil recruitment in animals undergoing reperfusion following MI diminish infarct size. Inhibition of C/EBP signaling in the adult epicardium confers cardioprotection and hence future studies focussing on the role of epicardium stimulated cytokines and chemokines as potential C/ EBP downstream targets may pave the way for identifying novel molecular targets and thus facilitate disovery of novel strategies to reduce reperfusion damage and enhance cardiac repair.

Huang GN, Thatcher JE, McAnally J, Kong Y, Qi X, Tan W, DiMaio JM, Amatruda JF, Gerard RD, Hill JA, Bassel-Duby R, Olson EN. C/EBP transcription factors mediate epicardial activation during heart development and injury. Science. 2012;338:1599-603.

Pregnancy imprints regulatory memory that sustains anergy to fetal antigen

Sustainance of pregnancy requires selective suppression of immune effector cells against fetal antigens. This requires the sustained expansion of immune-suppressive maternal Foxp3+ regulatory T-cells [T_{reg} cells]. Many idiopathic pregnancy complications have been proposed to originate from disrupted fetal tolerance with blunted maternal T_{reg} expansion. However, the antigen specificity and cellular origin of maternal Treg cells that accumulate during gestation have been incompletely defined. In this study, the authors show that pregnancy selectively stimulates the accumulation of maternal Foxp3+ CD4+ cells with fetal specificity using tetramer-based enrichment, a technique that allows the identification of rare endogenous T-cells. After delivery, fetal-specific T_{reg} cells were found to persist at elevated levels. To further characterize maternal Tregs with specificity to pre-existing fetal antigen that persist postpartum, the authors tracked these cells during subsequent pregnancy. They observed that recurrent pregnancy primes the accelerated accumulation of maternal Foxp3+ cells that expand from pre-existing Tregs retained from prior pregnancy. The accelerated expansion of T_{reg} cells during secondary pregnancy was found to be driven almost exclusively by proliferation of foetal-specific Foxp3+ cells retained from prior pregnancy, whereas induced Foxp3 expression and proliferation of pre-existing Foxp3+ cells each contributed to Treg expansion during primary pregnancy.

To further establish how maternal Tregs with fetal-specificity retained postpartum impacts subsequent pregnancy outcomes, the frequency of fetal resorption triggered by partial maternal Foxp3+ cell ablation

using Foxp3DTR/WT mice was compared between secondary and primary pregnancy. They found that secondary pregnancy became significantly more resilient to partial Treg ablation. Thus, pregnancy imprints Foxp3+ CD4+ cells that sustain protective regulatory memory to fetal antigen.

Comment

The findings from this study can have a big impact on maternal and fetal outcomes especially so in developing countries like India. Further extension of this study wherein the durability of pregnancy-induced regulatory memory and its sustainance needs to be further explored. This will in turn lead to novel therapeutic approaches for treating women with bad obsteric histories.

Rowe JH, Ertelt JM, Xin L, Way SS. Pregnancy imprints regulatory memory that sustains anergy to fetal antigen. Nature 2012;490:102-6. doi: 10.1038/nature11462. Epub 2012 Sep 26.

Seventy-five genetic loci influencing the human red blood cell

Anaemia is a chief determinant of global ill health, contributing to cognitive impairment, growth retardation and impaired physical capacity. A number of factors influence red blood cell formation and function. The authors carried out a meta-analysis of genome-wide association studies (GWAS) and staged follow-up genotyping of six red blood cell phenotypes i.e. haemoglobin, mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), mean cell volume (MCV), packed cell volume (PCV) and red blood cell count (RBC) in up to 135,367 individuals. The authors identified 75 independent genetic loci associated with one or more red blood cell phenotypes at $P<10^{-8}$, which together explain 4-9% of the phenotypic variance per trait. Among the 75 genomic loci identified, they found that 31 were associated with one red blood cell phenotype, and 44 with two or more phenotypes, at $P<10^{-8}$. At 8 of the 75 loci the authors found evidence for multiple single nucleotide polymorphisms (SNPs) independently associated with red blood cell phenotype at $P<10^{-8}$ in conditional analyses, suggesting the presence of possible secondary genetic mechanisms at these loci. Using expression quantitative trait loci and bioinformatic strategies, they identifed 121 candidate genes enriched in functions relevant to red blood cell biology. The candidate genes are expressed preferentially in red blood cell precursors, and 43 have haematopoietic phenotypes in Mus musculus or Drosophila melanogaster. Through open-chromatin and coding-variant analyses the authors identified potential causal genetic variants at 41 loci. The findings from this study provide extensive new insights into genetic mechanisms and biological pathways controlling red blood cell formation and function.

Comment

This work involves collaborative work-up from multiple disciplines. The collaborative work involving extensive genome wide association studies, bioinformatic and experimental data has thrown some light on the various aspects controlling red blood cell formation and function which are in turn reflected in the varous types of haemoglobinopathies expressed clinically in the form of anaemias. Further studies in this direction should definitely enhance our knowledge of the complex mechanisms underlying haemopoiesis which in turn should translate into better therapeutic stategies for correcting anaemia.

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Reviewers

Dr V. Suresh, Dr Aparna R.Bitla

Provenance and peer review commissioned; internally peer reviewed.