Adipocytes in their (CD)40s

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Immune cells play a crucial role in cardiometabolic diseases (obesity, atherosclerosis, non-alcoholic steatohepatitis). Cells associated with the innate (macrophages, monocytes, neutrophils, NK cells) and adaptive (T and B lymphocytes) immune responses are involved in disease onset and progression. Optimal T- and B-cell activation requires the involvement of co-stimulatory molecules including the CD40-CD40L receptor-ligand pair.[1] CD40L is detected on T cells, while CD40 is typically expressed on antigen-presenting cells such as dendritic cells, macrophages and B cells. Interestingly, CD40 expression was also observed on non-hematopoietic cells including fibroblasts, endothelial cells and epithelial cells. The functional significance of engaging the CD40-CD40L pathway in the development of cardiometabolic diseases has been documented.[2-4] Indeed, previous work demonstrated that myeloid cell-specific CD40 deletion on a pro-atherogenic genetic background led to the development of smaller atherosclerotic plaque lesions.[2] This was mainly due to the anti-inflammatory phenotype of CD40-deficient macrophages. Furthermore, besides antigen-presenting cells, adipocytes expressed functional MHC-II, suggesting a potential role in antigen presentation.[5] However, the potential role of adipocytes in immune responses remains poorly characterized.

In an article published in this issue of *Haematologica*, Reiche and colleagues describe the impact of CD40 deletion in mature adipocytes on inflammation and metabolic diseases.[6] The authors generated mice selectively lacking CD40 expression on mature adipocytes (AdipoQ^{cre} x CD40$^{fl/fl}$ mice) and observed decreased bone marrow hematopoietic stem cell numbers in adult and aged mice. Moreover, B-cell and T-cell homeostasis was altered, with decreased numbers of B cells and T cells displaying an activated pro-inflammatory phenotype. The presence of a large population of regulatory T cells (Treg) in visceral white adipose tissue has also been documented.[7] Visceral adipose tissue Treg display a sex-specific phenotype and are enriched in male mice in comparison to age-matched females.[8] Pioneering work defined a role for MHC-II, mainly expressed on CD11b^{+} and CD11c^{+} antigen-presenting cells, in Treg adipose tissue accumulation.[9] The study by Reiche *et al.* demonstrates that adipocyte CD40 expression is not involved in the generation and maintenance of visceral adipose tissue Treg. In a model of diet-induced obesity, adipocyte-specific CD40 deletion led to improved glucose tolerance and weight gain possibly linked to increased fat oxidation. When AdipoQ^{cre} x CD40$^{fl/fl}$ mice were bred on a pro-atherogenic (ApoE$^{-/-}$) background, CD40 pathway engagement on adipocytes had multiple impacts on atherosclerosis disease parameters, culminating in a protective phenotype as illustrated by decreased plaque area. Adipocyte CD40-deficient animals displayed increased myelopoiesis and lymphopoiesis, smaller atherosclerotic plaque area but, surprisingly, the necrotic area in the plaques was increased. Monocytes obtained from AdipoQ^{cre} x CD40$^{fl/fl}$ ApoE$^{-/-}$ mice had improved chemotaxis towards CCL2, suggesting potentially increased plaque recruitment.

Taken together these data suggest a major role of CD40 in both hematopoiesis and immune cell functions. However, precisely how cholesterol or lipid metabolism, altered in metabolic diseases, could affect CD40 signaling in adipocytes and its interaction with CD40L remains to be established. Likewise, Reiche *et al.* documented increased bone marrow adipocyte area in AdipoQ^{cre} x CD40$^{fl/fl}$ mice, but the molecular mechanisms underlying the role of CD40 in bone marrow-adipocyte interactions are yet to be identified. Furthermore, mechanisms linking adipocyte CD40 to monocyte migration or T-cell activation in adipose tissue, and whether these lead to the production of a specific set of cytokines, require further investigation. In both models of obesity and atherosclerosis, increased T-cell activation and plasma interferon-γ were observed in AdipoQ^{cre} x CD40$^{fl/fl}$ mice, in comparison to littermate control animals, suggesting a rather inhibitory role of adipocyte CD40 on T-cell activation. T cells play a major role during atherosclerosis development. While Th1 cell-derived interferon-γ and tumor necrosis factor-α are detrimental, Treg play a beneficial role through the production of interleukin-10.[10] It was demonstrated that T-cell activation during atherosclerosis depends, at least partially, on the presentation of ApoB-derived peptides by MHC-II. Whether adipocyte CD40 is required for optimal T-cell activation in this context remains to be defined.

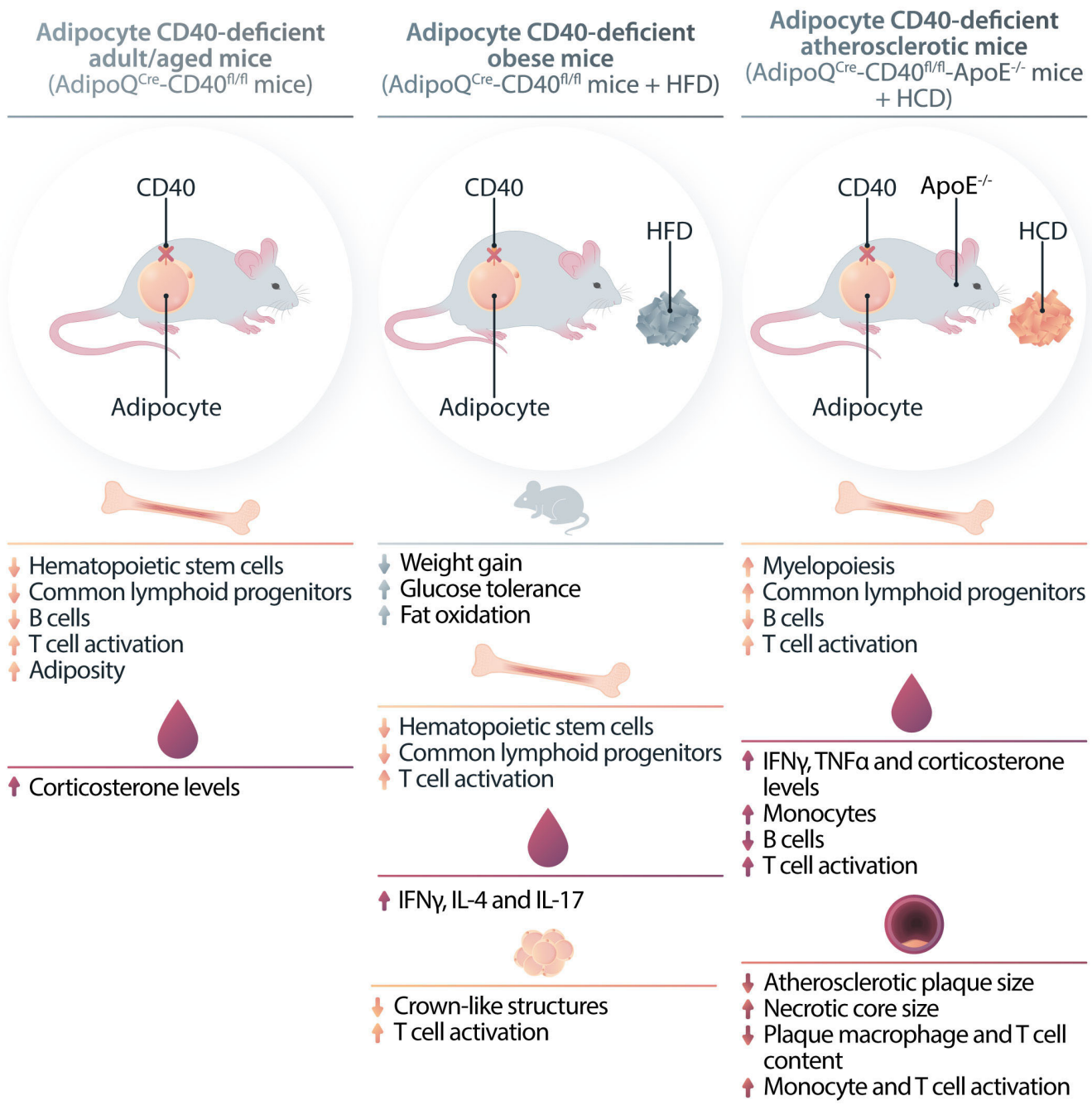

Figure 1. Effects of CD40 deficiency in adipocytes on hematopoiesis and cardiometabolic diseases Mice lacking CD40 in mature adipocytes had decreased bone marrow hematopoietic stem cells and altered B- and T-cell homeostasis with reduced B-cell counts and increased T-cell activation. These changes were associated with elevated bone marrow adiposity and plasma corticosterone levels. In a model of obesity induced by a high-fat diet, adipocyte-specific CD40 deficiency ameliorated weight gain and glucose tolerance, in line with increased fat oxidation. In an atherosclerosis-prone genetic mouse model, adipocyte-specific CD40 deficiency enhanced hypercholesterolemia-induced myelopoiesis and lymphopoiesis, and resulted in smaller atherosclerotic plaques but larger necrotic cores. The more activated phenotype of T cells in adipocyte CD40-deficient mice may eventually aggravate cardiometabolic diseases. HFD: high-fat diet; HCD: high-cholesterol diet; IFN: interferon; TNF: tumor necrosis factor; IL: interleukin.

In mammals, three major adipocyte subsets have been identified: namely white, beige and brown adipocytes. White adipocytes are implicated in energy storage and mobilization upon nutrient deprivation, while brown and beige adipocytes are involved in non-shivering thermogenesis during cold exposure, a process heavily relying on their Ucp1 expression. In the study by Reiche *et al.*, a pan-adipocyte CD40 deletion strategy was achieved. Whether CD40 plays a different role in different adipocyte subsets remains to be defined.

Disclosures

No conflicts of interest to disclose.

Acknowledgments

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References

1. Elgueta R, Benson MJ, de Vries VC, Wasiuk A, Guo Y, Noelle RJ. Molecular mechanism and function of CD40/CD40L engagement in the immune system. Immunol Rev. 2009;229(1):152-172.
2. Bosmans LA, van Tiel CM, Aarts SABM, et al. Myeloid CD40 deficiency reduces atherosclerosis by impairing macrophages' transition into a pro-inflammatory state. Cardiovasc Res.

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3. Reiche ME, den Toom M, Willemsen L, et al. Deficiency of T cell CD40L has minor beneficial effects on obesity-induced metabolic dysfunction. BMJ Open Diabetes Res Care. 2019;7(1):e000829.
4. Aarts S, Reiche M, den Toom M, et al. Depletion of CD40 on CD11c(+) cells worsens the metabolic syndrome and ameliorates hepatic inflammation during NASH. Sci Rep. 2019;9(1):14702.
5. Deng T, Lyon CJ, Minze LJ, et al. Class II major histocompatibility complex plays an essential role in obesity-induced adipose inflammation. Cell Metab. 2013;17(3):411-422.
6. Reiche ME, Poels K, Bosmans LA, et al. Adipocytes control hematopoiesis and inflammation through CD40 signaling. Haematologica. 2023;108(7):1873-1885.
7. Feuerer M, Herrero L, Cipolletta D, et al. Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. Nat Med. 2009;15(8):930-939.
8. Vasanthakumar A, Chisanga D, Blume J, et al. Sex-specific adipose tissue imprinting of regulatory T cells. Nature. 2020;579(7800):581-585.
9. Kolodin D, et al. Antigen- and cytokine-driven accumulation of regulatory T cells in visceral adipose tissue of lean mice. Cell Metab. 2015;21(4):543-557.
10. Wolf D, Ley K. Immunity and inflammation in atherosclerosis. Circ Res. 2019;124(2):315-327.