

Do polarized T lymphocytes and T regulatory lymphocytes play a role only in the animal model of atherosclerosis?

To the Editor We read a recent review by Jawień¹ with great interest. It is a significant voice in the field of atherosclerosis. Being excellent, this paper raises a few concerns for human studies in comparison with the animal model. However, a few opinions presented in the review, namely, that “humans lack Th1 and Th2 polarization that is observed in mice” and that “FoxP3 expression is a useful marker of T_{reg} cells in mice, but not in humans”, need some commentary.

The first point to be discussed is the polarization of T-helper (Th) 1 and Th2 lymphocytes in humans. Different infectious agents evoke an adequate adaptive immune response that clears an infection. The immune system adapts itself to the specific conditions of infection by producing different profiles of cytokines, which drive naïve CD4 T cells to differentiate into appropriate effector Th subset: Th1 or Th2. This step is critical for effective immune response because it determines its path – cellular or humoral. From these 2 subsets of T cells, Th1 are the main contributors to atherosclerosis and their characteristic cytokine, interferon- γ (IFN- γ), is observed in human plaques. The abundance of IFN- γ has not only dramatic consequences because of the activation of macrophages, but also causes decreased collagen fiber formation, higher expression of major histocompatibility complex class II, enhanced protease and chemokine secretion, upregulation of adhesion molecules, and induction of proinflammatory cytokines. Interleukin 4, the cytokine of Th2 lineage, is in fact rarely observed in human plaques, which, in line with the available data, proves the crucial role of Th1 subset in the pathogenesis of atherosclerosis, probably also in humans. The presence of Th1/Th2 polarized lymphocytes in humans has been confirmed in pregnancy and numerous clinical conditions, e.g., allergic disorders.^{2–4}

Second issue that needs to be clarified is forkhead box 3 (FoxP3) as a marker of human regulatory T (T_{reg}) lymphocytes. The characterization of T_{reg} cells by the expression of FoxP3 protein, initially in mice and subsequently in humans, was

a critical step in the elucidation of their biology. Mutation of the *FoxP3* gene in mice was originally connected with X-linked recessive inflammatory disease. Further studies in humans demonstrated that mutation in human *FoxP3* gene is responsible for X-linked immunodeficiency syndrome (also known as immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome). FoxP3 belongs to the family of transcription factors and is the main controller during T_{reg}-cell development, and a hallmark of active T_{reg} cells. Human T_{reg} cells were first characterized by the presence of CD4 and CD25 molecules, the same as in the mice model. In fact, the *FoxP3* gene was described as a master gene controlling the development of T_{reg} cells in mice. Subsequently, it was shown that the human version of FoxP3 protein is also crucial for the function of human T_{reg} cells. Furthermore, FoxP3 is exclusively expressed by CD25⁺CD4⁺ T_{reg} cells, while other T cells, B cells, and natural killer cells do not express it. T_{reg} cells are commonly classified as “natural” and “induced”. A natural subset, which develops and emigrates from the thymus, is CD4⁺CD25⁺. Induced T_{reg} cells are also characterized as CD4⁺CD25⁺, but they acquire CD25 (α chain of the interleukin 2 receptor) outside the thymus.

There have been several reports describing the role of T_{reg} cells in several pathologies both in humans and in the murine model.⁵ It is crucial to be aware of the pivotal differences but also similarities between animal models and humans.

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REFERENCES

- 1 Jawien J. Atherosclerosis in 2012: what is new? *Pol Arch Med Wewn.* 2012; 122: 170-173.
- 2 Zhu J, Yamane H, Paul WE. Differentiation of effector CD4 T cell populations (*). *Annu Rev Immunol.* 2010; 28: 445-489.
- 3 Sykes L, MacIntyre DA, Yap XJ, et al. The Th1:th2 dichotomy of pregnancy and preterm labour. *Mediators Inflamm.* 2012; 2012: 967 629.
- 4 Wisniewski JA, Borish L. Novel cytokines and cytokine-producing T cells in allergic disorders. *Allergy Asthma Proc.* 2011; 32: 83-94.
- 5 Bilate AM, Lafaille JJ. Induced CD4+Foxp3+ regulatory T cells in immune tolerance. *Annu Rev Immunol.* 2012; 30: 733-758.

Author response First of all, I would like to thank Dr Zimoch and Dr Baran for their interesting comments to my article.¹

As regards the sentence: “humans lack Th1 and Th2 polarization that is observed in mice”, the existence of Th1 and Th2 polarization was originally observed in mice. However, I agree that almost the same polarization was later detected in humans.

The conclusion that “FoxP3 expression is a useful marker of T_{reg} cells in mice, but not in humans” originated from the article published in the *Blood* in 2007.² Because biomedicine is ever-evolving activity, this view has already changed.

The objective of my review was to put emphasis on the fact that there is too little data from humans regarding atherogenesis. After all, mice are not humans and if we want to precisely describe the mechanisms of atherosclerosis in humans, we cannot rely only on the results derived from animals.^{3,4} Therefore, it is important to investigate more data from humans.

REFERENCES

- 1 Jawien J. Atherosclerosis in 2012: what is new? *Pol Arch Med Wewn.* 2012; 122: 170-173.
- 2 Tran DQ, Ramsey H, Shevach EM. Induction of FOXP3 expression in naive human CD4+FOXP3 T cells by T-cell receptor stimulation is transforming growth factor-beta dependent but does not confer a regulatory phenotype. *Blood.* 2007; 110: 2983-2990.
- 3 Bailey M, Christoforidou Z, Lewis MC. The evolutionary basis for differences between the immune systems of man, mouse, pig and ruminants. *Vet Immunol Immunopathol.* 2012 Sep 26. [Epub ahead of print].
- 4 Bryant CE, Monie TP. Mice, men and the relatives: cross-species studies underpin innate immunity. *Open Biol.* 2012; 2: 120015.