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Editorial

# Trained Immunity and Autoimmune Disease: Did Eve Sin before Adam?

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Antigen presentation is usually performed by monocytes/macrophages and dendritic cells, which constitutively express HLA class II molecules capable of presenting peptides to CD4 + T cells. Nevertheless, all the cells in the body can present peptides to CD8 + T cells via their HLA class I molecules. In addition, some non-hematopoietic cells such as renal and epithelial cells can express low levels of HLA class II molecules when stimulated by interferon gamma (IFN-γ) [1] or interleukin (IL)-1 [2].

In contrast, only a small contingent de cells has immune effector capabilities. Some cells belonging to the innate immune system do not carry receptors with high specificity for antigens. Examples include NK cells (the innate analogs of CD8 + T cells), type 1 innate lymphoid cells (ILCs) (the innate analogs of Th1 cells, which share with these the ability to release IFN-γ), type 2 ILCs (the innate analogs of Th2 cells, which release IL-25 and IL-33), and type 3 ILCs (the innate analogs of Th17 cells, which preferentially release IL-17 A and IL-22) [3]. Lymphocytes belonging to the adaptive immune system express surface receptors that have increased considerably in sophistication and diversification during evolution, with the production of antibodies by B cells and of Tγδ or αβ receptors by T cells. These surface receptors allow the cells to recognize only a limited number of antigens (for B cells) or HLA-presented peptides (for T cells).

Previous dogma held that only T and B cells were capable of building immunological memory of past insults, and, therefore, of responding more quickly and more strongly to subsequent exposures. This adaptive immunity results from the proliferation within lymphoid organs of T- and B-cell clones expressing receptors with high affinity for the antigen they are presented with, followed by transformation of some of the cells into memory lymphocytes, a phenotype subsequently maintained by intermittent contact with the antigens/peptides that persist at the surface of the very long-lived follicular dendritic cells found within lymphoid follicles.

This dogma long led clinicians and researchers to focus on the hypothesis that autoimmunity resulted from an excessive and sustained response of the adaptive immune system (via B or T cells) to self peptides. The presenting cells present within the damaged tissues were often viewed merely as innocent victims of this excessive response. Another reason for focusing on the adaptive immune system was that circulating lymphocytes and antibodies can be investigated readily in blood samples, whereas harvesting presenting cells from organs damaged by autoimmune disease is far more challenging, notably when the brain, pancreas, subchondral bone, or kidneys are involved.

Nonetheless, recent studies have established that several types of presenting cells can build memories of past encounters with various insults. Further exposure to the same or other insults then produces a stronger and faster immune response. The term “trained immunity” was coined in 2011 to designate this ability of innate immune cells (e.g., macrophages) to mount an exacerbated response to previously experienced insults, despite having no antigen-specific receptors [4–6]. In nude athymic mice, the memory response of presenting cells persisted, despite the absence of T cells [7].

Trained immunity was first demonstrated for monocytes/macrophages and NK cells then observed also in bone-marrow stem cells [8], which can transmit the trained immunity phenotype to their offspring. This transmission capability explains why innate memory responses can persist despite the short lifespan of monocytes/macrophages. Epithelial stem cells were recently reported to exhibit trained immunity and to transmit this trait to their offspring, thereby improving the ability of the epithelial apex to withstand further insults [9].

Just as regulator lymphocytes blunt the immune response, trained immunity may decrease the response to certain insults, as occurs for instance after repeated exposure to lipopolysaccharides [10]. This mechanism contributes to allow tolerance of antigens that are continuously in contact with the epithelial cells of the mucous membranes.

Although first demonstrated for innate immune cells then for epithelial stem cells, trained immunity also occurs with other types of cells [7]. For instance, the glial cells in the central nervous system have been proved capable of acquiring trained immunity, which may contribute to the pathogenesis of some forms of neuropathic pain [11].

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The ability of various presenting cells to accelerate their response to an insult on their own, before having been scrutinized then supported or eliminated by adaptive immune cells, is due to a variety of epigenetic mechanisms [9]. These produce stable chromatin rearrangements, which cause sustained changes in the transcription of specific genes, explaining how the cell memorizes previously experienced insults. The epigenetic changes ensure that repeated exposure to the same insult results in accelerated production of danger signals within the cell and/or accelerated and magnified release of defense cytokines such as IL-1 [12], after activation of various inflammasomes [13]. This state of heightened vigilance may even confer cross-protection against pathogens that have not been previously encountered [7,14]. It may be more effective in preventing the intrusion of new agents than in eliminating agents already present within cells, as noted in chronic *Candida* infection models [7] and in children given the BCG vaccine [14]. Although trained immunity is often insufficient to eradicate intracellular microorganisms, it results in substantial changes in cell metabolism [13], which may contribute to curb the replication of microorganisms already present in the cell. The metabolic changes associated with trained immunity include accelerated glycolysis and glutaminolysis, contrasting with increased production of cholesterol and mevalonate [13–15].

Trained immunity was first a topic of considerable interest to vaccination specialists [16]. However, a recent hypothesis is that trained immunity may contribute to the induction or expression of diseases believed to involve autoimmune processes such as psoriasis [9] and inflammatory joint diseases. Macrophages from the rheumatoid synovial membrane exhibit the same metabolic alterations as those associated with trained immunity. Other arguments supporting a role for trained immunity of presenting cells in the pathogenesis of various autoimmune or autoinflammatory diseases [14].

This new concept is particularly appealing as it may constitute a better explanation than an excessive adaptive (T- or B-cell) response to the following facts.

The continuum between autoinflammatory and autoimmune diseases: inflammasome activation during trained immunity may be amplified by the inflammasome sensitization characteristic of autoinflammatory diseases, with the resulting overexcitability of presenting cells secondarily promoting the emergence of autoimmune responses.

The usually greater effectiveness in inflammatory joint disease of drugs that dampen the activity of presenting cells (TNF antagonists, IL-6 antagonists, IL-1 antagonists, abatacept, and rituximab) compared to drugs that target only the effector T cells.

The often focal and at times haphazard distribution of lesions, notably in psoriasis and inflammatory joint diseases, with severe lesions of some skin or joint sites, whereas neighboring sites remain spared over time.

The occurrence before the onset of some diseases of epithelial infections (reactive arthritis before spondyloarthritis) or of transient or lasting alterations in the gut, lung, or skin microbiome. Temporary translocation of microorganisms from the mucous membranes to the joints and/or skin may contribute to induce trained immunity at these sites. Some inflammatory joint diseases may thus be due to a sustained excessive response to previous infections responsible for epigenetic modifications, which may be either confined to mature presenting cells (explaining the occurrence of transient polyarthritis) or extend to their progenitors (resulting in lasting polyarthritis).

In studies of chronic inflammatory joint disease, the cells where evidence of trained immunity should be sought preferentially are the very long-lived stem cells of the epithelia, synovial membrane, and subchondral bone (mesenchymatous stem cells), whose offspring may conserve the memory of past insults experienced by the progenitor cells [17]. Therefore, investigations of cells from blood samples are likely to remain unrewarding, as indicated by a recent study of rheumatoid arthritis [18].

**Fig. 1.** A number of chronic insults (the serpent), such as infections, can induce epigenetic modifications within presenting and/or stem cells (Eve), thereby allowing memorization of past insults and conferring activated cell status (trained immunity). This mechanism may contribute both to initiate and to perpetuate an excessive lymphocyte response (Adam) to presenting cells modified by trained immunity and to their offspring, which may inherit (original sin) these epigenetic modifications. Trained immunity may also promote the development of autoimmunity in the event of abnormal and sustained presentation of self-antigens (the apple) by the modified presenting cells.

According to several recent studies, bacteria and viruses that persist in the body preferentially seek refuge (usually in a dormant state) within very long-lived cells, whose immune privilege protects them from an excessive adaptive response (e.g., neurons for the herpesviruses, varicella-zoster virus, and *Mycobacterium leprae*; mesenchymatous and/or hematopoietic stem cells for *Mycobacterium hominis*; and epithelial stem cells for enterobacteria) [17].

An interesting line of research would therefore consist in using animal models to determine whether epithelial and/or bone stem cells previously targeted by an intracellular pathogen and/or harboring dormant infectious agents can develop chronic trained immunity, and whether this last can be sufficiently marked to contribute to an excessive cytokine response or even to abnormal presentation of self-antigens (already encouraged by the peptide loading abnormalities due to the xenophagia impairments that promote chronic bacterial carriage) [19].

Whether trained immunity can induce aberrant or excessive production of HLA class II molecules [1] by epithelial or mesenchymatous stem cells and their offspring will also have to be investigated. Increased expression of HLA class II molecules (not only DR, but also DQ and even DP) may be unable to promote the initiation of an autoimmune response (which must probably occur within the lymphoid organs after presentation by dendritic cells), but may contribute to perpetuate a multifocal autoimmune response by inducing autoreactive T cells to preferentially target presenting cells in the affected tissues that have undergone the

epigenetic modifications characteristic of trained immunity. Such a mechanism seems plausible, since some stromal cells can express HLA-DR, at least in the bowel. In addition, infected epithelial cells can also express HLA-DR [20]. Studies of epithelia may be particularly relevant, since trained immunity within epithelial cells affects the homeostasis of the microbiomes that colonize various mucosae [7].

Research into trained immunity of stem cells may be even more informative. The results may explain why diseases related to dysimmunity can recur even after allogeneic bone marrow transplantation. This fact suggests that modified cells (e.g., mesenchymatous stem cells) survive pretransplant conditioning and contribute, via their offspring bearing the same epigenetic modifications, to recurrence of the dysimmunity.

Although these speculations require investigation, it appears increasingly likely that, in the couple formed by the presenting cell (Eve), who is assumed to be innocent, and the effector cell (Adam), assumed to be guilty, the first may make the earliest contribution to the genesis of dysimmunity (Fig. 1).

## Disclosure of interest

The authors declare that they have no competing interest.

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Jean-Marie Berthelot [a,*]
Jean Sibilia [b]
[a] *Rheumatology Unit, Nantes University Hospital, Place Alexis Ricordeau, 44093, Nantes cedex 01, France*
[b] *Department of Rheumatology, Reference Center for Rare Autoimmune Diseases, Division of Internal Medicine, Hautepierre Hospital, University Hospital of Strasbourg, France*

* Corresponding author.
*E-mail address:* jeanmarie.berthelot@chu-nantes.fr
(J.-M. Berthelot)


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