Hepatology Snapshot:

Autoimmune hepatitis: Possible triggers, potential treatments

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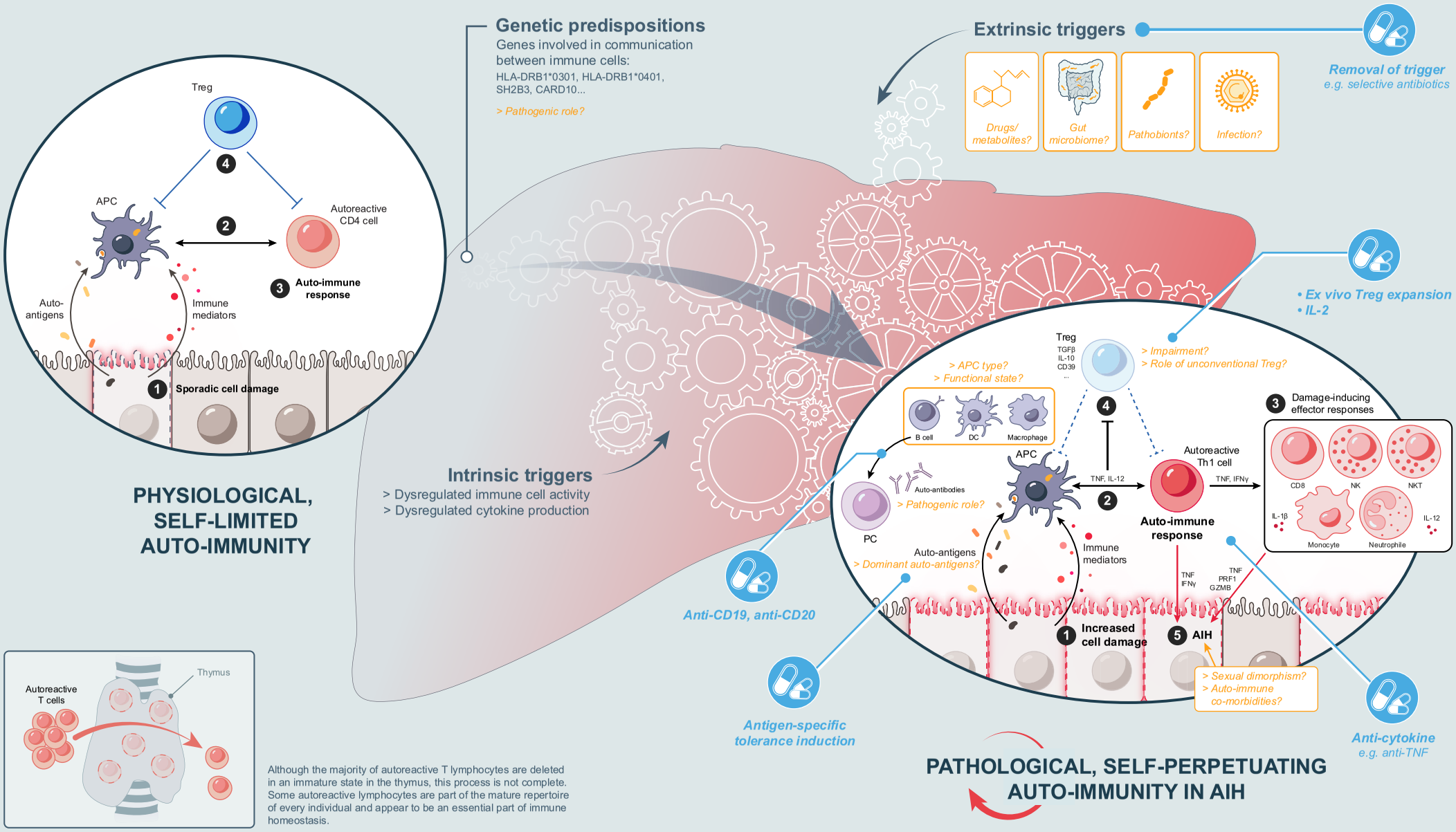

Although the majority of autoreactive T lymphocytes are deleted in an immature state in the thymus, this process is not complete. Some autoreactive lymphocytes are part of the mature repertoire of every individual and appear to be an essential part of immune homeostasis.

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Summary
Autoimmune hepatitis is an inflammatory liver disease, which develops as a result of an inadequate immune response directed against liver tissue. In this article, we consider possible triggers of such self-damaging immune responses, some of which might be promising targets for therapeutic intervention.

Self-limited autoimmunity
Autoimmune hepatitis (AIH) is an inflammatory liver disease that seems to be driven by an adaptive immune response wherein T lymphocytes recognize liver-derived antigens. Although the majority of such autoreactive T lymphocytes are already deleted in an immature state in the thymus, this process is not complete, and some autoreactive lymphocytes are part of the mature lymphocyte repertoire of every individual. Autoreactive lymphocytes appear to be an essential part of physiological immune homeostasis. Upon sporadic liver cell damage, these mature autoreactive T cells may be activated by antigen-presenting cells that have taken up liver autoantigens. However, regulatory T cells (Tregs), which are specialized lymphocytes that can suppress immune responses, normally dampen and restrict tissue-damaging autoimmunity. Thus, in the healthy individual, autoimmunity is usually restricted to local sub-clinical and self-limited autoinflammatory episodes. Only when autoimmune responses are sustained and augmented by additional factors, does autoimmune disease develop. The reasons for the development of sustained, tissue-damaging autoimmunity in AIH, like in other autoimmune diseases, are not clear. In fact, the pathogenesis of AIH is all the more puzzling, given that the liver actually has a distinct capability to suppress immune responses and normally induces immune tolerance.[1]

Possible triggers of sustained autoimmunity in AIH
Genetic factors influence an individual's susceptibility to developing AIH; genes involved in the communication between immune cells, such as HLA-DRB1, are the most important.[2] Additional risk factors include female sex and autoimmune comorbidities. The actual development of AIH in susceptible individuals might be initiated by an extrinsic or intrinsic trigger. Importantly, the triggering mechanisms may vary between individual patients. Potential extrinsic triggers include hepatotropic viral infections,[3] drugs or drug-metabolites,[4] alterations in the gut microbiome,[5] or pathobionts.[6] The common idea is that these extrinsic triggers expedite hepatocyte damage and co-stimulatory inflammatory signals, which then fuel autoimmune inflammation.

Potential intrinsic triggers relate to dysregulated activities of immune cells. APCs sense the state of the tissue through conserved pattern-recognition receptors, and it was found that a mere increase in these receptors could be sufficient to trigger fatal autoimmunity.[7] Therefore, it will be important to characterise the relevant APC types in AIH and their functional states. B cells that infiltrate the liver in AIH[8] can also function as APCs, or differentiate into plasma cells secreting autoantibodies. The functional relevance of autoantibodies in AIH is uncertain. It will be important to identify dominant autoantigens recognized by both autoreactive B and T lymphocytes in AIH, as this may enable induction of antigen-specific tolerance.[9]

Another possible intrinsic trigger of AIH could be dysregulated cytokine production. The dominant CD4 T cell response in AIH is a Th1 response, marked by production of IFNγ and TNF.[10] Of note, TNF production by T cells has been identified as an important driver of autoimmune pathology by inducing innate immune cells to produce IL-1β.[11] Besides CD4 T cells, other cell types with tissue-damaging activities are increased in AIH, including NK cells,[12] NKT cells,[13] and CD8 T cells.[8] Yet another possible intrinsic trigger could be dysfunctional Tregs[14,15] or impaired Tr-1 like effector cells[16] that fail to restrict tissue-damaging autoimmunity. Indeed, generalized[14] or selective Treg impairment in the inflamed hepatic microenvironment[15] has been proposed to drive AIH. Taken together, several different mechanisms might trigger AIH in individual patients, and most of these potential triggers can be targeted by specific therapies, as indicated in the figure. However, improved, more specific therapies might require individualised treatment regimens.

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Conflict of interest
Nothing to disclose.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
Conception and drafting of the manuscript: all authors. Critical revision of the manuscript: all authors. All authors read and approved the manuscript.

Supplementary data
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Author names in bold designate shared co-first authorship

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