A Pathway for Sexual Dimorphism in Innate Immunity Against Mycobacterium tuberculosis Infection

TO THE EDITOR—In a recent review article on sex differences, published in a supplement to The Journal of Infectious Diseases, Muenchhoff and Goulder summarized the evidence for sex differences in pediatric infectious diseases. They explain the T-helper type 1 (Th1) dominance in females [1]. It is well known that interferon γ (IFN-γ) expression is enhanced by estrogen [2]. They then mention the data on epigenetic programming of monocytes by BCG immunization through nucleotide binding oligomerization domain receptor 2 (NOD2), after elaborating on the hypothesis about a BCG-induced shift of the immune response to a Th1-dominated response as an explanation of the reduced mortality from infectious causes unrelated to tuberculosis in BCG-immunized children, which is only seen in females. The authors did not elaborate on a causal pathway explaining why BCG-induced epigenetic programming should favor females. To understand this, it is important to review data on immune regulation of NOD2. The first key finding on this was obtained in the context of inflammatory bowel disease research: Rosenstiel et al found that IFN-γ acted synergistically with tumor necrosis factor in upregulation of NOD2 in epithelial cells and that this effect was dependent on nuclear factor κ-light-chain enhancer of B cells (NF-κB) activity [3]. IFN-γ in isolation was also able to increase NOD2 expression in mouse macrophages [4]. This finding points to the possibility of a positive feedback loop wherein the presence of muramyl dipeptide from BCG in females with their enhanced IFN-γ production would increase NOD2 expression, thus increasing IFN-γ production further through activation of NF-κB, which, in turn, would upregulate NOD2 expression [5]. Nhamoyebonde and Leslie mention in the same supplement [6] that the progesterone contraceptive Depo-Provera impaired control of Mycobacterium tuberculosis in mice. Progesterone concentrations have been found to be negatively correlated with NOD2 expression in the human endometrium [7]. Future studies need to compare NOD2 expression levels between males and females in peripheral blood mononuclear cells of BCG-immunized children to test this hypothesis.

Note

Potential conflict of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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References


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