Women, autoimmunity, and cancer: a dangerous liaison between estrogen and activation-induced deaminase?

Robert W. Maul and Patricia J. Gearhart

Why women are more susceptible to autoimmune diseases is not completely clear, but new data suggest that the hormone estrogen may play an important role. A new study now shows that estrogen activates the expression of activation-induced deaminase (AID), a protein that drives antibody diversification by deaminating cytosine in DNA to uracil. If estrogen increases the level of AID, increased mutations could transform benign antibodies into anti-self pariahs. AID might also contribute to cancer—particularly in breast tissue, which is highly responsive to estrogen—by introducing mutations and strand breaks into the genome.

During the immune response to foreign antigens, B lymphocytes become activated and begin to diversify their immunoglobulin (Ig) genes to ensure the production of diverse, high-affinity antibodies against pathogens. This process involves somatic hypermutation (SHM) and class switch recombination (CSR), both of which require activation-induced deaminase (AID), an enzyme that deaminates dC to dU in the Ig loci. The resulting U:G mismatches can be resolved by several pathways involving base excision repair proteins, mismatch repair proteins, and low-fidelity DNA polymerases. During SHM, mutations are first introduced into rearranged Ig variable genes by AID. The spectrum of mutations is then expanded from the initial deaminated dC base to include neighboring nucleotides by the action of the DNA polymerase η during error-prone gap repair. Thus, the simple deamination of dC to dU produces a plethora of different amino acid changes within an antibody, which can then be selected to bind antigen with high affinity. Similarly, during CSR, uracil bases are introduced into intronic switch regions preceding each of the heavy chain constant genes. DNA strand breaks in the switch regions are generated when uracil is removed by uracil DNA glycosylase and the abasic site is nicked by an endonuclease. The breaks are then processed by the nonhomologous end-joining pathway to recombine variable genes from the μ constant gene to other constant genes. AID thus initiates mutations and strand breaks, a potentially catastrophic combination for genome stability. To harness its mutagenic activity, AID is extensively regulated at the level of transcript stability (1, 2), protein expression (3, 4), subcellular localization (5, 6), phosphorylation (7), and degradation (8). On page 99 of this issue, Pauklin et al. find that AID is activated by the sex hormone estrogen, revealing yet another level of AID regulation (9).

Estrogen regulation of AID

Estrogen functions as a transcriptional regulator by activating estrogen receptors, which then translocate to the nucleus, where they bind to estrogen response elements in gene promoters. Pauklin et al. found functional binding sites for estrogen receptors in the promoter region of the AID gene, based on electromobility shift and chromatin immunoprecipitation assays (9). Treating B cells with estrogen caused higher AID transcript and protein levels, and conversely, treating the cells with progesterone suppressed transcription of AID. The authors found that estrogen-induced activation of AID triggered modest increases in SHM and CSR, and increased the frequency of *Myc-IgH* translocations. Perhaps the most profound result of the study was the identification of AID transcripts in breast and ovarian tissues, which argues against the dogma that AID is only expressed in B cells. Thus, in tissues where estrogen levels are continuously high, deleterious mutations may accumulate over time (9).

AID in autoimmunity...

It is well-established that women are more prone to developing autoimmune diseases than men, but the reasons have largely remained unknown. These new findings by Pauklin et al. highlight an unexpected potential cause: estrogen-stimulated AID protein may generate pathogenic antibodies with high affinity for self-proteins. However, the connection between antibodies and autoimmunity is not always straightforward. For example, some autoimmune diseases are directly caused by self-reactive antibodies, such as antibodies specific for the acetylcholine receptor in myasthenia gravis. Other diseases, such as systemic sclerosis, are associated with elevated levels of autoantibodies, but no clear causative role has been established. Nonetheless, there is increasing evidence to support a link between estrogen, autoimmunity, and AID (Fig. 1). For example, estrogen levels are elevated in patients with systemic lupus erythematosus (for review see reference [10]). And in murine models, autoimmune B

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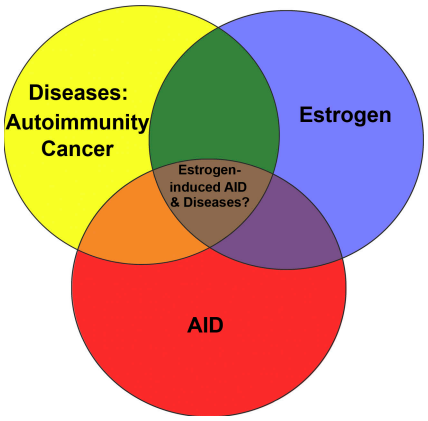

Figure 1. Potential interactions between estrogen, AID, and disease. Estrogen-driven transcription of AID may play a role in a variety of diseases, including certain types of autoimmunity and cancer. It will be interesting to examine the role of estrogen in AID-associated cancers, for which no gender bias has yet been reported.

cells have increased expression of AID with more antibody sequence diversity (11); and loss of AID results in weakened autoimmune responses (12). On the other hand, patients deficient for AID frequently develop autoimmune disorders (13), suggesting that unswitched, low-affinity IgM antibodies can also bind to self-antigens. Thus, the presence or absence of AID seems to influence autoimmunity, but much more work is required to dissect the exact role of estrogen in this complex group of diseases.

...and in cancer

AID is also associated with B cell cancers, but whether a gender bias exists in these diseases is not clear. Several forms of non-Hodgkin lymphoma have been linked to aberrant expression of AID. B cell–derived lymphomas and myelomas often result from altered CSR, in which oncogenes (i.e., *MYC*, *BCL1*, *BCL2*, and *BCL6*) are rearranged into switch regions containing AID-generated strand breaks (14). The translocated genes then become dysregulated and oncogenesis occurs. Indeed, a recent study showed increased AID expression in peripheral blood samples taken five years before diagnosis of non-Hodgkin lymphoma (15). Some other forms of cancer also show up-regulation of AID, such as gastrointestinal and hepatocellular cancers, which are associated with chronic inflammation caused by long-term infections (i.e., *Helicobacter pylori*) (16, 17) or tissue damage (liver cirrhosis) (18). This chronic inflammation may result in aberrant AID expression through the NF-κB pathway, and increased AID could then introduce mutations into oncogenes such as p53 (16).

Estrogen has previously been linked to various cancers, including breast, ovarian, and endometrial cancer. Two different mechanisms have been identified by which estrogen drives carcinogenesis (for review see reference [19]). Metabolism of estrogen could produce mutagenic metabolites, or estrogen could bind to estrogen receptors, thereby altering the expression of various genes. If one of those genes is AID in breast tissue, the enzyme could target genes outside the Ig loci. For example, *BRCA1* and *BRCA2* are tumor suppressor genes involved in DNA repair that are often mutated in breast and ovarian cancers. Thus, AID has the potential to wreak havoc on mechanisms devoted to maintaining genome stability.

Concluding remarks

The results presented by Pauklin et al. pose a new paradigm: increased estrogen levels produce higher levels of AID, which generates more mutations. This could be one explanation for the finding that women have better immune responses and develop more autoimmune diseases than do men. The findings also suggest that AID may play a role in cancer development in breast and ovarian tissues, although further work is needed to examine the delicate balance between estrogen and progesterone in regulating AID in vivo. If AID is involved in estrogen-driven diseases, screening for AID expression in women with certain pathologies could potentially be combined with treatments that regulate AID activity, perhaps by inhibition of catalysis with small molecules.

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