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RE: Immune Checkpoint Profiles in Luminal B Breast Cancer (Alliance)

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We read the article "Immune Checkpoint Profiles in Luminal B Breast Cancer (Alliance)," which was published in a recent issue of the Journal with great interest (1). The authors suggested that resistance to aromatase inhibitor treatment in Luminal B breast cancer results from immune tolerance and more precisely from immune checkpoint upregulation. We would like to refine their conclusion in the light of our own previous work on triple-negative breast cancer (TNBC) subtyping, based on transcriptomics, immunohistochemistry, and proteomics (2–4). We robustly identified 3 TNBC subtypes: molecular apocrine (C1), basal-like with immunosuppression (C2), and basal-like with immune response (C3). Analysis of the immunome of the 2 basal-like subtypes revealed that C2 was enriched in numerous immunosuppressive cells, including M2 macrophages, and that C3 was characterized by antitumorigenic immune cells, including M1 macrophages, plasma cell and B lymphocyte infiltrates, tertiary lymphoid structures, and high expression of 35 immune checkpoints, including *IDO1*, *PDCD1* (*PD1*), and *LAG3* (5). Furthermore, proteomic analysis identified immunoglobulins (IGKC, IGHM) and 5 interferon pathway (SYWC [*WARS*]; STAT1; SAMH1 [*SAMHD1*]; TYPH [*TYMP*]; AMPL [*LAG3*]) upregulated proteins in C3 compared with C2. Note that the previous 5 proteins belong to the best IDO1-correlated proteins identified by the authors (1). In our study, biological aggressiveness decreases (C2 > C3 > C1). Furthermore, pooled TNBC cohort (n = 427) showed that C3 patients have a better prognosis compared with C2 patients. In regard of our results, we strongly believe that aromatase inhibitor-resistant Luminal B breast cancers displayed the same kind of immune response than C3-TNBC patient. Therefore, "immune response failure" seems to be a better, more precise and specific statement than "immune tolerance." Because of numerous biological facts (tumor-infiltrating lymphocytes, IFNγ and STA1 interferon pathway, immune checkpoint upregulation), it is clear that an immune response takes place in aromatase inhibitor-resistant Luminal B breast cancers. However, the cause of the immune response failure still remains to be explained. The easiest explanation is that immune checkpoints are upregulated. But correlation does not mean causality. In contrast, immune response failure could result from an overwhelmed immune response or a lack of antibody specificity for key neoantigens. Activation of immune checkpoints encountered in these 2 categories of breast cancers should mainly be seen as the result of an immune inhibitory signal feedback that intrinsically counterbalances immune response (4,6). In other words, immune checkpoint upregulation could be triggered by a high antitumorigenic immune response, because of neoantigens, to fine-tune and limit global immune response—that is, to maintain immune self-tolerance to healthy cells—and it might therefore mark a partly inefficient immune antitumoral response. In C2-TNBC, immunosuppression is more likely due to immune suppressive cells.

In basal-like breast tumors, high expressions of *LAG3*, *PDCD1*, and *IDO1* are associated with good prognosis (7). This fact strengthens the notion that immune checkpoints are upregulated concomitantly with an immune response and that this response, although active, fails to eradicate the tumor. In all cases, even if upregulation of immune checkpoints participates moderately to immunosuppression, immune checkpoint inhibition strategy remains a promising therapeutic avenue.

Note

The authors have no disclosures.

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