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ABOUT THE COVER

CD96 is an immune checkpoint and is known to suppress T-cell and NK cell effector functions. Thus, CD96 can impair antitumor responses in the tumor microenvironment. Mittal et al. demonstrate that CD96 blockade can inhibit primary tumor growth in multiple tumor models. The effects of anti-CD96 are dependent on several host factors, including $CD8^+$ T cells, cytokines, and DNAM-1/CD226 signaling. Because CD96 is co-expressed with other immune checkpoints, especially PD-1, dual and triple blockade protocols were tested. Dual blockade of CD96 and other immune checkpoints is more effective than anti-CD96 monotherapy, and an optimal triple combination blocking CD96, PD-1, and TIGIT is superior over dual combinations. These treatments increase T-cell infiltration and enhance antitumor responses, highlighting that combining the targeting of CD96 with other immune checkpoints could be a strategy for augmenting T-cell responses that suppress tumor growth. Read more in this issue on page 559. Original image from Fig. 3A. Artwork by Lewis Long.