

Targeting IL-33 in patients with cancer under immune checkpoint inhibitors for a better antitumor response and prevent thromboembolism?

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We read with great interest the article by Nan *et al* on the possibility of targeting interleukin (IL)-33 to obtain an improved antitumor response to anti-programmed death-ligand 1 (PD-L1) immunotherapy, recently published in the Journal.

The authors demonstrate how by blocking both IL-33 and PD-L1 in the tumor micro-environment (TME) not only augmented T-cell responses but also modulated the TME toward an immunoinflammatory phenotype, suggesting that dual targeting IL-33 and PD-L1 therapeutic approaches hold promising potential for further clinical application.¹

In patients with cancer, thromboembolism (TE) is a well-known complication during chemotherapy, as was recently demonstrated in a higher-than-expected incidence in subjects treated with immune checkpoint blockade (ICB).²

The decrease of IL-33 and the increase of sST2 was recently described as a new valuable biomarker for diagnosis and mortality prediction in patients with pulmonary TE. In this context it suggested a potential beneficial therapeutic effect with the exogenous administration of IL-33. Although this hypothesis is interesting, the authors are also very cautious and underline the need for further studies.³ Based on these observations, it could be hypothesized that a therapy inhibiting IL-33, as proposed by Nan *et al*, could increase the risk of thrombosis. Those findings are consistent with other evidence of the significance of sST2 as a biomarker of vascular health, with diagnostic and/or prognostic value in various cardiovascular diseases, including coronary artery disease, acute myocardial infarction, heart failure, atherosclerosis, systemic and pulmonary hypertension, giant-cell arteritis, acute aortic dissection, and ischemic stroke, as well as in obesity and diabetes.⁴

Also, in the cytokine storm reported in COVID-19, IL-33 acts on its cognate receptor ST2 and the IL-33/ST2 axis plays a key role. High ST2 concentrations, related to endothelial or pneumocyte inflammation and damage, are a significant plasma biomarker associated with survival and thrombosis in hospitalized COVID-19 patients.

Instead, the role of IL-33 is more complicated; in fact, depending on the type of cell involved, this damage-associated molecular pattern can have both anti-inflammatory and proinflammatory actions.⁵ The actions of IL-33 in vivo, as a whole, are pleiotropic and can only be considered in the physiopathological context.

There is growing evidence that the pathophysiological role of IL-33 largely depends on cellular and temporal expression. A dose-dependent pleiotropic action of this cytokine, is assumed, also depending on which immune cells are activated and for how long or whether endothelial cells are engaged.

The action of IL-33 is exerted through the injury-related response of stromal/parenchymal cells, the protective and anti-inflammatory actions mediated by Treg cells, and the inflammatory actions of various recruited immune cell types, all of which are modulated by the dampening actions exerted by sST2.

IL-33 may also positively influence ST2 or sST2 levels in a dose-dependent manner and potentially suppress T cell responses through increased levels of myeloid-derived suppressor cells. On the role of IL-33 in regulating thrombosis, was recently reported that IL-33 stimulates the release of procoagulant microvesicles from human monocytes and differentially increases tissue factor in human monocyte subsets. In human endothelial

cells, IL-33 induces proinflammatory, proangiogenic and prothrombotic milieu.⁶

All these observations, contrary to what was stated at the beginning, lead us to hypothesize that the synergistic action highlighted by Nan *et al* may also obtain a protective action with respect to the increased thromboembolic risk detected in patients with cancer treated with ICBs.

Currently, respiratory diseases represent the most advanced clinical area for the study of anti-IL-33 monoclonal antibodies and also shows satisfactory results. In particular, the molecules for which phase II and III studies are underway are tozorakimab, itepekimab and etokimab. The results of the studies available so far are promising and it is likely that their field of use will be expanded.^{7,8}

In conclusion, the therapeutic potential of IL-33 is controversial and should be explored in detail under specific conditions. It could be useful in conditions such as myocardial infarction and ischemic stroke, and also as a metabolic modulator in obesity and type 2 diabetes. However, attention must be paid to its potential for damage, as occurs in the course of proinflammatory and autoimmune diseases where the molecule should be a target to obtain therapeutic advantages as it could be in patients with cancer under ICBs treatment.

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