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Monocyte Activation: The Link between Obstructive Sleep Apnea and Cardiovascular Disease?

Although obstructive sleep apnea (OSA) is an independent predictor of cardiovascular disease (CVD) (1), the underlying biological mechanisms mediating this relationship have remained elusive. One potential pathway may be via activation of circulating monocytes. Phenotypic markers of monocyte activation predict incident cardiovascular events above and beyond traditional CVD risk factors (2). Monocytes are increasingly recognized to play a key pathogenic role in the development of atherosclerosis, and the NLRP3 (Nod-like receptor protein 3) inflammasome plays a central role. Activation of the NLRP3 inflammasome stimulates monocytes to release IL-1β. IL-1β promotes surrounding immune and endothelial cells to secrete IL-6 and tumor necrosis factor-α and express vascular cell adhesion markers, which attract additional circulating monocytes to areas of vascular inflammation. These monocytes migrate across the vessel wall and differentiate into macrophages, whereupon, through engulfment of oxidized low-density lipoprotein, they develop into foam cells and contribute to atherosclerotic plaque formation (3). In addition, NLRP3 inflammasome activation leads to pyroptosis, a unique type of cell death, in which gasdermin-D induces cell permeability and lysis. This promotes further local inflammation through secretion of cytokines and microvesicles (4). Perhaps the most convincing evidence establishing a causal role of the NLRP3 inflammasome in CVD pathogenesis is that inhibition of IL-1β reduces recurrent cardiovascular events in patients with preexisting CVD (5).

Two steps are necessary in canonical NLRP3 inflammasome activation (6). First, priming of the pathway is triggered by activation of NF-κB (nuclear factor-κB) signaling, which induces production of

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the inactive components and substrates of the inflammasome, such as the NLRP3 domain and pro–IL-1β. Next, an activation signal leads to assembly of the multiprotein inflammasome complex, which includes NLRP3, an adaptor protein (ASC [apoptosis-associated speck-like protein containing a CARD]), and pro–caspase-1. Once assembled, the inflammasome cleaves pro–caspase-1 to caspase-1, which mediates pyroptosis and converts pro–IL-1β and pro–IL-18 to their active forms.

In this issue of the *Journal*, Díaz-García and colleagues (pp. 1337–1348) provide strong evidence that both NLRP3 priming and activation are upregulated in the monocytes of patients with severe OSA compared with control subjects without apnea (7). Circulating products of inflammasome activation are also greater in patients with OSA. *Ex vivo* inhibition of the inflammasome pathway led to reductions in intracellular IL-1β and active caspase-1 in the monocytes of patients with OSA but not those of control subjects, further supporting the contention that there is greater inflammasome activation in circulating monocytes of patients with OSA. The authors also demonstrate that HIF-1α (hypoxia-inducible factor-1α) is upregulated in monocytes of patients with OSA and that *ex vivo* inhibition of HIF-1α led to reductions in inflammasome transcription, suggesting that HIF-1α may play a prominent role in the priming step. *Ex vivo* exposure of monocytes from healthy participants to a severe intermittent hypoxia paradigm increased priming but was not sufficient to activate the inflammasome complex. The addition of plasma from patients with OSA to the intermittent hypoxia exposure, however, increased both priming and activation, suggesting the presence of an activation signal circulating in patients with OSA.

This study extends results from animal and tissue models in which exposure to intermittent hypoxia induces NLRP3 inflammasome priming and activation (8, 9). A prior study evaluating inflammasome activation in patients with OSA showed that circulating IL-1β and IL-18 concentrations correlated with markers of OSA severity, but intracellular protein concentrations were not assessed to directly evaluate inflammasome function (10).

Although Díaz-García and colleagues demonstrate that OSA is associated with monocyte activation via the NLRP3 inflammasome, the potential for confounding or reverse causation remains. In particular, although results were robust to adjustment for body mass index, whether more subtle differences in adipose distribution patterns, such as proportion of visceral fat, explain the greater activation in patients with OSA remains to be seen. Certainly, the reversibility of monocyte inflammasome activation with OSA therapy will be important to assess in fully elucidating the causal nature of the relationships described.

Although the authors make a compelling case that hypoxia, via HIF-1α, can be an important driver of NLRP3 inflammasome priming in OSA, the relevance of other OSA-related exposures, such as sleep fragmentation, remains to be determined. This is particularly important given evidence that nonhypoxic sleep disturbances are also associated with elevated CVD risk (11, 12).

Further research is also needed to identify any circulating damage-associated molecular patterns in OSA that may serve as the signal for triggering activation of the inflammasome. Plasma biomarkers of gut permeability and LPS binding protein have been found to be upregulated in OSA, and so microbial products translocated from the gut may be one source of activation signaling (13, 14). Extracellular microvesicles associated with vascular dysfunction in OSA may be another trigger (15).

Assuming the findings identified by Díaz-García and colleagues do indeed identify an important causal pathway linking OSA with CVD, measures of monocyte inflammasome activation may prove to be useful surrogate biomarkers in identifying patients with OSA who are at elevated apnea-related CVD risk. This may inform both personalized decision making about whether to initiate OSA treatment and allow more efficient clinical trial designs aimed at reducing cardiovascular and other inflammasome-related diseases by identifying a high-risk subpopulation. Treatments aimed at suppressing the inflammasome pathway may represent a novel option for reducing the risk of long-term OSA complications, although the benefits will need to be weighed against the risks of immune dysfunction and infection (5).

Overall, the findings from Díaz-García and colleagues support inflammasome activation as a plausible mechanism by which circulating monocytes may play a key pathogenic role in mediating the long-term cardiovascular consequences of OSA. Further research into monocyte function in OSA, including the impact of treatment, may prove fruitful in understanding how to reduce the elevated cardiovascular burden faced by patients living with OSA. ■

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