arterial hypertension in systemic sclerosis: the DETECT study. *Ann Rheum Dis* 2014;73:1340–1349.
9. Humbert M, Yaici A, de Groote P, Montani D, Sitbon O, Launay D, *et al.* Screening for pulmonary arterial hypertension in patients with systemic sclerosis: clinical characteristics at diagnosis and long-term survival. *Arthritis Rheum* 2011;63:3522–3530.
10. Waxman A, Restrepo-Jaramillo R, Thenappan T, Ravichandran A, Engel P, Bajwa A, *et al.* Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N Engl J Med* 2021;384:325–334.

miR-roring Changes in Blood: miR-210 Reflects Hypoxic Disease Dynamics in Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a disease characterized by episodes of apnea and hypopnea during sleep, severely compromising quality of life and driving significant health complications. It is caused by upper airway obstruction during sleep and is associated with comorbidities such as metabolic syndrome and obesity (1). Intermittent hypoxia is a hallmark of OSA resulting in arterial oxygen desaturation during episodes of suboptimal sleep and can contribute to the development of a number of chronic complex diseases. These include vascular diseases such as atherosclerosis, myocardial infarction, pulmonary hypertension, and cerebrovascular events, in which endothelial dysregulation plays crucial, but still poorly understood, roles.

Endothelial dysfunction in OSA has been examined through the lens of basic biological mechanisms involving inflammation, autonomic neurobiology, redox biology, and cellular metabolism (2). Particularly strengthening the clinical association between OSA and pulmonary hypertension, the complex processes driven by hypoxia in the pulmonary endothelium are believed to underlie many of these mechanisms (3). Yet, gaps in our knowledge exist regarding the panvascular complications seen in OSA and how they relate to the intermittent nature of hypoxia, primarily seen in lung tissue, in this disease.

Over the past two decades, evidence has emerged that microRNAs (miRs), non–protein-coding RNA modulators of gene expression and function, are crucial and pleiotropic drivers of human disease (4). miR-210 is a hypoxia- and hypoxia-inducible factor-α–responsive miR (a "hypoxamir") (5) that represses ISCUs (iron-sulfur cluster assembly enzymes) and mitochondrial function (6) and is particularly important in endothelial function in the pulmonary vasculature (7). In pulmonary hypertension, miR-210 originating from the bone marrow can be transported directly from plasma into pulmonary endothelium, triggering hemodynamic and vascular changes, thus supporting the notion that circulating miR-210 contributes to disease pathogenesis (8).

In this issue of the *Journal*, Shang and colleagues (pp. 323–335) offer an intriguing chapter to this story by generating elegant evidence in support of miR-210's pathogenic endothelial activity in intermittent hypoxia and OSA (9). Using both *in vitro* and *in vivo* mouse discovery platforms of OSA, they defined a mechanism in intermittent hypoxia involving the transcriptional regulation of miR-210 via SREBP2 (sterol regulatory element-binding protein 2), which in turn contributes to downstream ISCU-dependent endothelial dysfunction (Figure 1). Emphasizing the translational relevance of this mechanism, the authors found consistent upregulation of circulating miR-210 across OSA serum in discovery and validation patient cohorts, and such OSA serum-derived miR-210 was responsible for driving ISCU-dependent endothelial alterations *in vitro*.

These findings carry fundamental implications for our understanding of intermittent hypoxia and miR biology in OSA. Given SREBP2's emerging functions in metabolic and inflammatory mechanisms in obesity (10), the molecular network of SREBP2–miR-210–ISCU provides much-needed conceptual order to the hypoxic, inflammatory, and metabolic processes already suspected to be important in endothelial dysfunction in intermittent hypoxia and OSA. This intersystem regulation further underscores the complexity of hypoxia-driven OSA, which is not restricted to one physiological domain. Beyond the pulmonary vasculature, the authors additionally noted that aortic intima displayed decreased SREBP2 and ISCU1/2 concentrations in OSA, suggesting the relevance of this axis in peripheral, as well as pulmonary, vascular beds. Given the evidence of the activity of serum-derived miR-210 in OSA, the authors propose that such panvascular pathobiology may depend on the activity of circulating miR-210, similar to what Zhao and colleagues reported in pulmonary hypertension (8). Thus, it is tempting to speculate that circulating miR-210 may serve as a unifying and master pathogenic regulator that may explain the still-mysterious molecular link between pulmonary hypertension and OSA (11).

These findings also set the stage for novel diagnostic and therapeutic development in OSA. Currently, circulating miRNAs have recently been used as clinical biomarkers in so-called "liquid biopsies," holding promise for early cancer detection (12). By leveraging such advancing technologies, it may be feasible to study miR-210 as a prognostic or even diagnostic biomarker in hypoxia-related diseases such as OSA and pulmonary hypertension. This may be particularly appealing if future studies show that miR-210

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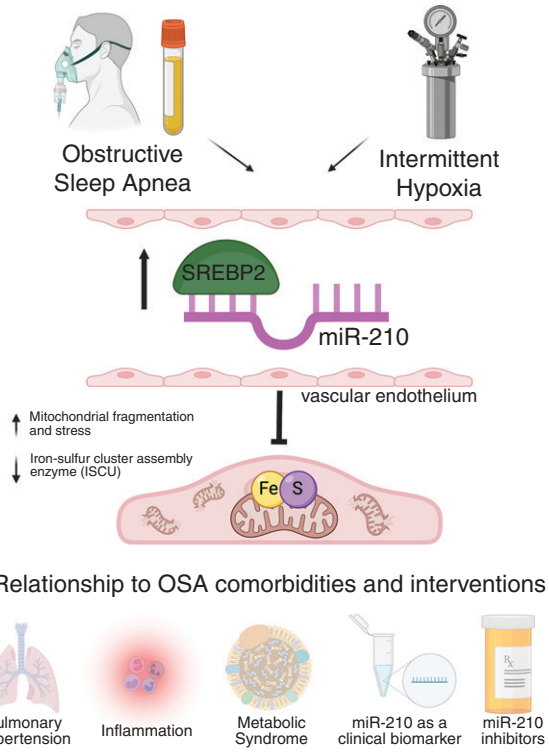

Figure 1. Obstructive sleep apnea (OSA) and intermittent hypoxia induce elevated concentrations of endothelial and circulating microRNA-210 (miR-210). SREBP2 (sterol regulatory element-binding protein 2) directly binds to the promoter of miR-210, leading to suppression of ISCUs (iron-sulfur assembly enzyme) in the mitochondria of the vascular endothelium. Hypoxic stressors in addition to further input from the proposed axis drive compromised mitochondrial respiration and function. These findings may have broad relevance to numerous human pathological states affected by intermittent hypoxia, as seen in OSA, and pave the way for future research into the utility of miR-210 as a therapeutic and prognostic marker. Images created with BioRender.

concentrations decline and correlate with implementation of currently available OSA therapies such as continuous positive airway pressure (CPAP) or corrective surgery. If so, circulating miR-210 concentrations could aid in risk stratifying patients as well as monitoring disease progression and response to therapy. Yet, because miR-210 is ubiquitously expressed across multiple hypoxic and physiologic states, its specificity may complicate data interpretation. Finally, the ability to inhibit or even remove circulating miR-210 concentrations from the bloodstream has increasing appeal as a viable therapeutic measure. This has timely relevance, given the currently limited treatment options for OSA and variable response to those therapies (13). However, these possibilities come with historic challenges: miRNA concentrations vary greatly based on the origin of biological fluids or physiologic state, and circulating miR-210 is found in and outside of extracellular vesicles (14), complicating their detection and feasibility for specific therapeutic targeting (15).

In conclusion, these findings offer new molecular perspectives on OSA pathogenesis and important complementary evidence of the role of miR-210 and its circulating forms on endothelial function. As we progress in our understanding of circulating microRNA dynamics, it should now be a priority to focus on miR-210 as both a molecular gauge and disease driver in an ever-growing network of relevant hypoxic vascular diseases. ■

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References

1. Abbasi A, Gupta SS, Sabharwal N, Meghrajani V, Sharma S, Kamholz S, *et al.* A comprehensive review of obstructive sleep apnea. *Sleep Sci* 2021;14:142–154.
2. Peracaula M, Torres D, Poyatos P, Luque N, Rojas E, Obrador A, *et al.* Endothelial dysfunction and cardiovascular risk in obstructive sleep apnea: a review article. *Life (Basel)* 2022;12:537.
3. Prabhakar NR, Peng YJ, Nanduri J. Hypoxia-inducible factors and obstructive sleep apnea. *J Clin Invest* 2020;130:5042–5051.
4. Saliminejad K, Khorram Khorshid HR, Soleymani Fard S, Ghaffari SH. An overview of microRNAs: biology, functions, therapeutics, and analysis methods. *J Cell Physiol* 2019;234:5451–5465.
5. Chan SY, Loscalzo J. MicroRNA-210: a unique and pleiotropic hypoxamir. *Cell Cycle* 2010;9:1072–1083.
6. Chan SY, Zhang YY, Hemann C, Mahoney CE, Zweier JL, Loscalzo J. MicroRNA-210 controls mitochondrial metabolism during hypoxia by repressing the iron-sulfur cluster assembly proteins ISCU1/2. *Cell Metab* 2009;10:273–284.
7. White K, Lu Y, Annis S, Hale AE, Chau BN, Dahlman JE, *et al.* Genetic and hypoxic alterations of the microRNA-210-ISCU1/2 axis promote iron-sulfur deficiency and pulmonary hypertension. *EMBO Mol Med* 2015;7:695–713.
8. Zhao J, Florentin J, Tai YY, Torrino S, Ohayon L, Brzoska T, *et al.* Long range endocrine delivery of circulating miR-210 to endothelium promotes pulmonary hypertension. *Circ Res* 2020;127:677–692.
9. Shang F, Wang S-C, Gongol B, Han SY, Cho Y, Schiavon CR, *et al.* Obstructive sleep apnea-induced endothelial dysfunction is mediated by miR-210. *Am J Respir Crit Care Med* 2023;207:323–335.
10. Jeon TI, Osborne TF. SREBPs: metabolic integrators in physiology and metabolism. *Trends Endocrinol Metab* 2012;23:65–72.
11. Sharma S, Stansbury R, Hackett B, Fox H. Sleep apnea and pulmonary hypertension: a riddle waiting to be solved. *Pharmacol Ther* 2021;227:107935.
12. Larrea E, Sole C, Manterola L, Goicoechea I, Armesto M, Arestin M, *et al.* New concepts in cancer biomarkers: circulating miRNAs in liquid biopsies. *Int J Mol Sci* 2016;17:627.

13. Gottlieb DJ, Punjabi NM. Diagnosis and management of obstructive sleep apnea: a review. *JAMA* 2020;323:1389–1400.
14. Hale A, Lee C, Annis S, Min PK, Pande R, Creager MA, *et al.* An Argonaute 2 switch regulates circulating miR-210 to coordinate hypoxic adaptation across cells. *Biochim Biophys Acta* 2014;1843: 2528–2542.
15. Drula R, Ott LF, Berindan-Neagoe I, Pantel K, Calin GA. MicroRNAs from liquid biopsy derived extracellular vesicles: recent advances in detection and characterization methods. *Cancers (Basel)* 2020; 12:2009.

Tuberculosis, Wildfires, and Case-crossover Studies: An Epidemiological Trifecta?

Tuberculosis is a leading cause of illness and death worldwide. Indeed, more than 1.7 billion people are thought to be infected with tuberculosis (1), with an estimated 10 million disease episodes and 1.5 million deaths in 2020 (2). Risk factors for tuberculosis include impaired immunity including HIV disease, birth in a tuberculosis endemic country, increased exposure to infected people through household contacts, living in crowded or poorly ventilated dwellings, or exposure to high-risk settings such as hospitals, prisons, nursing homes, and homeless shelters (3). In the United States, the highest burden of tuberculosis occurs among immigrants from endemic countries. Specifically, in 2021, the case rate for this group was 12.2 per 100,000 people compared with 2.4 per 100,000 people in the general population (3).

Environmental exposures have become increasingly recognized as important risk factors for tuberculosis. Currently, there is strong epidemiological evidence linking both occupational exposures to silica from mining (4) and tobacco smoking (5) with an increased risk of tuberculosis disease. Air pollution is a less well-studied risk factor with mounting evidence. One large cohort study in New Taipei City, Taiwan (6), consisting of 106,678 participants, found that higher ambient nitrogen dioxide (adjusted hazard ratio, 1.33 per 10 ppb; 95% confidence interval, 1.04–1.70) and nitrogen oxide (1.21 per 100 ppb; 95% confidence interval, 1.04–1.41) concentrations estimated using information from 16 monitoring stations were positively associated with the 418 cases of active tuberculosis (67% of which were culture-confirmed) registered over a 6.7-year (median) follow-up period but failed to find the same associations with either fine or coarse particulate matter, or for all pollutants when using land use regression (a statistical method commonly used to estimate spatial variation in air pollution concentrations for population exposure assessment).

A time series analysis in the city of Wulumuqi (population, 2.7 million), Xinjiang Uygur Autonomous Region, China, that analyzed 10,238 cases of pulmonary tuberculosis and monthly averages of multiple air pollutants ($PM_{2.5}$ [particulate matter that is <2.5 μm in size], PM_{10} [particulate matter that is <10 μm in size], SO_2, NO_2, CO, and O_3) adjusting for seasonality and other meteorological variables found positive associations between higher concentrations of all air pollutants and a higher number of tuberculosis cases (7). A recent meta-analysis involving 24 studies and 437,000 tuberculosis cases examined the role of ambient air pollution and tuberculosis disease and found that higher ambient concentrations of both fine and coarse particulate matter and SO_2 were all associated with a higher incidence of pulmonary tuberculosis (8). Most of the studies were either time series ($n = 10$), ecological analyses ($n = 5$), or cohort studies ($n = 5$), and the overall assessment by the authors about the quality of evidence was low. Moreover, the associations reported above do not necessarily mean causation. The link between household air pollution from biomass burning and tuberculosis is even less clear, with some studies showing positive relationships and others showing no relationship (9, 10).

In this issue of the *Journal*, Linde and colleagues (pp. 336–346) provide additional evidence of a link between air pollution from wildfire smoke and tuberculosis in California (11). They used a case-crossover study of 6,238 subjects aged 15 years or older diagnosed with active tuberculosis disease between 2014 and 2019 in eight California counties to determine if wildfire events, determined using $PM_{2.5}$ concentrations from more than 250 monitors of the California Air Resources Board statewide air monitor network and crosschecked against satellite maps of smoke plume boundaries using the National Oceanic and Atmospheric Administration Hazard Mapping System, could be associated with a higher risk of tuberculosis diagnosis. Specifically, they found that wildfire-associated $PM_{2.5}$ events were associated with 23% higher odds of tuberculosis diagnosis over a 6-month observation period.

Despite potential limitations related to the latency between the time window of wildfire smoke exposure and development of active tuberculosis, lack of control for time-varying confounders within the same individual, and inaccuracies in air pollution exposure assignments (which was limited to the participant's home address using inverse distance weighing estimation), the analysis conducted by Linde and colleagues provides further evidence of the potential role of air pollution in the development of tuberculosis. Moreover, it uses an epidemiological design that has become increasingly used to study the relationship between air pollution and other respiratory conditions, including asthma (a PubMed search yielded 58 studies when searching "asthma exacerbations" and "case-crossover") and chronic obstructive pulmonary disease exacerbations (26 studies when searching "chronic obstructive pulmonary disease exacerbations" and "case-crossover"). Indeed, the case-crossover

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