COVID-19 AND AGING

Blocking eicosanoid signalling prevents severe COVID-19

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COVID-19 is most severe in older adults. The efficacy of recent SARS-CoV-2 vaccines can be hampered by more-infectious SARS-CoV-2 variants. The development of anti-SARS-CoV-2 therapies with increased efficacy to protect older people is thus warranted. Writing in *Nature*, Wong and colleagues described mouse-adapted SARS-CoV-2 strains, isolated from mouse lungs upon growth in iterations. These viral strains were highly virulent in young and old mice, infected only the lungs and contained a set of mutations (K417N or K417T, E484K, Q493R, Q498R and N501Y) located in the spike protein that have also arisen in human SARS-CoV-2 variants. Taking advantage of previous observations that elevated levels of an eicosanoid, prostaglandin D_2 (PGD_2), and of a phospholipase, PLA_2G2D, led to poor outcomes in SARS-CoV-2-infected mice, the authors infected 8–12-month-old *Pla2g2d*$^{-/-}$ and *Ptgdr*$^{-/-}$ (which encodes PGD_2 receptor (PTGDR)) mice with a lethal dose of SARS-CoV-2(N501Y). Lethality in mice was almost completely abrogated upon genetic depletion of PLA_2G2D or PTGDR expression. Corroborating these data, mRNA levels of PGD_2 synthases (PTGDS), the enzymes required for the production of PGD_2, and of PTGDR increased with aging in human lung samples. Once-daily administration of asapiprant (a potent antagonist of human PGD_2 and PTGDR signalling) to middle-aged mice starting two days after SARS-CoV-2 infection (a relevant timing for symptomatic patients) reduced mortality by more than 90%. Asapiprant is used as an antiallergic drug and is currently in clinical trials to help patients with COVID-19 who are at risk of respiratory failure. The study by Wong et al. provides experimental and causal evidence that the PLA_2G2D–PGD_2/PTGDR pathway is a useful target for therapeutic interventions against COVID-19.

Manlio Vinciguerra

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