Estradiol influence on matrix metalloproteinase levels is linked to phospholipase A2 activity on lipid metabolism and protective effects in COVID-19 pathogenesis

Pedro Nobre Azevedo[1,2], Pedro Vieira da Silva Neto[2], Diana Mota Toro[1], Jonatan Constança Silva de Carvalho[3], Raquel Fernanda Gerlach[4], Cristina Ribeiro de Barros Cardoso[3], Carlos Arterio Sorgi[1,2]

[1.] FMRP-USP, Faculdade de Medicina de Ribeirão Preto, Avenida Bandeirantes, 3900, Ribeirão Preto, São Paulo, Brazil;
[2.] FFCLRP-USP, Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto, Avenida Bandeirantes, 3900, Ribeirão Preto, São Paulo, Brazil;
[3.] FCFRP-USP, Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Avenida Bandeirantes, 3900, Ribeirão Preto, São Paulo, Brazil;
[4.] FORP-USP, Faculdade de Odontologia de Ribeirão Preto, Avenida Bandeirantes, 3900, Ribeirão Preto, São Paulo, Brazil;

The coronavirus disease 2019 (COVID-19) pandemic is widely regarded as the most significant health crisis of our time. When the body's defenses falter, it can result in immune-related complications. During viral infections, certain proteins require post-translational modifications through proteolysis, and MMPs contribute to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pathogenesis. Notably, inflammatory responses and pro-oxidant agents can trigger MMPs activation. Individuals with COVID-19 often exhibit elevated levels of various MMP classes in their tissues and blood compared to those non-infected. This elevation may be associated with disease severity and the necessity for hospitalization. Furthermore, disparities in MMPs levels between genders and the influence of sex-hormones on these enzymes have been observed in other illnesses. Hence, comprehending the molecular pathways and specific mechanisms that regulate MMPs function could be crucial for improving health outcomes during COVID-19. This study evaluated a cohort of healthy controls (n = 29) and COVID-19 patients (n = 129) of both genders, for clinical outcomes, plasma estradiol (E2) hormone levels, inflammatory markers, MMPs expression and plasma lipidome, prior to vaccination. Examination of these interactions data uncovered gender-specific control of MMPs in COVID-19, suggesting that E2 production might offer protection against severe symptoms, particularly among females. Furthermore, monitoring MMPs changes throughout the disease progression revealed a two-phase pattern, with certain MMPs (referred to as MMP-1, MMP-7, and MMP-13) demonstrating protective effects compared to others (MMP-2, MMP-3, MMP-8 and MMP-9), which correlated with disease severity. Intriguingly, the protective MMPs were linked to immune response-related substrates, whereas the severity-associated MMPs targeted structural and matrix components by bioinformatic network approach. In this way, our results suggested that Phospholipase A2 (PLA2) enzyme, which are the major regulator of the arachidonic acid cascade and lysophospholipids (LPL) metabolism, was indirectly affected by MMPs activity and lead to plasma reprogramming of lipid metabolism in COVID-19 patients. Indeed, we described by lipidome, an increased production of free-fatty acids (FA) and Lyso-PLs species with decreased phospholipids levels in plasma of severity patients compared to mild/moderate subjects. Moreover, it was postulated in the literature that PLA2 activation is induced by chemokines, whose ability to signal inflammation is regulated in a tissue-specific fashion by MMPs. Overall, there are puzzling links between MMPs and lipid metabolism, making MMPs attractive targets for changing the course of inflammatory or metabolic diseases, whose etiology is notoriously complicated by comorbidities such as obesity, atherosclerosis, diabetes, as observed for COVID-19 pathogenesis. Our findings underscore the potential utility of

MMPs as gender-specific indicators for disease prognosis or advancement, as well as novel therapeutic targets in COVID-19.

Agradecimentos: FAPESP, CAPES, CNPq