Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to Editors

Testicles, adipose organ and heart: A new axis in the management of SARS-CoV-2?

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The SARS-CoV-2 pandemic has highlighted the need to investigate the physiopathological dynamics related to the virus-host interaction.

Male sex represents a risk factor; several studies [1,2] showed that men had higher risk of developing severe illness and higher mortality. Obesity is another important risk factor [3,4], as higher BMI was correlated with worse clinical course and increased mortality irrespective of age, diabetes or hypertension4. We can hypothesize that ACE2 expression, combined with adipose organ endocrine contribution, heart and testicles, may play an important role in inflammatory and immune balance. Androgens can modulate inflammation [5,6]; soluble androgen receptor (AR) activation can positively regulate ACE2 expression2 and increase IL-6 transcription, activating in turn the expression of the AR gene creating a circuit of mutual STAT3-mediated amplification [7,8]. AR can be considered an important co-factor in development of severe forms of illness and is the only promoter described for the transcription of TMPRSS2 gene [9–12], expressed in several tissues [13].

Adipose tissue is considered an endocrine organ [14,15] exerting an effect on immune system and inflammatory cascades, due to adipocytokines and production of TNF-α, IL-6 and chemokines [16]. Leptin levels are directly proportional to fat mass levels [17] and can exert proinflammatory effects through structural similarities with cytokines such as IL-6, GM-CSF or IL-12 [16]. Granulocytes, monocytes, macrophages and lymphocytes can also express leptin receptors [18–21] activating other immune cells [22]. Leptin and STAT3 transcription factor-induced by tyrosine phosphorylation has been observed in endothelial cells of human umbilical veins [23]. Should these data be confirmed as general mechanism, this may overlap with the IL-6 associated AR activation in other cellular lines, potentially turning on and feeding the previously described self-alimenting circuit. Also, long-term high-fat diet in mouse reduces ACE2 activity in adipose tissue due to increased expression of ADAM17, a protease responsible for ACE2 shedding, inducing elevation of angiotensin II levels, vasoconstriction, enhanced inflammation and thrombosis [24]. This effect could be enhanced by ACE2 downregulation induced by viral invasion [25], thus being especially detrimental in people with baseline ACE2 dysregulation as in obesity.

Furthermore, preclinical evidence in vitro (cardiomyocytes) and in vivo (rodents) show that cardiac natriuretic peptides production could be downregulated by nutrients such as glucose and hormones such as leptin, which levels are elevated in obesity, as noted. These observations introduced the "natriuretic handicap" concept and several studies confirmed these findings in obese humans [26,27]. Considering natriuretic peptide system involvement either in inflammation regulation, as Atrial natriuretic peptide (ANP) reduces production of the proinflammatory cytokine TNF-α through NPR-A signalling pathway and consequent reduction of proinflammatory transcription factors NF-κB [28], is tempting to speculate that natriuretic handicap could contribute to an excessive immune response. Understanding relationships between these mechanisms could promote development of new therapeutic solutions in a perspective of tailored medicine, deserving further studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Guan W, Ni Z, Hu Y, et al. Clinical characteristics of Coronavirus Disease 2019 in China. N Engl J Med. February 2020. doi: 10.1056/nejmoa2002032.
[2] Wei X, Xiao Y-T, Wang J, et al. Sex Differences in Severity and Mortality Among Patients With COVID-19: Evidence from Pooled Literature Analysis and Insights from Integrated Bioinformatic Analysis. March 2020. http://arxiv.org/abs/2003.13547. Accessed April 8, 2020.
[3] Dietz W, Santos-Burgoa C. Obesity and its implications for COVID-19 mortality. 1005 Obesity (Silver Spring) 2020;28(6):1005. https://doi.org/10.1002/oby.22818.
[4] Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity 2020;28(7):1195–9. https://doi.org/10.1002/oby.22831.
[5] Di Florio DN, Sin J, Coronado MJ, Atwal PS, Fairweather DL. Sex differences in inflammation, redox biology, mitochondria and autoimmunity. Redox Biol 2020;31:101482. https://doi.org/10.1016/j.redox.2020.101482.
[6] Becerra-Díaz M, Strickland AB, Keselman A, Heller NM. Androgen and androgen receptor as enhancers of M2 macrophage polarization in allergic lung inflammation. J Immunol 2018;201(10):2923–33. https://doi.org/10.4049/jimmunol.1800352.

https://doi.org/10.1016/j.mehy.2021.110587
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[7] Malinowska K, Neuwirt H, Cavarretta IT, Bektic J, Steiner H, Dietrich H, et al. Interleukin-6 stimulation of growth of prostate cancer in vitro and in vivo through activation of the androgen receptor. Endocr Relat Cancer 2009;16(1):155–69. https://doi.org/10.1677/ERC-08-0174.
[8] Dong H, Xu J, Li W, Gan J, Lin W, Ke J, et al. Reciprocal androgen receptor/interleukin-6 crosstalk drives oesophageal carcinoma progression and contributes to patient prognosis. J Pathol 2017;241(4):448–62. https://doi.org/10.1002/path.2017.241.issue-410.1002/path.4839.
[9] TMPRSS2 transmembrane serine protease 2 [Homo sapiens (human)] - Gene - NCBI. https://www.ncbi.nlm.nih.gov/gene/7113. Accessed April 19, 2020.
[10] Lucas JM, Heinlein C, Kim T, Hernandez SA, Malik MS, True LD, et al. The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. Cancer Discov 2014;4(11):1310–25. https://doi.org/10.1158/2159-8290.CD-13-1010.
[11] Afar DEH, Vivanco I, Hubert RS, et al. Catalytic cleavage of the androgen-regulated TMPRSS2 protease results in its secretion by prostate and prostate cancer epithelia. Cancer Res 2001;61(4):1686–92.
[12] Lin B, Ferguson C, White JT, et al. Prostate-localized and androgen-regulated expression of the membrane- bound serine protease TMPRSS2. Cancer Res 1999;59(17):4180–4.
[13] Jacquinet E, Rao NV, Rao GV, Zhengming W, Albertine KH, Hoidal JR. Cloning and characterization of the cDNA and gene for human epitheliasin. Eur J Biochem 2001;268(9):2687–99. https://doi.org/10.1046/j.1432-1327.2001.02165.x.
[14] Cinti S. Anatomy of the adipose organ. Eat Weight Disord 2000;5(3):132–42. https://doi.org/10.1007/BF03354443.
[15] Koerner A, Kratzsch J, Kiess W. Adipocytokines: leptin – the classical, resistin – the controversical, adiponectin – the promising, and more to come. Best Pract Res Clin Endocrinol Metab 2005;19(4):525–46. https://doi.org/10.1016/j.beem.2005.07.008.
[16] Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006;6(10):772–83. https://doi.org/10.1038/nri1937.
[17] Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996;334(5):292–5. https://doi.org/10.1056/NEJM199602013340503.
[18] Zhao Y, Sun R, You L, Gao C, Tian Z. Expression of leptin receptors and response to leptin stimulation of human natural killer cell lines. Biochem Biophys Res Commun 2003;300(2):247–52. https://doi.org/10.1016/S0006-291X(02)02838-3.
[19] Sánchez-Margalet V, Martín-Romero C, González-Yanes C, Goberna R, Rodríguez-Baño J, Muniain MA. Leptin receptor (Ob-R) expression is induced in peripheral blood mononuclear cells by in vitro activation and in vivo in HIV-infected patients. Clin Exp Immunol 2002;129(1):119–24. https://doi.org/10.1046/j.1365-2249.2002.01900.x.
[20] Fujita Y, Murakami M, Ogawa Y, et al. Leptin inhibits stress-induced apoptosis of T lymphocytes. Clin Exp Immunol 2002;128(1):21–6. https://doi.org/10.1046/j.1365-2249.2002.01797.x.
[21] Caldefie-Chezet F, Poulin A, Tridon A, Sion B, Vasson MP. Leptin: a potential regulator of polymorphonuclear neutrophil bactericidal action? J Leukoc Biol 2001;69(3):414–8. https://doi.org/10.1189/jlb.69.3.414.
[22] Matarese G. Leptin and the immune system: how nutritional status influences the immune response. Eur Cytokine Netw. 2000;11(1):7-14. http://www.ncbi.nlm.nih.gov/pubmed/10705294. Accessed April 12, 2020.
[23] Sierra-Honigmann MR, Nath AK, Murakami C, et al. Biological action of leptin as an angiogenic factor. Science (80-) 1998;281(5383):1683–6. https://doi.org/10.1126/science.281.5383.1683.
[24] Gupte M, Boustany-Kari CM, Bharadwaj K, Police S, Thatcher S, Gong MC, English VL, Cassis LA. ACE2 is expressed in mouse adipocytes and regulated by a high-fat diet. Am J Physiol Regul Integr Comp Physiol. 2008 Sep;295(3):R781-8. doi: 10.1152/ajpregu.00183.2008. Epub 2008 Jul 23. PMID: 18650320; PMCID: PMC2536864.
[25] Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. Eur J Intern Med. 2020 Jun;76:14-20. doi: 10.1016/j.ejim.2020.04.037. Epub 2020 Apr 20. PMID: 32336612; PMCID: PMC7167588.
[26] Moro C. Targeting cardiac natriuretic peptides in the therapy of diabetes and obesity. Expert Opin Ther Targets 2016;20(12):1445–52. https://doi.org/10.1080/14728222.2016.1254198. Epub 2016 Nov 9 PMID: 27786597.
[27] Sarzani R, Bordicchia M, Spannella F, Dessì-Fulgheri P, Fedecostante M. Hypertensive heart disease and obesity: a complex interaction between hemodynamic and not hemodynamic factors. High Blood Press Cardiovasc Prev 2014;21(2):81–7. https://doi.org/10.1007/s40292-014-0054-3.
[28] Vollmar AM. The role of atrial natriuretic peptide in the immune system. Peptides 2005;26(6):1086–94. https://doi.org/10.1016/j.peptides.2004.08.034.

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