

A bélflóra és a szöveti oxigénhiány szerepe a bél gyulladásos megbetegedéseiben

Fábián Zsolt

Semmelweis Egyetem Általános Orvostudományi Kar
Orvosi Vegytani, Molekuláris Biológiai & Patobiokémiai Intézet

Összefoglalás

Az oxigénhiányra adott sejt szintű válasz megértése a modern molekuláris biológiai egyik nagy eredménye. A kutatások nyomán egy olyan molekuláris szabályozó rendszer képe tárult elénk, amely kiterjedt kapcsolatokat tart fent olyan klasszikus jelátviteli útvonalakkal, mint amilyen például a gyulladásos válasz klasszikus mediátora, az NF- κ B. A hipoxia és gyulladásos jelátvitel kapcsolatának feltérképezése egyúttal ahhoz a felismeréshez is elvezetett, hogy a hipoxiának, illetve az arra adott sejt szintű válasznak központi szerepe van az olyan gyulladásos megbetegedések patofiziológiájában is, mint amilyen a *colitis ulcerosa*, illetve a Crohn betegség. Az utóbbi évek vonatkozó vizsgálatai alapján úgy tűnik, hogy a gasztrointesztinális rendszer krónikus gyulladásos megbetegedései mögött rejlő folyamatokban fontos, ha nem egyenesen alapvető szerepe van az intesztinális epitélium sajátos metabolikus homeosztázisának, amelyet – legalább részben – a normális bélflóra idéz elő több, a hipoxia-indukálható faktorok által közvetített intracelluláris folyamaton keresztül. Rövid összefoglalónkban a terület legutóbbi eredményeit tekintjük át.

Kulcsszavak: gyulladásos bélbetegségek, bélflóra, hipoxia, HIF-1

Role of the intestinal microbiome and hypoxia in gut inflammation

Summary

Understanding the molecular background of the cellular response to oxygen depletion is one of the greatest achievements of contemporary molecular biology. What has emerged is a pathway with multiple connections with classical signaling mechanisms including the NF- κ B inflammatory signaling machinery. Appreciation of this interaction led to the discovery of the role of hypoxia in pathologies like the *colitis ulcerosa* or Crohn's disease. Recent advances in the field indicate that the pathophysiology underlying the chronic inflammatory disorders of the human gastrointestinal system includes the unique metabolic homeostasis of the intestinal epithelium maintained by the intestinal microbiome via various measures mediated by the hypoxia-inducible factors, master regulators of the cellular hypoxic response. Here, we provide a short overview of the latest results of the field.

Keywords: inflammatory bowel diseases, gut microbiota, hypoxia, HIF-1

Irodalom

1. Ferlay, J., et al., Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*, **2013**. 49(6): p. 1374-403.
2. Nichols, M., et al., Cardiovascular disease in Europe 2014: epidemiological update. *Eur Heart J*, **2014**. 35(42): p. 2950-9.
3. Kent, B.D., P.D. Mitchell, and W.T. McNicholas, Hypoxemia in patients with COPD: cause, effects, and disease progression. *Int J Chron Obstruct Pulmon Dis*, **2011**. 6: p. 199-208.
4. Garvey, C., Interstitial lung disease and pulmonary rehabilitation. *J Cardiopulm Rehabil Prev*, **2010**. 30(3): p. 141-6.
5. Camp, N.E., Methemoglobinemia. *J Emerg Nurs*, **2007**. 33(2): p. 172-4.
6. Perutz, M.F., Mechanisms regulating the reactions of human hemoglobin with oxygen and carbon monoxide. *Annu Rev Physiol*, **1990**. 52: p. 1-25.
7. Sarkar, K., et al., Adenoviral transfer of HIF-1alpha enhances vascular responses to critical limb ischemia in diabetic mice. *Proc Natl Acad Sci U S A*, **2009**. 106(44): p. 18769-74.
8. Aboul-Enein, F. and H. Lassmann, Mitochondrial damage and histotoxic hypoxia: a pathway of tissue injury in inflammatory brain disease? *Acta Neuropathol*, **2005**. 109(1): p. 49-55.
9. Eltzschig, H.K. and P. Carmeliet, Hypoxia and inflammation. *N Engl J Med*, **2011**. 364(7): p. 656-65.
10. Genbacev, O., et al., Regulation of human placental development by oxygen tension. *Science*, **1997**. 277(5332): p. 1669-72.
11. Sugishita, Y., M. Watanabe, and S.A. Fisher, Role of myocardial hypoxia in the remodeling of the embryonic avian cardiac outflow tract. *Dev Biol*, **2004**. 267(2): p. 294-308.
12. Dunwoodie, S.L., The role of hypoxia in development of the Mammalian embryo. *Dev Cell*, **2009**. 17(6): p. 755-73.
13. Cowden Dahl, K.D., et al., Hypoxia-inducible factors 1alpha and 2alpha regulate trophoblast differentiation. *Mol Cell Biol*, **2005**. 25(23): p. 10479-91.
14. Webster, W.S. and D. Abela, The effect of hypoxia in development. *Birth Defects Res C Embryo Today*, **2007**. 81(3): p. 215-28.
15. Tandara, A.A. and T.A. Mustoe, Oxygen in wound healing--more than a nutrient. *World J Surg*, **2004**. 28(3): p. 294-300.
16. Wang, G.L., et al., Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O₂ tension. *Proc Natl Acad Sci U S A*, **1995**. 92(12): p. 5510-4.
17. Maxwell, P.H., et al., The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature*, **1999**. 399(6733): p. 271-5.
18. Willam, C., et al., The prolyl hydroxylase enzymes that act as oxygen sensors regulating destruction of hypoxia-inducible factor alpha. *Adv Enzyme Regul*, **2004**. 44: p. 75-92.
19. Schodel, J., et al., High-resolution genome-wide mapping of HIF-binding sites by ChIP-seq. *Blood*, **2011**. 117(23): p. e207-17.

20. Taylor, C.T. and S.P. Colgan, Hypoxia and gastrointestinal disease. *J Mol Med (Berl)*, **2007**. 85(12): p. 1295-300.
21. Hindryckx, P., et al., Hydroxylase inhibition abrogates TNF-alpha-induced intestinal epithelial damage by hypoxia-inducible factor-1-dependent repression of FADD. *J Immunol*, **2010**. 185(10): p. 6306-16.
22. Hirota, S.A., et al., Hypoxia-inducible factor signaling provides protection in *Clostridium difficile*-induced intestinal injury. *Gastroenterology*, **2010**. 139(1): p. 259-69 e3.
23. Taylor, C.T., et al., Hypoxia-dependent regulation of inflammatory pathways in immune cells. *J Clin Invest*, **2016**. 126(10): p. 3716-3724.
24. Whiteside, S.T. and A. Israel, I kappa B proteins: structure, function and regulation. *Semin Cancer Biol*, **1997**. 8(2): p. 75-82.
25. Israel, A., The IKK complex, a central regulator of NF-kappaB activation. *Cold Spring Harb Perspect Biol*, **2010**. 2(3): p. a000158.
26. Lawrence, T., The nuclear factor NF-kappaB pathway in inflammation. *Cold Spring Harb Perspect Biol*, **2009**. 1(6): p. a001651.
27. Fitzpatrick, S.F., et al., An intact canonical NF-kappaB pathway is required for inflammatory gene expression in response to hypoxia. *J Immunol*, **2011**. 186(2): p. 1091-6.
28. Oliver, K.M., et al., Hypoxia activates NF-kappaB-dependent gene expression through the canonical signaling pathway. *Antioxid Redox Signal*, **2009**. 11(9): p. 2057-64.
29. Schmedtje, J.F., Jr., et al., Hypoxia induces cyclooxygenase-2 via the NF-kappaB p65 transcription factor in human vascular endothelial cells. *J Biol Chem*, **1997**. 272(1): p. 601-8.
30. Figueroa, Y.G., et al., NF-kappaB plays a key role in hypoxia-inducible factor-1-regulated erythropoietin gene expression. *Exp Hematol*, **2002**. 30(12): p. 1419-27.
31. Fitzpatrick, S.F., et al., Prolyl hydroxylase-1 regulates hepatocyte apoptosis in an NF-kappaB-dependent manner. *Biochem Biophys Res Commun*, **2016**. 474(3): p. 579-86.
32. Udalova, I.A., et al., Functional consequences of a polymorphism affecting NF-kappaB p50-p50 binding to the TNF promoter region. *Mol Cell Biol*, **2000**. 20(24): p. 9113-9.
33. Furuta, G.T., et al., Hypoxia-inducible factor 1-dependent induction of intestinal trefoil factor protects barrier function during hypoxia. *J Exp Med*, **2001**. 193(9): p. 1027-34.
34. Tambuwala, M.M., et al., Loss of prolyl hydroxylase-1 protects against colitis through reduced epithelial cell apoptosis and increased barrier function. *Gastroenterology*, **2010**. 139(6): p. 2093-101.
35. He, G., et al., Noninvasive measurement of anatomic structure and intraluminal oxygenation in the gastrointestinal tract of living mice with spatial and spectral EPR imaging. *Proc Natl Acad Sci U S A*, **1999**. 96(8): p. 4586-91.
36. Kelly, C.J., et al., Crosstalk between Microbiota-Derived Short-Chain Fatty Acids and Intestinal Epithelial HIF Augments Tissue Barrier Function. *Cell Host Microbe*, **2015**. 17(5): p. 662-71.
37. Machiels, K., et al., A decrease of the butyrate-producing species *Roseburia hominis* and *Faecalibacterium prausnitzii* defines dysbiosis in patients with ulcerative colitis. *Gut*, **2014**. 63(8): p. 1275-83.
38. Hamer, H.M., et al., Review article: the role of butyrate on colonic function. *Aliment Pharmacol Ther*, **2008**. 27(2): p. 104-19.
39. Ploger, S., et al., Microbial butyrate and its role for barrier function in the gastrointestinal tract. *Ann N Y Acad Sci*, **2012**. 1258: p. 52-9.

40. Blouin, J.M., et al., Butyrate elicits a metabolic switch in human colon cancer cells by targeting the pyruvate dehydrogenase complex. *Int J Cancer*, 2011. 128(11): p. 2591-601.
41. Davie, J.R., Inhibition of histone deacetylase activity by butyrate. *J Nutr*, **2003**. 133(7 Suppl): p. 2485S-2493S.
42. Benita, Y., et al., An integrative genomics approach identifies Hypoxia Inducible Factor-1 (HIF-1)-target genes that form the core response to hypoxia. *Nucleic Acids Res*, **2009**. 37(14): p. 4587-602.
43. Linn, T.C., F.H. Pettit, and L.J. Reed, Alpha-keto acid dehydrogenase complexes. X. Regulation of the activity of the pyruvate dehydrogenase complex from beef kidney mitochondria by phosphorylation and dephosphorylation. *Proc Natl Acad Sci U S A*, **1969**. 62(1): p. 234-41.
44. Aihara, E., K.A. Engevik, and M.H. Montrose, Trefoil Factor Peptides and Gastrointestinal Function. *Annu Rev Physiol*, **2017**. 79: p. 357-380.
45. Buda, A., M.A. Jepson, and M. Pignatelli, Regulatory function of trefoil peptides (TFF) on intestinal cell junctional complexes. *Cell Commun Adhes*, **2012**. 19(5-6): p. 63-8.
46. Saeedi, B.J., et al., HIF-dependent regulation of claudin-1 is central to intestinal epithelial tight junction integrity. *Mol Biol Cell*, **2015**. 26(12): p. 2252-62.
47. Kucharzik, T., et al., Neutrophil transmigration in inflammatory bowel disease is associated with differential expression of epithelial intercellular junction proteins. *Am J Pathol*, **2001**. 159(6): p. 2001-9.
48. Kelly, C.J., et al., Fundamental role for HIF-1 α in constitutive expression of human beta defensin-1. *Mucosal Immunol*, **2013**. 6(6): p. 1110-8.
49. Sankaran-Walters, S., R. Hart, and C. Dills, Guardians of the Gut: Enteric Defensins. *Front Microbiol*, **2017**. 8: p. 647.
50. McKinley, B.A. and B.D. Butler, Comparison of skeletal muscle PO₂, PCO₂, and pH with gastric tonometric P(CO₂) and pH in hemorrhagic shock. *Crit Care Med*, **1999**. 27(9): p. 1869-77.
51. Saltzman, D.J., et al., Oxygen tension distribution in postcapillary venules in resting skeletal muscle. *Am J Physiol Heart Circ Physiol*, **2003**. 285(5): p. H1980-5.
52. Johnson, P.C., et al., Effect of acute hypoxia on microcirculatory and tissue oxygen levels in rat cremaster muscle. *J Appl Physiol* (1985), **2005**. 98(4): p. 1177-84.
53. Wild, J.M., et al., 3D volume-localized pO₂ measurement in the human lung with 3He MRI. *Magn Reson Med*, **2005**. 53(5): p. 1055-64.
54. Wolfle, D. and K. Jungermann, Long-term effects of physiological oxygen concentrations on glycolysis and gluconeogenesis in hepatocyte cultures. *Eur J Biochem*, **1985**. 151(2): p. 299-303.
55. Jungermann, K. and T. Kietzmann, Role of oxygen in the zonation of carbohydrate metabolism and gene expression in liver. *Kidney Int*, **1997**. 51(2): p. 402-12.
56. Roy, S., et al., Characterization of perceived hyperoxia in isolated primary cardiac fibroblasts and in the reoxygenated heart. *J Biol Chem*, **2003**. 278(47): p. 47129-35.
57. Welch, W.J., et al., Nephron pO₂ and renal oxygen usage in the hypertensive rat kidney. *Kidney Int*, **2001**. 59(1): p. 230-7.
58. Mik, E.G., et al., Quantitative determination of localized tissue oxygen concentration in vivo by two-photon excitation phosphorescence lifetime measurements. *J Appl Physiol* (1985), **2004**. 97(5): p. 1962-9.

59. Whalen, W.J., R. Ganfield, and P. Nair, Effects of breathing O₂ or O₂ +CO₂ and of the injection of neurohumors on the PO₂ of cat cerebral cortex. *Stroke*, **1970**. 1(3): p. 194-200.
60. Nwaigwe, C.I., et al., Effect of hyperventilation on brain tissue oxygenation and cerebrovenous PO₂ in rats. *Brain Res*, **2000**. 868(1): p. 150-6.
61. Dunn, J.F., et al., Noninvasive assessment of cerebral oxygenation during acclimation to hypobaric hypoxia. *J Cereb Blood Flow Metab*, **2000**. 20(12): p. 1632-5.
62. Hemphill, J.C., 3rd, et al., Relationship between brain tissue oxygen tension and CT perfusion: feasibility and initial results. *AJNR Am J Neuroradiol*, **2005**. 26(5): p. 1095-100.
63. Buerk, D.G., et al., O₂ gradients and countercurrent exchange in the cat vitreous humor near retinal arterioles and venules. *Microvasc Res*, **1993**. 45(2): p. 134-48.
64. Yu, D.Y. and S.J. Cringle, Retinal degeneration and local oxygen metabolism. *Exp Eye Res*, **2005**. 80(6): p. 745-51.
65. Tondevold, E., J. Eriksen, and E. Jansen, Observations on long bone medullary pressures in relation to arterial PO₂, PCO₂ and pH in the anaesthetized dog. *Acta Orthop Scand*, **1979**. 50(6 Pt 1): p. 645-51.
66. Chow, D.C., et al., Modeling pO₂ distributions in the bone marrow hematopoietic compartment. II. Modified Kroghian models. *Biophys J*, **2001**. 81(2): p. 685-96.