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**EVOLIUCINĖ MEDICINA:
ŽMOGAUS RAIDOS PERSPEKTYVOS IR SVEIKATA
BESIKEIČIANČIOJE APLINKOJE**

**EVOLUTIONARY MEDICINE:
PERSPECTIVES ON HUMAN DEVELOPMENT AND HEALTH
CONSEQUENCES IN A CHANGING ENVIRONMENT**

Rengėjas:

Vilniaus universiteto Medicinos ir sveikatos mokslų
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Organized by

the Doctoral School of Medicine and Health sciences
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EVOLVED REGIONAL IMMUNE ZONATION OF THE HUMAN ILEOCOLIC MUCOSA AND ITS BREAKDOWN ALONG THE ADENOMA–CARCINOMA SEQUENCE

Jurate VALCIUKIENE¹, Egle LASTAUSKIENE², Aida LAURINAVICIENE^{3,4}, Matas JAKUBAUSKAS¹, Marius KRYZAUSKAS¹, Ruta Barbora VALKIUNIENE^{3,4}, Eugenijus JASIUNAS⁵, Renaldas AUGULIS³, Ausra GARNELYTE³, Ieva STUNDIENE¹, Justinas KAVOLIUNAS², Ugne SILINSKAITE⁶, Tomas POSKUS¹

¹Clinic of Gastroenterology, Nephro-Urology and Surgery, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

²Institute of Biosciences, Life Sciences Center, Vilnius University, Vilnius, Lithuania

³National Center of Pathology, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania

⁴Department of Pathology and Forensic Medicine, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

⁵Medical Science Centre, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

⁶Faculty of Medicine, Vilnius University, Vilnius, Lithuania

Contact e-mail: jurate.valciukiene@santa.lt

Background and Aim: The gut harbours the body's largest immune compartment, organised into an evolutionarily conserved regional architecture in which the antigen-rich terminal ileum and the colon are immunologically specialised. Colorectal carcinogenesis evolves through a stepwise adenoma–carcinoma sequence shaped, in part, by mucosal immune surveillance, yet how this evolved regional architecture changes during dysplastic progression—including in mucosa distant from the lesion—remains incompletely defined. We aimed to map immune cell density along the healthy human ileocolic axis and characterise its breakdown across the adenoma–carcinoma sequence.

Materials and Methods: In this observational study (MIMICA-1), we performed compartment-resolved immunohistochemistry for CD3, CD8, CD20, and CD68 with epithelium- and stroma-resolved digital image analysis on 820 sections from 57 individuals (14 healthy controls, 16 small adenomas ≤ 1 cm, 17 large adenomas > 1 cm, 10 carcinomas), with mismatch-repair characterisation of all carcinomas. Group differences were assessed by omnibus Kruskal–Wallis testing with Holm-adjusted Dunn's post-hoc comparisons.

Results: In the healthy bowel, T cells were strongly zoned, enriched in the terminal ileum and declining distally (CD3⁺ stroma $P < 0.001$, $\epsilon^2 = 0.45$; CD8⁺ stroma $P < 0.001$, $\epsilon^2 = 0.58$), and consistently more abundant in stroma than epithelium. This zonation broke down progressively along the sequence: lesional CD3⁺ density was higher in small than large adenomas ($P = 0.001$),

a difference that tracked with adenoma size rather than villous histology. In macroscopically normal mucosa distant from the lesion, two coordinated alterations emerged—CD8⁺ depletion in the terminal ileum ($P=0.018$) and CD68⁺ macrophage expansion in the right-colonic epithelium ($P=0.006$)—both robust across sensitivity analyses.

Conclusions: The healthy ileocolic mucosa shows reproducible, evolutionarily patterned immune zonation that breaks down progressively along the adenoma–carcinoma sequence, with coordinated perturbations extending into normal-appearing mucosa. Viewing colorectal neoplasia as a disruption of evolved mucosal immune homeostasis may offer an integrative, evolutionary-medicine perspective on early tumorigenesis.

Keywords: colorectal adenoma, evolutionary medicine, field cancerization, immune zonation, mucosal immunity