"OMICS" LANGUAGE METAGENOMICS IS IN WAIT FOR PRECISION MEDICINE AS A NEW CLINICAL FRONTIER: FOCUS ON COLORECTAL CANCER

PRECISION MEDICINE
www.e-precisionmed.com/pmj

COMMENTARY

HIGHLIGHTS

This article aims to highlight the potential applications and opportunities of metagenomics in colorectal cancer as part of individualized approach

An initiative by
PRECISION-MEDICINE.IN

ABSTRACT

With the completion of the Human Genome Project in 2003 and the rapid development in genomics such as the high-throughput genomics technologies we are now in the 'postgenomics era'. The concept of precision medicine which is an emerging approach evolved over time and was popularized only recently for to disease prevention and treatment considering the genetic makeup and environment of each individual. In principle, "precision medicine" integrate multiple -omics profiles, such as genomics, pharmacogenomics, proteomics, metabolomics, transcriptomics, epigenomics, metagenomics and "exposome" together with lifestyles factors in an effort to improve the prediction, prevention, diagnosis, and treatment of these disorders to make more tailored diagnostic and therapeutic strategies to a particular patient with different monogenic and multifactorial polygenic complex diseases, such as colorectal cancer. Knowing that a significant percentage of many cancers are induced because of micro-organisms, future studies in metagenomics will undoubtedly reinforce to explore the role of human microbiota in cancer development contributing significantly in understanding the disease at molecular level.

Candan Hizel, PhD
Consultant-expert in Genomics for Health Biotechnology & Molecular Predictive Medicine
OPTI-THREA Inc.,, Montreal, QC, Canada

*Corresponding author:** candan.hizel@gmail.com, **Tel.:** +1 514 716 5979

COMMENTARY

Ever since the international human genome project was completed in 2003, we have been in the post genomic era, marked by the application of genetic knowledge to daily life and development of this project has set the stage for rapid development of "omics" laguages -transcriptomics, proteomics, lipidomics, metabolomics, epigenomics, metagnomics thereafter encouraging hopes for scientists better understand the molecular arguments of different multifactorial complex diseases, such as cancer by increasing the ability to measure and manage huge data sets [1]. In this 'postgeneomic' era rapid developments and advances in high-throughput genomics technologies lay the groundwork for individualized approach for many common complex conditions, such as targeted therapy, screening, prediction and prevention in order to fulfil the promise of precision medicine underpinning more the stratification of molecular-level information [2]. Colorectal cancer (CRC) is a multifactorial polygenic complex disorder that represents the supremacy of healthcare being third most common form of cancer becoming ever-growing and alarming public health problem particularly in western countries with a large economic burden on the health care systems for society [3, 4]. However, wide geographic variation with lower incidence rates are reported in Africa, Asia and South America [5-10] suggesting that besides genetic factors environmental inputs/ behavioural lifestyle risk factors, such nutrition, obesity, diabetes and physical activity could play crucial walk-on in the aetiology of CRC [11-19]. While 75% - 80% of CRCs are considered to be sporadic, familial CRC accounts for about 20% - 25% of which 5% are associated with well-established inherited syndrome such as hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome) and familial adenomatous polyposis (FAP) presenting important challenges to the clinician [20-24]. Sporadic CCR which is the term given to those patients affected with the disease without any obvious reason and family history, however, it involves interaction between age, environment, lifestyle factors, such diet and genetic factors and it is preventable [25-27]. Genetic event frequently occurring, such as inactivation of tumor suppressor genes p53, DCC, DPC4, APC along with activation of the oncogenes such as KRAS and BRAF have been reported in different studies [24]. Moreover, the role of microRNAs on susceptibility in the transformation from benign to malignant in CRC is also described suggesting that microRNAs may be potential early detection biomarkers and therapeutic targets for CRC. [28-30]. Despite genomic inputs as an accumulation of sporadic gene mutations acquired throughout life are important components for identifying "Achilles heel" for the subject affected by sporadic multifactorial complex CRC, it is only one piece of the puzzle [10, 23]. Thereby, the creation of robust data from genomic risk to the "exposome" together with medical histories, social factors, and life style factors is crucial in understanding of sporadic CRC for precise treatment as an individual approach. In addition to genomic information better comprehension of the role of gut microbiota together with novel gut microbiota biomarkers could provide encouraging direction in early diagnosis, prognosis, prevention and treatment of CRC [31, 32]. Normal colonocytes faced with unfavourable environment can transform into cancer cells through epigenetic reprogramming affecting gene expression which could accelerate proliferation of cancer cells. Accordingly, nutrition is of outmost importance having an impact on epigenetic changes leading to different phenotypes and alters disease susceptibilities in CRC carcinogenesis [26, 33-35]. Close relationship between obesity and CRC was already demonstrated in many studies [36-38].

Since the advent of metagenomics which is one of the fastest growing scientific disciplines [39-41] the recent research studies that link between metabolic diseases and bacterial populations in the gut may be crucial [42]. The composition of the gut microbiome was originally coined by Joshua Lederberg as "the ecological community of symbiotic, and pathogenic microorganisms sharing our body space and describing the collective genome of our indigenous microbes (microflora), and so it is equivalent to the gut metagenome. [43]. Microbiome could be considered an environmental factor modulating the host metabolism and includes more than 100 trillion cells of 400 species (approximately ten times the total number of cells in the human body) [44] and its modulation, perturbation seems to be important for body metabolic disorders such as obesity, T2D and cancer [37, 45, 46]. The human microbiome encompasses the collection of microorganism, including, eukaryotes, archaea, bacteria and viruses. Moreover, it is also important to note that the human microbiome contains 150 times more genes than the human genome [47]. Therefore, Manipulation of the gut microbiota may be an important therapeutic strategy to regulate energy balance in individuals [32]. There are evidence suggest an inverse relationship between the level of dietary fibres, which is source of Short-Chain Fatty Acid (SCFA), and the incidence of human CRC [48-50]. As the main energy sources for the host SCFAs can be used for de novo synthesis of lipids and glucose [51, 52]. Distinct composition of gut microbiota produce different SCFAs and butyrate is one of the SCFA end product of colonic fermentation known to modulate several cellular processes such as cell differentiation, inhibition of cell proliferation in different tumour cell lines [53-56]. Effect of butyrate on epigenetic gene regulation is also demonstrated leading the conclusion that different composition of gut microbiota in obesity, T2D and cancer could affect the epigenetic regulation of genes, such as genes encoding SCFAs receptors FFAR2 and FFAR3 causing changes in gene expression and signalling of FFARs by histone deacetylases (HDACs) inhibition and hyperacetylation [57-60].

The knowledge of the composition of the gut microbiome ecosystem and gut microbial marker, such as the ratio of SCFA are future important key elements of precision medicine, though much more research is needed to achieve more precise diagnosis, therapeutic intervention and might eventually aid in lifestyle interventions for disease prevention and or modulation [61]. Accordingly, dietary interventions such as high dietary fibre intakes which are the important source of SCFAs influencing microbial composition could be considered as an option in the personal nutritional in order to increase, for example, butyrate concentrations and reduce insulin resistance for the engagement against metabolic syndrome such as diabetes and also it could be important avenue in an drug development (example NaB might be a promising molecule) for the prevention and treatment of CRC [55, 58, 62, 63]. However, since every individual is different, gut microbiota should be evaluated at personalized level in context with lifestyle factors for its putative triggering development of CRC.

CONFLICT OF INTEREST
None.

ACKNOWLEDGEMENT
None.

FINANCIAL DISCLOSURE
None.

REFERENCES

[1]   Garay JP, Gray JW. Omics and therapy - a basis for precision medicine. Mol Oncol. 2012; 6(2):128-39.

[2]   Jameson JL, Longo DL. Precision medicine--personalized, problematic, and promising. N Engl J Med. 2015; 372 (23):2229-34.

[3]   Ferlay J., Shin H.R., Bray F., Forman D., Mathers C., Parkin D.M. Estimates of worldwide burden of cancer in 2008: Globocan 2008. Int. J. Cancer. 2011; 127(12):2893–2917

[4]   Ferlay J., Parkin D.M., Steliarova-Foucher E. Estimates of cancer incidence and mortality in europe in 2008. Eur. J. Cancer. 2010;46(4):765–781

[5]   Lindblom A, Zhou XL, Liu T, Liljegren A, Skoglund J, Djureinovic T; Swedish Low-Risk Colorectal Cancer Group. Colorectal cancer as a complex disease: defining at-risk subjects in the general population - apreventive strategy. Expert Rev Anticancer Ther. 2004 ;4(3):377-85.

[6]   Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ Cancer statistics, 2008. CA Cancer J. Clin. 2008;58:71-96.

[7]   Center MM, Jemal A, Smith RA, Ward E Worldwide variations in colorectal cancer. CA Cancer J. Clin. 2009;56:366-378

[8]   Favoriti P, Carbone G, Greco M, Pirozzi F, Pirozzi RE, Corcione F. Worldwide burden of colorectal cancer: a review. Updates Surg. 2016;68(1):7-11.

[9]   Huhn S, Pardini B, Naccarati A, Vodicka P, Hemminki K, Försti A. Ancestral susceptibility to colorectal cancer. Mutagenesis. 2012;27(2):197-204.

[10]   Raskov H, Pommergaard HC, Burcharth J, Rosenberg J. Colorectal carcinogenesis--update and perspectives. World J Gastroenterol. 2014;20(48):18151-64.

[11]   Potter JD. Risk factors for colon neoplasia--epidemiology and biology. Eur J Cancer. 1995;31A(7-8):1033-8.

[12]   Terry P, Giovannucci E, Michels KB, et al. Fruit, vegetables, dietary fiber, and risk of colorectal cancer. J Natl Cancer Inst 2002;93(7):525–33.

[13]   Norat T, Scoccianti C, Boutron-Ruault MC, Anderson A, Berrino F, Cecchini M, Espina C, Key T, Leitzmann M, Powers H,Wiseman M, Romieu I1. European Code against Cancer 4th Edition: Diet and cancer. Cancer Epidemiol. 2015;39 Suppl 1:S56-66.

[14]   Hutter CM, Chang-Claude J, Slattery ML, et al. Characterization of gene-environment interactions for colorectal cancer susceptibility loci. Cancer Res. 2012;72(8):2036-44.

[15]   Samad AK, Taylor RS, Marshall T, Chapman MA. A meta-analysis of the association of physical activity with reduced risk of colorectal cancer. Colorectal Dis 2005;7(3):204–13.

[16]   Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst 2005;97(22):1679–87

[17]   Gonzalez CA. Nutrition and cancer: the current epidemiological evidence. Br J Nutr 2006; 96 Suppl 1:S42-5.

[18]   Watson AJ, Collins PD. Colon cancer: a civilization disorder. Dig Dis. 2011;29(2):222-8.

[19]   Guraya SY. Association of type 2 diabetes mellitus and the risk of colorectal cancer: A meta-analysis and systematic review. World J Gastroenterol. 2015;21(19):6026-31.

[20]   Half E, Bercovich D, Rozen P. Familial adenomatous polyposis. Orphanet J Rare Dis. 2009;12;4:22.

[21]   Cunningham D, Atkin W, Lenz HJ, Lynch HT, Minsky B, Nordlinger B, Starling N. Colorectal cancer. Lancet. 2010;375(9719):1030-47.

[22]   Gala M, Chung DC. Hereditary colon cancer syndromesSemin Oncol. 2011;38(4):490-9

[23]   Carethers JM, Jung BH. Genetics and Genetic Biomarkers in Sporadic Colorectal Cancer. Gastroenterology. 2015;149(5):1177-1190. 2015 Jul 26.

[24]   Yamagishi H, Kuroda H, Imai Y, Hiraishi H. Molecular pathogenesis of sporadic colorectal cancers. Chin J Cancer. 2016 ;35(1):4.

[25]   Vogelstein B., Kinzler K.W. The multistep nature of cancer. Trends Genet. 1993;9:138–

141.

[26] *Young GP, Hu Y, Le Leu RK, Nyskohus L. Dietary fibre and colorectal cancer: a model for environment–gene interactions. Mol Nutr Food Res. 2005;49(6):571-84.*

[27] *Fung KY, Ooi CC, Zucker MH, Lockett T, Williams DB, Cosgrove LJ, Topping DL. Colorectal carcinogenesis: a cellular response to sustained risk environment. Int J Mol Sci. 2013 ;14(7)*

[28] *Sarver AE, Li L, Kartha RV, Subramanian S. microRNAs in the Malignant Transformation Process. Adv Exp Med Biol. 2015;889:1-21.*

[29] *Zhao Y, Du Y, Zhao S, Guo Z. Single-nucleotide polymorphisms of microRNA processing machinery genes and risk ofcolorectal cancer. Onco Targets Ther. 2015;8:421-5.*

[30] *Kang BW, Jeon HS, Chae YS, Lee SJ, Park JS, Choi GS, Kim JG. Impact of Genetic Variation in MicroRNA-binding Site on Susceptibility to Colorectal Cancer. Anticancer Res. 2016;36(7):3353-61.*

[31] *Cho M, Carter J, Harari S, Pei Z. The interrelationships of the gut microbiome and inflammation in colorectal carcinogenesis. Clin Lab Med. 2014;34(4):699-710.*

[32] *Manzat-Saplacan RM, Mircea PA, Balacescu L, Chira RI, Berindan-Neagoe I, Balacescu O. Can we change our microbiome to prevent colorectal cancer development? Acta Oncol. 2015;54(8):1085-95.*

[33] *Bingham SA, Day NE, Luben R, et al.; European Prospective Investigation into Cancer and Nutrition. Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. Lancet. 2003;361(9368):1496-501.*

[34] *Huxley RR, Ansary-Moghaddam A, Clifton P, Czernichow S, Parr CL, Woodward M.. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. Int J Cancer. 2009;125(1):171–180.*

[35] *Akin H, Tözün N. Diet, microbiota, and colorectal cancer. J Clin Gastroenterol. 2014;48 Suppl 1:S67-9.*

[36] *Laiyemo AO, Doubeni C, Badurdeen DS, Murphy G, Marcus PM, Schoen RE, Lanza E, Smoot DT, Cross AJ. Obesity, weight change, and risk of adenoma recurrence: a prospective trial. Endoscopy. 2012;44(9):813-8. 27*

[37] *Greiner T., Backhed F. (2011) Effects of the gut microbiota on obesity and glucose homeostasis. Trends Endocrinol. Metab. 22:117–123.*

[38] *Moghaddam AA, Woodward M, Huxley R. Obesity and risk of colorectal cancer: a meta-analysis of 31 studies with 70,000 events. Cancer Epidemiol Biomarkers Prev. 2007;16(12):2533-47.*

[39] *Banerjee J, Mishra N, Dhas Y. Metagenomics: A new horizon in cancer research. Meta Gene. 2015;5:84-9.*

[40] *Maccaferri S, Biagi E, Brigidi P. (2011) Metagenomics: key to human gut microbiota. Dig Dis. 29:525-30.*

[41] *Proctor LM (2016) The National Institutes of Health Human Microbiome Project. Semin Fetal Neonatal Med. . pii: S1744-165X(16)30016-6.*

[42] *Kim B.-S., Jeon Y.-S., Chun J. (2013). Current status and future promise of the human microbiome. Pediatr. Gastroenterol. Hepatol. Nutr. 16, 71–79*

[43] *Hooper LV, Gordon JI. Commensal host-bacterial relationships in the gut. Science. 2001;292(5519):1115-8.*

[44] *Bourlioux P., Koletzko B., Guarner F., Braesco V. The intestine and its microflora are partners for the protection of the host: Report on the Danone Symposium "The Intelligent Intestine", held in Paris, June 14, 2002. Am. J. Clin. Nutr. 2003; 78(4):675–683*

[45] *Baothman OA, Zamzami MA, Taher I, Abubaker J, Abu-Farha M. The role of Gut Microbiota in the development of obesity and Diabetes. Lipids Health Dis. 2016; 15:108.*

[46] *Banerjee J, Mishra N, Dhas Y. Metagenomics: A new horizon in cancer research. Meta Gene. 2015;5:84-9.*

[47] *Qin J., Li R., Raes J., et al. MetaHIT Consortium, Bork P, Ehrlich SD, Wang J. A human gut microbial gene catalogue established by metagenomics sequencing. Nature. 2010; 464 (7285):59–65.*

[48] *Harig J.M., Soergel K.H., Komorowski R.A., Wood C.M. Treatment of diversion colitis with short-chain-fatty acid irrigation. N. Engl. J. Med. 1989;320(1):23–28.*

[49] *Park Y, Hunter DJ, Spiegelman D, et al.. Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. JAMA : the journal of the American Medical Association. 2005;294(22):2849–2857.*

[50] *Donohoe D.R., Garge N., Zhang X., Sun W., O'Connell T.M., Bunger M.K., Bultman S.J. The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon. Cell Metab. 2011;13(15):517–526*

[51] *Wolever TM, Brighenti F, Royall D, Jenkins AL, Jenkins DJ. Effect of rectal infusion of short chain fatty acids in human subjects. Am J Gastroenterol. 1989;84(9):1027-33.*

[52] *den Besten G., van Eunen K., Groen A.K., Venema K., Reijingoud D.J., Bakker B.M. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J. Lipid Res. 2013;54:2325–2340.*

[53] *Hague A, Butt AJ, Paraskeva C. The role of butyrate in human colonic epithelial cells: an energy source or inducer of differentiation and apoptosis? Proc Nutr Soc. 1996; 55: 937–943.*

[54] *D'Argenio G, Mazzacca G. Short-chain fatty acid in the human colon. Relation to inflammatory bowel diseases and colon cancer. Adv Exp Med Biol. 1999; 472:149-58.*

[55] *Hizel C, Maurizis JC, Rio P, Communal Y, Chassagne J, Favy D, Bignon YJ, Bernard-Gallon DJ. Isolation, purification and quantification of BRCA1 protein from tumour cells by affinity perfusion chromatography. J Chromatogr B Biomed Sci Appl. 1999;721(2):163-70.*

[56] *Comalada M, Bailon E, de Haro O, Lara-Villoslada F, Xaus J, et al. The effects of short-chain fatty acids on colon epithelial proliferation and survival depend on the cellular phenotype. J Cancer Res Clin Oncol. 2006;132(8): 487–497.*

[57] *Davie JR Inhibition of histone deacetylase activity by butyrate. J Nutr. 2003; 133 (7 Suppl) 2485S-2493S.*

[58] *Kasubuchi M, Hasegawa S, Hiramatsu T, Ichimura A, Kimura I. Dietary gut microbial metabolites, short-chain fatty acids, and host metabolic regulation. Nutrients. 2015; 7(4):2839-49.*

[59] *Khan S, Jena G. The role of butyrate, a histone deacetylase inhibitor in diabetes mellitus: experimental evidence for therapeutic intervention. Epigenomics. 2015; 7(4):669-80.*

[60] *Alenghat T. Epigenomics and the microbiota. Toxicol Pathol. 2015; 43(1):101-6.*

[61]   *Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, Al-Soud WA, Sørensen SJ, Hansen LH,Jakobsen M. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS One. 2010;5:e9085*

[62]   *Houghton D, Stewart CJ, Day CP, Trenell M. Gut Microbiota and Lifestyle Interventions in NAFLD. Int J Mol Sci. 2016;17, Pii : E447.*

[63]   *Conlon MA, Bird AR. The impact of diet and lifestyle on gut microbiota and human health. Nutrients. 2014 7(1):17-44.*