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Does obesity promote the development of colorectal cancer?

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Obesity is rapidly becoming the leading cause of morbidity and mortality in the U.S. and world [1]. Two-thirds of U.S. adults are overweight (body mass index (BMI) >25 kg/m^2), of which half are obese (BMI >30 kg/m^2). This epidemic reflects the intersection of reinforcing lifestyle choices, including reduced energy use associated with enhanced access to calorie-intense foods, deregulating the metabolic axis. Obesity is associated with co-morbidities that decrease life span and produce substantial economic burden, including cancer, cardiovascular disease, hypertension, stroke, diabetes, liver disease, sleep apnea, depression, infertility, and osteoarthritis [2]. The molecular mechanisms underlying the relationship between obesity and some of these co-morbidities, for example cardiometabolic diseases, are well characterized. By contrast, mechanisms linking obesity to cancer risk, including colorectal cancer, remain incompletely defined.

The intestinal epithelium is dynamic and continuously regenerating, replacing itself once every 3-5 days [3]. Stem cells at the base of the crypt give rise to proliferating transit amplifying cells that migrate up the crypt-surface axis. Midway up this axis, cells shift from proliferation to terminally differentiate into all of the mature cell types of the intestine, including enterocytes, goblet cells, enteroendocrine cells, and Paneth cells. These differentiated cells continue to migrate up the axis and ultimately undergo apoptosis at the surface. This continuous regeneration and replacement depends on tight integration of homeostatic mechanisms including proliferation, metabolic programming, differentiation, genomic integrity, and epithelial-mesenchymal interactions. It is noteworthy here that these homeostatic mechanisms are the same canonical pathways that are universally dysregulated in cancer initiation in all tissues [4].

Colorectal cancer is a disease of several molecular subtypes which all share these pathophysiologic hallmarks of cancer. Molecularly, these subtypes include the chromosome

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instability pathway (CIN), the microsatellite instability pathway (MSI) and the CpG island methylator phenotype (CIMP) pathway [5,6]. The CIN is the “classic” pathway of tumorigenesis, where genomic instability leads to loss of heterozygosity (LOH) of tumor suppressor genes including the adenomatous polyposis coli (APC) gene, the most common genetic defect in CRC[5]. MSI involves the loss of mechanisms that repair single base-pair changes in areas of DNA that occur in non-coding regions known as microsatellites, which in turn leads to oncogenic mutations to BRAF, TGFβ and other genes [5]. CIMP produces disease through DNA hypermethylation, leading to a loss of expression of tumor suppressor genes [5]. Although mechanistically different, this disease subtype functionally resembles MSI, also demonstrating high levels of BRAF mutation. Still other, more putative mechanisms of tumorigenesis have been identified and are being actively studied [5].

GUCY2C is a member of the particulate guanylyl cyclase family, expressed principally by intestinal epithelial cells [7]. Ligands for this receptor are structurally-related peptides and include the endogenous hormones uroguanylin, produced in small intestine, and guanylin, expressed in colorectum, and the exogenous heat-stable enterotoxins (STs) produced by diarrheagenic bacteria [8]. In epithelial cells, GUCY2C is expressed in apical microvillus membranes, where it plays a role in fluid and electrolyte balance. In that context, the best-defined function for GUCY2C is in ST-induced traveler's diarrhea [7,8]. Indeed, binding of ligand to the extracellular GUCY2C domain activates the cytoplasmic enzymatic domain which converts intracellular GTP to cyclic GMP (cGMP). In small intestine, this second messenger activates cGMP-dependent protein kinase PKGII [8]. In contrast, in colorectum cGMP inhibits phosphodiesterase type 3 (PDE3) elevating intracellular concentrations of cyclic AMP [8]. These signaling mechanisms lead to phosphorylation of the cystic fibrosis transmembrane conductance regulator, a chloride channel, which mediates the concentration-dependent efflux of chloride and bicarbonate ions from intestinal cells [8]. This flow of anions drives electrogenic sodium efflux, generating an osmotic gradient resulting in fluid accumulation in intestine manifesting as diarrhea.

Beyond fluid and electrolyte secretion, GUCY2C regulates regenerative mechanisms along the crypt-surface axis, serving as a tumor suppressor to maintain the integrity of the colorectum. Mice lacking GUCY2C (*Gucy2c*$^{-/-}$) exhibit epithelial dysfunction characterizing tumorigenesis, including an increased proliferating compartment, amplified DNA damage, glycolytic metabolic reprogramming, amplified oncogenic kinase signaling, and dysregulated epithelial-mesenchymal crosstalk producing desmoplasia [9-11]. Moreover, intestinal tumorigenesis produced by the carcinogen azoxymethane (AOM) or by mutations in APC is augmented in *Gucy2c*$^{-/-}$, compared to wild-type, mice [10]. In that context, guanylin is the most commonly lost gene product in intestinal tumorigenesis in rodents and humans, producing epithelial dysfunction which phenocopies *Gucy2c*$^{-/-}$ mice. In preliminary studies in mice and humans, guanylin mRNA was lost early in tumorigenesis, and adenomas, as well as adenocarcinomas, were devoid of guanylin expression [12-14]. Moreover, guanylin mRNA and protein was lost by >85% of tumors compared to matched normal adjacent tissue in a cohort of ~300 patients with colorectal cancer [15]. This universal loss of guanylin expression at the earliest stages of transformation, which is conserved across species, suggests that silencing the GUCY2C tumor suppressor plays an essential role in the pathophysiology of colorectal cancer.

Traditionally, mechanisms linking obesity and colorectal tumorigenesis have considered endocrine, adipokine, microbiome and inflammatory alterations that reflect overnutrition and adiposity [16-19]. However, in the context of the dearth of evidence to support these links, molecular mechanisms which connecting obesity and colorectal cancer continue to be defined. In that regard, previous observations underscored the role of guanylin loss silencing GUCY2C in sporadic colorectal cancer, presenting a plausible mechanism in which disruption of the GUCY2C axis contributes to the initiation of tumorigenesis. Indeed, obesity abolished guanylin expression in colorectum in mice and humans [20]. Guanylin loss silenced GUCY2C signaling and obese mice exhibited reductions in phosphorylation of intestinal VASP. Loss of GUCY2C signaling produced epithelial dysfunction and amplified intestinal tumorigenesis, phenocopying *Gucy2c*$^{-/-}$ mice. Importantly, conditional expression of a guanylin transgene which could not be suppressed in obesity eliminated epithelial dysfunction and tumorigenesis in mice a high-fat diet.

In contrast to traditional models which link cancer risk to obesity through adiposity, guanylin loss in obesity is independent of body mass [20]. Indeed, mice on a high-carbohydrate diet maintain lean body weights while eating ~40% excess calories. Also, there is a polymorphism in C57BL/6 mice in which some (~5%) consume excess calories from fat but maintain lean body weights. Further, Balb/C mice maintain lean body weights while consuming excess calories from fat. Importantly, suppression of guanylin expression occurs in each of these models, linking guanylin loss to calories consumed, rather than changes in adipose mass [20]. Moreover, guanylin expression is restored in mice switched from a high to a low calorie diet, despite their remaining persistently obese [20].

Hypercaloric intake produces intestinal endoplasmic reticulum (ER) stress leading to a compensatory unfolded protein response in intestinal epithelial cells [20-22]. Diet-induced ER stress is associated with loss of guanylin in colorectum in obese mice [20]. Also, induction of ER stress pharmacologically by thapsigargan or tunicamycin, or genetically by eliminating XBP1 expression, in lean mice replicated diet-induced obesity and produced guanylin loss. Further, ER stress produces an unfolded protein response directed at preserving homeostasis, mediated by inositol-requiring enzyme 1 and activating transcription factor 6, which increase chaperone transcription, and PKR-like ER-localized eIF2α kinase (PERK), which blocks protein translation. In that context, pharmacologic or genetic inhibition of PERK signaling blocks guanylin loss produced by ER stress. Moreover, the chemical chaperone tauroursodeoxycholic acid, which relieves ER stress, restores guanylin expression in obese mice.

There is an emerging field of cancer risk analysis known as molecular pathologic epidemiology (MPE). Whereas traditional epidemiologic studies attempt to link an exposure (i.e. obesity) to a clinical disease (i.e. colorectal cancer), MPE takes these studies a step further by looking at the association between these exposures and specific molecular events in the disease model of interest [23,24]. This approach allows for the translation of molecular epidemiologic findings into more precise patient management. To this end, there is now an international meeting for MPE, known as the International Molecular Pathological Epidemiology (MPE) Meeting Series (Cancer Causes Control 2015). In that context, recent evidence suggests that colonoscopy, long considered the gold standard of cancer prevention,

is significantly more effective in preventing certain molecular subtypes than others [25,26]. Further, certain risk factors have been shown to lead to a higher incidence of a slower-progressing disease, actually resulting in *lower* mortality in colorectal cancer patients with these risk factors [25]. Taken together, this new avenue of research stratifies patients by their molecular risk and develops clinical approaches accordingly. This paradigm allows investigators for the first time to test mechanistic hypotheses in the context of human epidemiology, reframing the questions from the more rudimentary "Does obesity cause colorectal cancer" to the more precise "Does obesity cause a molecular subset of colorectal cancer and by what mechanism". In the context of colorectal cancer, the loss of guanylin expression and silencing of GUCY2C is nearly universal in colorectal cancer, suggesting that this event spans multiple molecular subtypes of CRC [15]. Despite the high prevalence of this molecular defect, additional studies will be needed to demonstrate which specific molecular subtypes of CRC are most affected by obesity-induced GUCY2C silencing.

These observations suggest a novel pathophysiological hypothesis in which colorectal cancer in obesity recapitulates molecular pathways universally contributing to sporadic tumorigenesis. In that regard, calorie-induced ER stress mediates guanylin loss which silences the GUCY2C tumor suppressor, producing epithelial dysfunction underlying transformation. This hypothesis expands the paradigm of intestinal tumorigenesis in obesity from a disease reflecting dysregulation of the adipose mass, to one of calorie-induced local paracrine hormone insufficiency inactivating a tumor suppressor. The correlative prevention hypothesis suggests that oral GUCY2C hormone replacement might block obesity-related colorectal cancer. The tractability of this novel approach to cancer prevention can be appreciated by considering that the oral GUCY2C agonist linaclotide (*Linzess™*) is approved to treat chronic constipation [27]. Indeed, clinical trials are exploring the ability of oral linaclotide to activate GUCY2C, induce cGMP signaling, and regulate homeostatic pathways, including epithelial cell proliferation, across the rostralcaudal axis of the colorectum (ClinicalTrials.gov Identifier: NCT01950403). The ultimate goal of this clinical program is to expand the therapeutic paradigm to evaluate the utility of linaclotide for chemoprevention of intestinal transformation in populations at risk, including obese individuals.

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References

1. James WP. The epidemiology of obesity: the size of the problem. Journal of internal medicine. 2008; 263(4):336–352. [PubMed: 18312311]
2. Kopelman P. Health risks associated with overweight and obesity. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2007; 8(Suppl 1):13–17. [PubMed: 17316295]
3. Sato T, Vries RG, Snippert HJ, et al. Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche. Nature. 2009; 459(7244):262–265. [PubMed: 19329995]

4. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144(5):646–674. [PubMed: 21376230]
5. Colussi D, Brandi G, Bazzoli F, Ricciardiello L. Molecular pathways involved in colorectal cancer: implications for disease behavior and prevention. International journal of molecular sciences. 2013; 14(8):16365–16385. [PubMed: 23965959]
6. Kocarnik JM, Shiovitz S, Phipps AI. Molecular phenotypes of colorectal cancer and potential clinical applications. Gastroenterology report. 2015; 3(4):269–276. [PubMed: 26337942]
7. Schulz S, Green CK, Yuen PS, Garbers DL. Guanylyl cyclase is a heat-stable enterotoxin receptor. Cell. 1990; 63(5):941–948. [PubMed: 1701694]
8. Lucas KA, Pitari GM, Kazerounian S, et al. Guanylyl cyclases and signaling by cyclic GMP. Pharmacological reviews. 2000; 52(3):375–414. [PubMed: 10977868]
9. Gibbons AV, Lin JE, Kim GW, et al. Intestinal GUCY2C prevents TGF-beta secretion coordinating desmoplasia and hyperproliferation in colorectal cancer. Cancer research. 2013; 73(22):6654–6666. [PubMed: 24085786]
10. Li P, Schulz S, Bombonati A, et al. Guanylyl cyclase C suppresses intestinal tumorigenesis by restricting proliferation and maintaining genomic integrity. Gastroenterology. 2007; 133(2):599–607. [PubMed: 17681179]
11. Lin JE, Li P, Snook AE, et al. The hormone receptor GUCY2C suppresses intestinal tumor formation by inhibiting AKT signaling. Gastroenterology. 2010; 138(1):241–254. [PubMed: 19737566]
12. Cohen MB, Hawkins JA, Witte DP. Guanylin mRNA expression in human intestine and colorectal adenocarcinoma. Laboratory investigation; a journal of technical methods and pathology. 1998; 78(1):101–108.
13. Notterman DA, Alon U, Sierk AJ, Levine AJ. Transcriptional gene expression profiles of colorectal adenoma, adenocarcinoma, and normal tissue examined by oligonucleotide arrays. Cancer research. 2001; 61(7):3124–3130. [PubMed: 11306497]
14. Zhang L, Zhou W, Velculescu VE, et al. Gene expression profiles in normal and cancer cells. Science. 1997; 276(5316):1268–1272. [PubMed: 9157888]
15. Wilson C, Lin JE, Li P, et al. The paracrine hormone for the GUCY2C tumor suppressor, guanylin, is universally lost in colorectal cancer. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2014; 23(11):2328–2337.
16. Endo H, Hosono K, Uchiyama T, et al. Leptin acts as a growth factor for colorectal tumours at stages subsequent to tumour initiation in murine colon carcinogenesis. Gut. 2011; 60(10):1363–1371. [PubMed: 21406387]
17. Sandhu MS, Dunger DB, Giovannucci EL. Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their biologic interactions, and colorectal cancer. Journal of the National Cancer Institute. 2002; 94(13):972–980. [PubMed: 12096082]
18. Martinez-Useros J, Garcia-Foncillas J. Obesity and colorectal cancer: molecular features of adipose tissue. Journal of translational medicine. 2016; 14(1):21. [PubMed: 26801617]
19. Aleman JO, Eusebi LH, Ricciardiello L, Patidar K, Sanyal AJ, Holt PR. Mechanisms of obesity-induced gastrointestinal neoplasia. Gastroenterology. 2014; 146(2):357–373. [PubMed: 24315827]
20. Lin JE, Colon-Gonzalez F, Blomain E, et al. Obesity-Induced Colorectal Cancer Is Driven by Caloric Silencing of the Guanylin-GUCY2C Paracrine Signaling Axis. Cancer research. 2016; 76(2):339–346. [PubMed: 26773096]
21. Ozcan U, Yilmaz E, Ozcan L, et al. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. Science. 2006; 313(5790):1137–1140. [PubMed: 16931765]
22. Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D. Hypothalamic IKKβ/NF-κB and ER stress link overnutrition to energy imbalance and obesity. Cell. 2008; 135(1):61–73. [PubMed: 18854155]
23. Ogino S, Chan AT, Fuchs CS, Giovannucci E. Molecular pathological epidemiology of colorectal neoplasia: an emerging transdisciplinary and interdisciplinary field. Gut. 2011; 60(3):397–411. [PubMed: 21036793]

24. Ogino S, Lochhead P, Chan AT, et al. Molecular pathological epidemiology of epigenetics: emerging integrative science to analyze environment, host, and disease. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2013; 26(4):465–484.

25. Nishihara R, VanderWeele TJ, Shibuya K, et al. Molecular pathological epidemiology gives clues to paradoxical findings. European journal of epidemiology. 2015; 30(10):1129–1135. [PubMed: 26445996]

26. Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. The New England journal of medicine. 2013; 369(12):1095–1105. [PubMed: 24047059]

27. Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. N Engl J Med. 2011; 365(6):527–536. [PubMed: 21830967]