The Association of *Helicobacter pylori* Seropositivity with All-Cause Mortality among Colorectal Cancer Patients Undergoing PET/CT Scans

Haim Shmuely MD[1,5], Baruch Brenner MD[2,6], David Groshar MD[3,6], Nir Hadari MD[4], Ofer Purim MD[2,6], Meital Nidam MD[3,6], Merab Eligalashvili MD[3,6], Jacob Yahav MD[1,5] and Hanna Bernstine MD[3,6]

[1]Department of Internal Medicine D and Helicobacter Research Institute, Kaplan Medical Center, Rehovot, Israel
[2]Institute of Oncology, Davidoff Cancer Center and [3]Department of Nuclear Medicine, Rabin Medical Center (Beilinson Campus), Petah Tikva, Israel
[4]Dan District, Clalit Health Services, Or Yehuda, Israel
[5]Faculty of Medicine, Hebrew University, Jerusalem, Israel
[6]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT: **Background:** Evidence has been emerging that *Helicobacter pylori* may also impact colorectal cancer (CRC). Positron emission tomography/computed tomography (PET/CT) imaging can predict overall survival in CRC patients.

Objectives: To determine a possible association between *H. pylori* seropositivity and all-cause mortality among CRC patients evaluated by PET/CT scans.

Methods: This prospective cohort study was comprised of 110 consecutive CRC patients who had undergone a PET/CT evaluation in a tertiary academic medical center. Data included demographics, body mass index (BMI), tumor node metastasis stage at diagnosis, treatment, time from diagnosis to PET/CT, and PET/CT findings. All patients were tested for anti-*H. pylori* immunoglobulin G (IgG) antibodies and followed for 36 months from the day of the PET/CT scan. Mortality was documented. Univariate and multivariate Cox regression was used to estimate the hazard ratio (HR) of *H. pylori* serological status.

Results: During the follow-up period, of the 110 CRC patients 41 (37.3%) died and 69 (62.7%) survived. Of the 41 patients, 26 (63.4%) were *H. pylori* seropositive and 15 (36.6%) were seronegative. Multivariate analysis showed that *H. pylori* seropositivity (HR 3.46, 95% confidence interval 1.63–7.32), stage IV at diagnosis, metastatic disease found on PET/CT, longer time from diagnosis to PET/CT, lower BMI, and older age were associated with increased mortality.

Conclusions: Our findings suggest that *H. pylori* infection may be a risk factor for all-cause mortality among CRC patients who are evaluated by PET/CT. Multicenter studies with larger patient groups are needed to confirm our findings.

IMAJ 2018; 20: 504–508

KEY WORDS: colorectal cancer (CRC), *Helicobacter pylori*, positron emission tomography/computed tomography (PET/CT)

Helicobacter pylori (*H. pylori*) has been classified by the International Agency for Research on Cancer as a group 1 carcinogen and the major etiological factor for stomach cancer, the second most common cause of cancer death in the world [1].

Evidence has been emerging that *H. pylori* may also impact colorectal cancer (CRC) [2,3], one of the most commonly diagnosed cancers in the world, the third most common cancer, and the fourth most common cause of death from cancer worldwide. CRC accounts for roughly 1.2 million new cases of cancer diagnoses and 600,000 deaths per year [3]. A large study of computerized databases that reviewed surgical pathology reports confirmed this association [4]. The study, which comprised 156,000 subjects who underwent a colonoscopy and esophagogastroduodenoscopy with biopsy results from both procedures, demonstrated that *H. pylori* gastritis occurred more frequently among patients with CRC. Approximately 20% to 25% of these patients are metastatic at the time of diagnosis and nearly 50% of the remainder will develop metastases post-treatment [5]. Evaluation by positron emission tomography/computed tomography (PET/CT) imaging has proven very useful in the clinical staging and restaging of metastases or local recurrence of CRC [6]. This powerful tool can predict progression-free survival and overall survival in CRC patients [7].

The progressive decline in *H. pylori* prevalence may explain the reduction in gastric cancer mortality over the past 80 years. Since *H. pylori* is acquired almost exclusively in childhood and usually persists for a lifetime unless antimicrobial therapy is given, serum immunoglobulin G (IgG) antibodies against *H. pylori* infection are considered a valid test for long-term infection [8]. It is important to evaluate the influence of *H. pylori* seropositivity on all-cause mortality in CRC patients.

To the best of our knowledge, the association between *H. pylori* infection and mortality in CRC patients has not yet

been reported. The objective of this prospective non-interventional study was to determine the impact of *H. pylori* seropositivity on mortality in CRC patients evaluated by PET/CT.

PATIENTS AND METHODS

STUDY DESIGN AND POPULATION

A prospective cohort study included all consecutive patients, older than 18 years of age with a histopathological confirmed colorectal adenocarcinoma who presented as outpatients for fludeoxyglucose (^{18}F-FDG) PET/CT scans at the nuclear medicine department, at Rabin Medical Center from 1 February 2011 to 31 December 2011. This 900-bed university-affiliated tertiary hospital serves urban and non-urban populations and serves as a first-line and tertiary facility for approximately 1 million individuals. The most common indications for ^{18}F-FDG PET/CT scans were initial staging and evaluating response to therapy. Those who agreed to participate were subsequently included in the study cohort.

Patients were excluded if they were hyperglycemic (blood glucose levels > 200 mg/dl) on the day of the PET/CT investigation, were unable to remain in a prone position, or were unable or unwilling to provide informed consent. Height and weight at study entry were recorded. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. The study was reviewed and approved by the institutional review board at the Rabin Medical Center. Informed consent was obtained from each patient. The study was supported by a research grant from the Chief Scientist's Bureau of the Israeli Ministry of Health.

PET/CT

After fasting for 4 hours, all patients underwent an ^{18}F-FDG PET/CT executed by a GE Discovery STE Whole Body PET/CT scanner (GE Medical Systems, Milwaukee, WI, USA). Blood glucose levels were examined before the ^{18}F-FDG injection to ensure a blood glucose level < 200 mg/dl. CT images were acquired at 120 kV and 80 mA, pitch 1.75, 0.8s per tube rotation, and slice thickness of 3.75 mm. During the whole-body CT examination, 80 ml of a contrast agent (Ultravist 300, Schering AG, Berlin, Germany) was intravenously administered to ensure fully diagnostic CT data. The PET scan was performed 45–90 minutes after an intravenous injection of 10–15 mCi of ^{18}F-FDG. The contrast-enhanced CT was used for attenuation correction of the PET data. The PET scan was performed from the base of the skull to the mid-thigh, 2–3 minutes per bed position, resulting in a total scan time of approximately 20–25 min (7 bed positions). An ^{18}F-FDG PET/CT study without abnormal ^{18}F-FDG uptake was considered as physiological or benign. An abnormal FDG uptake of the primary tumor or distant metastases was also evaluated.

SEROLOGY

Serum samples were obtained on the same day as the PET/CT scan and stored at -20°C until assayed. IgG antibodies against *H. pylori* infection were tested by an enzyme-linked immunosorbent assay (ELISA; Orion Diagnostica, Espoo, Finland). This method was validated in our laboratory by a pilot study of patients who had undergone an endoscopy at our hospital that had yielded a sensitivity of 94%, specificity of 90%, and positive and negative predictive values of 100 and 90%, respectively. The kit contains a partially purified protein preparation of the *H. pylori* collection strain, NCTC 11637. A single cut-off level of 20 ELISA U/ml is recommended by the manufacturer. Values of ≥ 20 U/ml were considered seropositive for *H. pylori* and values of < 20 U/ml were considered seronegative.

DATA SOURCE/MEASUREMENT

The following data were extracted from the clinical records and recorded: demographic data, smoking status (never smoked, current smoker, former smoker), disease duration until PET/CT scan, surgery, and chemotherapy treatment in an adjuvant or metastatic setting. Surgical data included the date of surgery, pathology of the tumor, and status of any distant metastasis. These data served to determine the tumor stage at diagnosis classified according to the 7th edition of the tumor node metastasis (TNM) staging system for CRC [9] and grouped into three subgroups: early stages = I and II, locally advanced stage = III, and metastatic stage = IV. PET/CT lesion uptake was classified as: normal evaluation, colon uptake only, and metastatic disease.

FOLLOW-UP

All patients were followed for 36 months from the day of their PET/CT. Patient mortality was documented as recorded in the Central Population Registry (death of an Israeli resident is reported and registered in the Central Population Registry within 48 hours). Duration of follow-up was defined as the interval from the day of the PET/CT to the day of death or 36 months later.

BIAS

H. pylori infection status was based only on serology, consequently not only patients with an active infection were classified as *H. pylori*-positive as patients with a long-standing infection in which the bacteria had disappeared during the progression of histological alterations (i.e., atrophic gastritis) could have been included. *H. pylori* seropositivity tests have high sensitivity and specificity; therefore, we believe that classification biases of the exposure were minimalized. Outcome was defined as all-cause mortality according to the Central Population Registry to avoid classification bias. Selection bias was minimized by selecting consecutive patients. Participants were offered no remuneration; thus, we believe that the selection bias was minimal.

STATISTICAL ANALYSIS

Continuous variables were observed for normal distribution using a histogram and expressed as median and interquartile range (IQR). Categorical variables were summarized as frequencies and proportions. Continuous variables were compared between seropositive and seronegative patients by the Mann–Whitney test. Differences in proportions among categorical data were assessed using the chi-squared or Fisher exact test, as appropriate. The Kaplan–Meier curve was used to describe mortality during follow-up in seropositive and seronegative patients. The log-rank test was used to compare the seropositive and seronegative patients. Univariate and multivariate Cox regression was used to evaluate the association between *H. pylori* serostatus and possible confounders with all-cause mortality. The multivariate Cox regression included 2 blocks: the Enter method, which included *H. pylori* serostatus age and gender, and the Backward Stepwise (Likelihood Ratio) method, which included all variables in the study.

Hazard ratios (HR) with a 95% confidence interval (95%CI) were reported. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, NY, USA) and R version 3.2.3 (Foundation for Statistical Computing, Vienna, Austria). All statistical analyses were two tailed. *P* value < 0.05 was considered statistically significant. A statistical review of the study was conducted by an experienced epidemiologist.

RESULTS

A total of 110 patients, 61 males and 49 females, met the inclusion criteria, of whom 64 (58%) were *H. pylori* seropositive.

Table 1. Clinical characteristics by *H. pylori* status in all study groups

	Entire study population (n=110)	*H. pylori*		*P*
		Positive (n=64)	Negative (n=46)	
Age, years, IQR (median)	67 (59.8–73.0)	69.5 (60–74)	65 (59–73)	0.608
Male, n (%)	61 (55.5)	36 (56.3)	25 (54.3)	0.843
Smoking history, n (%)				
Never	74 (68.5)	41 (65.1)	33 (73.3)	0.597
Current	18 (16.7)	11 (17.5)	7 (15.6)	
Former	16 (14.8)	11 (17.5)	5 (11.1)	
Time, years from diagnosis to PET, IQR (median)	1.5 (0.3–3.6)	1.4 (0.3–3.5)	1.6 (0.4–3.7)	0.709
BMI, kg/m², IQR (median)	26.5 (24.7–29.1)	26.2 (24.7–29.2)	26.7 (24.6–28.0)	0.823
Chemotherapy, n (%)	68 (61.8)	37 (57.8)	31 (67.4)	0.308
Colectomy, n (%)	58 (53.2)	32 (50.8)	26 (56.5)	0.554
PET results, n (%)				
Normal evaluation	48 (43.6)	24 (37.5)	24 (52.2)	0.014
Only colon uptake	18 (16.4)	16 (25.0)	2 (4.3)	
Metastatic disease	44 (40.0)	24 (37.5)	20 (43.5)	
Stage at diagnosis, n (%)				
I–II	37 (33.6)	26 (40.6)	22 (23.9)	0.175
III	38 (34.5)	19 (29.7)	19 (41.3)	
IV	35 (31.8)	19 (29.7)	16 (34.8)	

BMI = body mass index, *H. pylori* = *Helicobacter pylori*, IQR = interquartile range, PET = positron emission tomography/computed tomography

The demographic, clinical and laboratory characteristics of the entire cohort, by subgroups, with positive or negative *H. pylori* serology, are shown in Table 1. *H. pylori* seropositive and seronegative patients did not differ in age, gender, smoking status (never smoked, current smoker, former smoker), disease duration until PET/CT scan, colectomy, chemotherapy, and TNM staging at diagnosis. Seropositive patients had a lower rate of colon uptake on PET/CT.

During the 36 month follow-up period, 41 patients (37.3 %) died and 69 (62.7 %) survived. Of the 41 patients who died, 26 (63.4%) were in the *H. pylori* seropositive group and 15 (36.6%) in the seronegative group (crude HR 1.39, 95%CI 0.74–2.62, $P = 0.311$) [Table 2]. The variables associated with increased mortality on univariate analysis were: stage IV at diagnosis, metastatic disease on PET/CT scans, and older age. Multivariate analysis demonstrated that *H. pylori* seropositivity was associated with increased mortality (HR 3.46, 95%CI 1.63–7.32, $P = 0.001$) [Table 2, Figure 1]. Other factors associated with higher mortality were: stage IV at diagnosis (HR 11.75, 95%C3.58–38.52, $P < 0.001$), metastatic disease found on PET/CT (HR 3.01, 95%CI 1.28–7.09, $P = 0.015$), longer time from diagnosis to PET/CT (HR 1.16, 95%CI 1.03–1.31, $P = 0.018$), lower BMI (HR 0.88, 95%CI 0.79–0.97, $P = 0.012$) and older age (HR 1.04, 95%CI 1.01–1.08, $P = 0.005$) [Table 2]. Figure 1 shows an adjusted survival curve relating to the association between *H. pylori* status and mortality.

DISCUSSION

To the best of our knowledge, our study is the first to evaluate the association of an *H. pylori* infection with all-cause mortality rates in CRC patients undergoing PET/CT scans, which is a powerful imaging tool that can predict progression-free survival and overall survival in CRC patients [7]. The most interesting finding of this prospective cohort study is the significant association between *H. pylori* seropositivity and all-cause mortality in CRC patients (HR 3.46, 95%CI 1.13–7.32, $P < 0.001$).

Soveri and colleagues [10] reported that functional dyspeptic symptoms associated with the presence of *H. pylori* have misled diagnostic workup in CRC patients and may lead to a diagnostic delay of CRC. Although this study did not show inferior disease-free or overall survival in *H. pylori*-positive patients compared with *H. pylori*-negative patients, the authors recommended that a diagnostic CRC workup should not be terminated due to a diagnosis of a chronic *H. pylori* infection.

In our study, *H. pylori* positive patients had a higher rate of metastatic disease associated with a higher mortality, possibly due to a delayed diagnosis. The highest mortality in the studied population was strongly associated with stage IV at diagnosis and a longer period from diagnosis to a PET/CT scan. Thus, in our CRC patients a diagnostic delay in *H. pylori* positive patients might have caused the significantly inferior outcome of

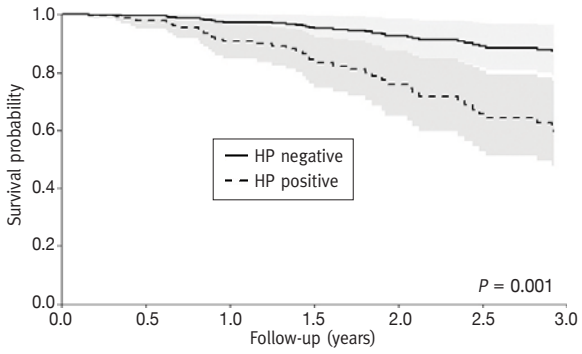
Table 2. Univariate and multivariate analyses using a cox regression model to find risk factor mortality*

	Demographic data		Univariate analysis			Multivariate analysis		
	Dead (n=41)	**Alive (n=69)**	**HR**	**95%CI**	***P***	**HR**	**95%CI**	***P***
H. pylori positive	26 (63.4%)	38 (55.1%)	1.39	0.74–2.62	0.313	3.46	1.63–7.32	0.001
Age, years (range)	69 (62–75)	63 (58–72.5)	1.04	1.01–1.07	0.023	1.04	1.01–1.08	0.005
Male	23 (56.1%)	38 (55.1%)	0.99	0.53–1.82	0.967	1.25	0.60–2.61	0.541
Smoking history								
Never	29 (72.5%)	45 (66.2%)	1		0.381			
Current	4 (10.0%)	14 (20.6%)	0.51	0.18–1.45				
Past	7 (17.5%)	9 (13.2%)	1.17	0.51–2.66				
Time from diagnosis to PET, years (range)	2.68 (0.72–3.68)	0.83 (0.24–3.34)	1.09	0.99–1.20	0.081	1.16	1.03–1.31	0.018
BMI, kg/m² (range)	26.42 (24.64–28.08)	26.51 (24.68–29.84)	0.97	0.90–1.04	0.363	0.88	0.79–0.97	0.012
Chemotherapy	29 (70.7%)	39 (56.5%)	1.56	0.80–3.06	0.194			
Colectomy	24 (58.5%)	34 (50%)	1.27	0.68–2.37	0.451	1.88	0.91–3.89	0.087
Present PET								
Normal evaluation	9 (22.0%)	39 (56.5%)	1	0.35–3.73	‹ 0.001	1		0.015
Only colon uptake	4 (9.8%)	14 (20.3%)	1.15	2.43–		0.86	0.25–2.97	
Metastatic disease	28 (68.3%)	16 (23.2%)	5.18	11.02		3.01	1.28–7.09	
Stage at diagnosis								
I-II	4 (9.8%)	33 (47.8%)	1	0.95–9.34	‹ 0.001	1	0.75–8.13	‹ 0.001
III	11 (26.8%)	27 (39.1%)	2.97	4.39–		2.47	3.58–	
IV	26 (63.4%)	9 (13.0%)	12.67	36.50		11.75	38.52	

*Continuous variables are presented as median (interquartile range) and categorical variables as frequency (percentage).

95%CI = 95% confidence interval, BMI = body mass index, *H. pylori* = *Helicobacter pylori*, HR = hazard ratio, PET = positron emission tomography/computed tomography

Figure 1. Overall adjusted survival curve of patients with colorectal carcinoma with respect to *Helicobacter pylori* (HP) status: HP positive (dotted line) or HP negative (solid line)



this group. In patients diagnosed with CRC, stage at diagnosis is reported as the most important prognostic factor [9]. Use of this imaging technique has become an indispensable staging modality for CRC [11] and was determined to predict worse prognosis in patients with metastatic CRC [12].

Multivariate analysis showed that lower BMI on inclusion to the study was associated with increased mortality. The positive prognostic relationship between low BMI and death may suggest that patients with a lower BMI may have been cachectic. Cancer cachexia affects approximately 50% of patients with colon cancer. Across all tumor groups, cachexia is associated with a 20% mortality rate [13]. In addition, we found that older age was independently associated with mortality, as reported in other studies [14,15].

The physiopathological mechanisms underlying the association between *H. pylori* and colonic neoplasms are not completely clear. In previous studies, we [16] and others [17] demonstrated that fecal shedding of viable *H. pylori* and *H. pylori* antigens occur, under certain circumstances, and are detected in colonic tissue samples [18]. Thus, either by a direct carcinogenic effect of the bacteria on the colorectal mucosa or an indirect action through hypergastrinemia, a trophic effect on the mucosal cells of the colon is produced [19].

Gastrin has been implicated in the tumor genesis of the gastrointestinal tract as a growth factor, increasing the tumor's spread and angiogenesis. It can also impart anti-apoptotic properties, thus activating the transcription of factors involved in the transformation of colon adenomas into malignant carcinomas [20]. The association between *H. pylori* and elevated gastrin levels has been well established [21].

STUDY STRENGTHS AND LIMITATIONS

Despite the demonstration of a strong prognostic significance of *H. pylori* status, our study has several potential limitations. First, the follow-up duration was relatively short. However, other than a 3 year follow-up, the patients in this study also had

a median time of 1.5 years from diagnosis to PET/CT. Second, this was a hospital-based study, hence our patients may not have been sufficiently representative of the general population in Israel. The study was performed in central Israel where a PET/CT scan is an accessible diagnostic modality. Moreover, our study did not include measurements of potential mediators of *H. pylori*-related risks, such as gastrin levels and atrophic gastritis. Despite these limitations, our study seems to have clinical relevance, as to the best of our knowledge, it is the first report investigating the relationship between *H. pylori* status and prognosis in CRC patients with a 3 year follow-up. Large prospective studies with additional measurements of such mediators would be desirable.

CONCLUSIONS

Seropositivity for *H. pylori* antibodies found in CRC patients evaluated by PET/CT scans may be significantly associated with increased all-cause mortality. A diagnostic delay in *H. pylori* positive patients might have caused the significantly inferior outcome of this group. Investigating the mechanisms by which *H. pylori* may increase all-cause mortality in these patients is essential to our comprehensive understanding of the biology of both *H. pylori* and CRC.

Acknowledgements

The authors thank Ms. Phyllis Curchack Kornspan for her editorial services.

Funding

This study was supported by a grant from the Chief Scientist's Bureau, Ministry of Health, Israel (#5665). The funders had no role in the design of the study, data collection and analysis, or preparation of and decision to publish the manuscript.

Correspondence

Dr. H. Shmuely

Dept. of Internal Medicine D, Kaplan Medical Center, Rehovot 76100, Israel

Phone: (972-8) 944-1996

Fax: (972-8) 944-1866

email: hshmuely@zahav.net.il

References

1. Parsonnet J, Friedman GD, Vandersteen DP, et al. Helicobacter pylori infection and the risk of gastric carcinoma. *N Engl J Med* 1991; 325: 1127-31.
2. Shmuely H, Passaro D, Figer A, et al. Helicobacter pylori infection is associated with advanced colorectal neoplasia. *Am J Gastroenterol* 2001; 96: 3406-10.
3. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010: 127: 2893-917.
4. Sonnenberg A, Genta RM. Helicobacter pylori is a risk factor for colonic neoplasms. *Am J Gastroenterol* 2013;108: 208-15.
5. Edwards MS, Chadda SD, Zhao Z, Barber BL, Sykes DP. A systematic review of treatment guidelines for metastatic colorectal cancer. *Colorectal Dis* 2012; 14: e31-47.
6. O'Connor OJ, McDermott S, Slattery J, Sahanj D, Blake MA. The use of PET-CT in the assessment of patients with colorectal carcinoma. *Int J Surg Oncol* 2011; 2011: 846512.
7. Shmuely H, Melzer E, Braverman M, Domnitz N, Yahav J. Elevated risk of colorectal adenoma with Helicobacter pylori-related chronic gastritis: a population-based case-control study. *Scand J Gastroenterol* 2014; 49: 516-7.
8. Perez-Perez GI, Salomaa A, Kosunen TU, et al. Evidence that cagA (+) Helicobacter pylori strains are disappearing more rapidly than cagA (-) strains. *Gut* 2002; 50: 295-8.
9. Brenner H, Kloor M, Pox CP. Colorectal cancer. *Lancet* 2014; 383: 1490-1502.
10. Soveri LM, Osterlund P, Ruotsalainen T, Poussa T, Rautelin H, Bono P. Helicobacter pylori and gastrointestinal symptoms in diagnostics and adjuvant chemotherapy of colorectal cancer. *Oncol Lett* 2014; 7: 553-9.
11. Fernandez FG, Drebin JA, Linehan DC, Dehdashti F, Siegel BA, Strasberg SM. Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). *Ann Surg* 2004; 240: 438-47.
12. Petersen RK, Hess S, Alavi A, Høilund-Carlsen PF. Clinical impact of FDG-PET/CT on colorectal cancer staging and treatment strategy. *Am J Nucl Med Mol Imaging* 2014; 4: 471-82.
13. Argiles JM, Busquets S, Stemmler B, Lopez-Soriano F. Cancer cachexia: understanding the molecular basis. *Nat Rev Cancer* 2014; 14: 754-62.
14. Zahir MN, Azhar EM, Rafiq S, Ghias K, Shabbir Moosajee M. Clinical features and outcome of sporadic colorectal carcinoma in young patients: a cross sectional analysis from a developing country. *ISRN Oncol* 2014; 2014: 461570.
15. 15.Yeo SA, Chew MH, Koh PK, Tang CL. Young colorectal carcinoma patients do not have a poorer prognosis: a comparative review of 2,426 cases. *Tech Coloproctol* 2013; 17: 653-61.
16. Parsonnet J, Shmuely H, Haggerty T. Fecal and oral shedding of Helicobacter pylori from healthy infected adults. *JAMA* 1999; 282: 2240-5.
17. Thomas JE, Gibson GR, Darboe MK, Dale A, Weaver LT. Isolation of Helicobacter pylori from human feces. *Lancet* 1992; 340: 1194-5.
18. Collins D, Hogan AM, Winter DC. Microbial and viral pathogens in colorectal cancer. *Lancet Oncol* 2011; 12: 504-12.
19. Takeda H, Asaka M. Helicobacter pylori and colorectal neoplasm: a mysterious link? *J Gastroenterol* 2005; 40: 919-20.
20. Hartwich J, Konturek SJ, Pierzchalski P, et al. Molecular basis of colorectal cancer-role of gastrin and cyclooxygenase-2. *Med Sci Monit* 2001; 7: 1171-78.
21. Steele IA, Dimaline R, Pritchard DM, et al. Helicobacter and gastrin stimulate Reg1expression in gastric epithelial cells through distinct promoter elements. *Am J Physiol Gastrointest Liver Physiol* 2007; 293: G347-54.

Capsule

Inflammatory decoy control

Bacterial infection can lead to sepsis, inflammation, and death. **Li** et al. found that the long noncoding RNA MEG3-4 and the mRNA encoding the proinflammatory cytokine interleukin-1β (IL-1β) competitively bound to the microRNA miR-138 in the lungs of bacterially infected mice. Initially, MEG3-4 binding to miR-138 facilitated IL-1β production, but it ultimately shut down IL-1β-dependent inflammation. Lung-specific overexpression of MEG3-4 prolonged infection and exacerbated inflammation and lung injury in mice, whereas intravenously delivering miR-138 mimics to infected mice enhanced their survival.

Sci Signal 2018; 11: eaao2387

Eitan Israeli