Colon Cancer Risk and VacA Toxin of *Helicobacter pylori*

Dear Editors:

Butt et al[1] observed an increased risk of developing colon rectal cancer in individuals possessing circulating antibodies to the vacuolating toxin (VacA) of *Helicobacter pylori*. Such a risk was particularly high for African Americans.[1] Indeed, VacA forms chloride (Cl^-) channels that become inserted into the cell and mitochondrial membranes,[2] thereby reducing the membrane potential and mitochondrial energy production. The paradigm of altered Cl^- handling is cystic fibrosis, and it is well-known that patients with this disease have a 5- to 10-fold increased risk of colon rectal cancer,[3] as well of other gastrointestinal tract cancers,[4] owing to the irregular activity of Cl^- exchange by the cystic fibrosis transmembrane regulator. The transmembrane ionic equilibrium controls membrane potential, which in turn was shown to control cell proliferation.[5] In fact, the manipulation of Cl^- concentrations in the environment was shown to control carcinogenesis in tadpoles.[6] It is also known that entry of Cl^- into the cells, cancer cells in particular, increases cell energy,[7] that cells can spend to increase their growth.[7] Therefore, it is biologically plausible that the VacA toxin of *H pylori* could increase the risk of colon cancer, by chronically altering ionic equilibrium of enterocytes exposed to the toxin. In turn, this might open the opportunity for a strategy of noninvasively checking the risk of colon cancer in patients with cystic fibrosis and in the general population.

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Reply. We thank Drs Ponzetto and Figura for their interest in our study entitled "Serological response to *Helicobacter pylori* proteins associate with risk of colorectal cancer among diverse populations in the United States." We appreciate their comments on a potential causal relation between *H pylori* VacA protein and colorectal cancer development. Their hypothesis that VacA may increase the risk of colorectal cancer through a mechanism that is similar to that identified for cystic fibrosis could be of great importance to the question of how *H pylori* might contribute to colorectal carcinogenesis.

We would like to point out, though, that we only indirectly and systemically assessed the presence of VacA through antibody responses against this protein in serum samples. Our data do not verify the presence of the bacterium nor the respective protein in colorectal cancer tissue. Further studies are needed to prove the presence of *H pylori* in the colon epithelium, as well as its potential direct effect. Assessing the presence of VacA and its potential to form chloride channels in host cells, as proposed by Drs Ponzetto and Figura, could thereby serve as a promising approach.

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Correction

Parlato M, Charbit-Henrion F, Abi Nader E, et al. Efficacy of ruxolitinib therapy in a patient with severe enterocolitis associated with a STAT3 gain-of-function mutation. Gastroenterology 2019;156:1206–1210.

In the above article, the surname and given name of the 3rd author, Elie Abi Nader, were reversed. The online version of the article has been updated to correct this oversight.