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Helicobacter, gamma-glutamyltransferase and cancer: Further intriguing connections

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Abstract

Virulence of *Helicobacter pylori*, *Helicobacter suis* and other bacteria appears to be partly mediated through a release of gamma-glutamyltransferase (GGT), an enzyme activity capable of promoting biochemical reactions ultimately resulting in damage to gastric epithelium and suppression of immune response. Recently published studies show that secretion of bacterial GGT occurs in the form of exosome-like vesicles. Very similar GGT-rich exosomes have been described to originate from human cancer cells, and the hypothesis is thus forwarded that in the resistant and invasive phenotype of malignant cells such vesicular/exosomal GGT may play roles akin to those described for *Helicobacter* infection, thus providing a significant contribution to the establishment of cancer metastases.

Key words: *Helicobacter pylori*; *Helicobacter suis*; Virulence; Gamma-glutamyltransferase; Immunosuppression; Cancer metastasis

Core tip: Biochemical reactions promoted by gamma-glutamyltransferase (GGT) of *Helicobacter* is capable of causing damage to gastric epithelium and suppression of immune response. Bacterial GGT is secreted as exosome-like vescicles, and very similar GGT-rich exosomes are released from human cancer cells. In the resistant and invasive phenotype of malignant cells, such secreted GGT may play roles akin to those described for *Helicobacter* infection, concurring to the establishment of cancer metastases.

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TO THE EDITOR

The recent Topic Highlight article by Ricci *et al*[1] is a thorough and comprehensive scrutiny of the mechanisms possibly underlying the recently reported implication of *Helicobacter pylori* (*H. pylori*) gamma-glutamyltransferase (GGT) as a virulence factor. The authors discuss how-among other effects-*H. pylori* GGT causes glutathione consumption and reactive oxygen species generation in the host cells, thus causing in turn cell-cycle arrest, apoptosis, and necrosis in gastric epithelial cells. Importantly, GGT also induces immune tolerance through the inhibition of T cell-mediated immunity and dendritic cell differentiation, overall favouring *H. pylori* persistence and gastric colonization[1].

Now, secretion of GGT appears to also occur by other bacteria related with gastric diseases, *e.g.*, *Campylobacter jejuni*[2], and recent reports are adding intriguing observations. Zhang *et al*[3] have shown that GGT of *H.*

suis-a related Helicobacter, also involved in gastric pathology - is secreted in the form of bacterial outer membrane vesicles (OMV), *i.e.*, submicroscopic structures 20-50 nm in diameter normally budding from the cell surface. These OMV's can translocate across the epithelial layers and deliver GGT enzyme to the lymphocytes residing in the lamina propria of gastric mucosa. As a result, inhibition of lymphocyte proliferation is induced, and bacterial invasion and proliferation are facilitated.

The association of bacterial GGT enzyme with OMV's may be the factor determining its targeting to host lymphocytes, but additional studies are needed to verify this point. In any case, one aspect of the matter calling for attention is represented by the connections possibly linking these observations with data stemming from oncologic research. Interestingly enough, secretion of similar GGT-containing submicroscopic particles has in fact been documented also from eukaryotic cells, and remarkably, from human cancer cells. GGT activity is expressed in a number of human malignancies, and increasing levels are usually detectable along with progression of the disease and in metastases[4,5]. GGT activity of cancer cells can affect intracellular redox equilibria, along with modulatory effects on the S-thiolation status of extracellular proteins[6], including cell surface receptors related with the cell survival/apoptosis balance[7]. Recent studies from our laboratory[8,9] have shown that active GGT can be released from cancer cells in association with vesicles similar to exosomes, 20-40 nm in diameter. The resemblance of such structures with GGT-rich OMV particles of *H. suis* is indeed obvious.

Thus, in the light of the mentioned studies on the virulence of *H. pylori,* the intriguing hypothesis could be forwarded that GGT-rich exosomes released by cancer cells can produce-in host's surrounding tissues-effects comparable to those apparent for bacterial GGT, *i.e.*, depletion of glutathione, oxidative stress and perturbation/suppression of immune response. This could contribute significantly to the increased ability of malignant cells to survive and colonize host's tissues, thus at least partially explaining the reportedly higher metastatic potential of GGT-expressing tumors[4]. The potential role in tumor evolution of GGT released by gastric cancer cells has not been investigated to date. Nevertheless, basing on the considerations above, clinical studies specifically addressing this point are warranted.

In conclusion, the GGT-dependent processes documented in bacterial virulence as well as in biology of malignant tumors may represent an example of "convergent evolution"-in unrelated species, and in different cells of the same species-of closely related molecular strategies, aimed at improving the survival and expansion of cellular populations in the context of a hostile/resisting environment. Future investigation will hopefully further elucidate these fascinating phenomena.

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