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REVIEW ARTICLE

Pathogenetic mechanisms involved in stomach infection caused by Helicobacter pylori

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Helicobacter pylori bacterium colonizes the gastric mucosa in humans causing chronic active gastritis type B and peptic ulcer disease. It is the commonest cause of antral gastric and duodenal ulceration. Furthermore, it is implicated in gastric adenocarcinoma, mucosal atrophy and low grade B-cell lymphoma of mucosa associated lymphoid tissue (MALT lymphoma). Re-infection of peptic ulcer is associated with re-infection by the bacterium. In contrast to other pathogens of the gastrointestinal tract, which invade the mucosal barrier, Helicobacter pylori, rarely penetrates the gastric epithelium. Typical histological pattern of inflammation is though observed in the submucosal layer. Antigens constantly found in all strains as well as some other found in certain strains of the bacterium, play an important role in the immune response of the human organism, apoptosis and signal transduction. Pathogenetic mechanisms involved in pathogenesis of various disease processes induced by helicobacter pylori are not yet fully elucidated. Adhesion molecules, interleukins and other inflammation mediators, participate in the hole process. In the present review article all these pathogenetic mechanisms are discussed in detail.
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Helicobacter pylori (Hp) is a negative flagellated spiral bacterium that colonizes the gastric mucosa in humans, causing chronic active gastritis type B and peptic ulcer disease[1,2] .The bacterium, member of the campylobacter family, was at first described by Marshall in 1985 in Australia[3]. Hp is the commonest cause of antral gastric and duodenal ulceration. Furthermore, it has been implicated in gastric adenocarcinoma, mucosal atrophy, and low grade B cell lymphoma of mucosa associated lymphoid tissue (MALT lymphoma)[4,5]. This evidence comes from several nested case control studies and from numerous pathologic studies suggesting that the natural history of the Hp infection in that of chronic active gastritis, which may ultimately result in premalignant gastric mucosal athrophy, intestinal metaplasia and achlorydria[6,7]. Additionally, Hp is almost always found in gastric dysplasia and early gastric cancer. Recurrence of peptic ulcer disease is associated with reinfection by the bacterium[8].

Gastritis induced by Hp (type B gastritis) is characterized histologically by a dense infiltration with granulocytes. Neutrophilic infiltrates are a hallmark in many bacterial infections including shigella, salmonella, listeria, and yersinia[9-11]. These pathogens are able to invade the musosa and establish an intercellular niche. Lymphocytes, nononuclear and plasma cells beyond polymorphonuclear leukocytes, may also be accumulated in submucosal infiltrates. Sometimes, infiltrates are associated with epithelial erosions of the ulceration. In several cases of Hp colonization several epithelial changes consisting of parietal cell loss, hyperplasia of the surface epithelium, and intestinal metaplasia may be observed.

Most pathogenic microorganisms virtually invade the gastric tissue barrier. This does not happen with the Hp. It is an interesting phenomenon that this flagellated bacterium only infrequently invades the epithelium or even the deeper areas. Typically Hp adheres to but does not invade the gastric epithelium or the underlying lamina propria. Patients infected with Hp are described as having chronic active gastritis. However, infection is asymptomatic in most infected individuals, estimated as 2 billion people worldwide. Disease versus asymptomatic colonization is believed to depend both on host factors and on genetic differences among different Hp strains[12]. In order the Hp to act as a pathogen, at first has to survive in the acidic environment of the stromach ; then has to penetrate the gastric mucus, and finally to colonize gastric mucosa. Consequently, the bacterium has to proliferate, avoiding the human organism defense mechanisms. Therefore, some bacterium factors are essential in these processes including urease (Ure A-1), endotoxin lipopolysaccharide (LPS), flagellins (fla A, fla B), adhesins (hpa, bab A1, hopZ, alp A, alp B), and a protein which activates neutrophils (nap, neutrophil activating protein). All the above mentioned factors are constantly found in all strains of HP. Sometimes, factors like antigen cag A, molecules PAI, vacA/s1, ice-A1, oip A, pic B as well as protein bab A2 may be found[13-16].

Strains of HP presenting all the abovementioned molecules appear a strong infectious potential and are associated with upregulation of cytokines (IL-8, IL-1B, and TNFa), as well as of other mediators of the inflammation like RNS and ROS; a severe disease such as peptic ulcer and gastric cancer may be then developed. Hp has been characterized as an extracellular colonizer, but there are data supporting an intracellular location of the bacterium in vivo [17]. Thus, the human organism immune response is carried out by Th1 lymphocyte subpopulation. This is surprising since extracellular bacteria activate Th2 immune response (Th1 and Th2 are functioning subpopulations of helper $CD4^+$ T-lymphocytes)[18]. The Hp antigens cag A and vac A accelerate apoptosis[19-20].

With the use of selective inhibitors, it was concluded that the uptake of Hp either occurs through receptor – mediated endocytosis, or by a closely related pathway. These data on bacterial internalization are also in line with the clinical observation that therapies using antibiotics unable to enter eukariotic cells, such amoxicillin, are less effective in eradicating Hp, despite the high in vitro susceptibility of the organism. Therefore, some one may assume that bacterial components or products cross the epithelial barrier inducing local inflammation. The mechanisms of pathogenesis are not well established; there is some evidence that inflammation can be induced by the organism itself or through its association with the gastric epithelium[21]. Vascular participation is very possible. Factors with the potential to induce inflammatory lesions are cell membrane proteins of the bacterium, which are even overproduced by some gram-negative bacteria. The presence of antibodies to membrane proteins of Hp in serum, clearly shows that these proteins access and are presented to the human immune system[22]. Several studies have shown that soluble surface proteins from HP can activate monocytes and also be chemotactic for granulocytes.

Usually granulocytes are attracted by chemotactic stimuli, eg LTB4, C5a, or chemokines [interleukin-6,-8 (IL-6, IL-8)] as well as tumor necrosis factor (TNF). Most of these substances are indirect signals after contact of defined cells with bacterial products. Emigration of neutrophils into surrounding tissues, is mediated by adhesion molecules expressed during their activation. Adhesion molecules of beta integrins in leukocytes and endothelial cells as well as selectins play an important role in the migration of leukocytes into the extravascular space and are involved in cytokine-mediated tissue injuries[23,24].

A common pathway in the action of chemotactic stimuli is the upregulation of some adhesion molecules on granulocytes. From these the β_2-integrins CD11b/CD18 (Mac-1) and CD11c/Cd18 show the most vigorous and fastest response due to their storage in granules in granulocytes[25,26]. Thus, granulocytes rolling along the endothelial surface as well as their migration and recruitment into the lamina propria occur after strong adhesion to the endothelium. In gastric T cells α^E- and β_7-integrins are present as part of the $\alpha^E\beta_7$ heterodimer, which also is found on intestinal intraepithelial lymphocytes and mediate adhesion with E-cadherin on epithelial cells[27-29]. The β_7 integrin is also present as part of the $\alpha_4\beta_7$ Payer's patch homing receptor [30].

Invasion by bacterial pathogens including Hp into host cells involves interaction with specific cellular receptors such as integrins, whose occupancy leads to activation of signaling pathways in the host. Integrins are cell surface receptors involved in numerous cellular processes including migration, differentiation, and adherence extracellular matrix and other cells. Members of the family are αβ-heterodimeric transmembrane proteins that are involved in both inside-out and outside-in signaling[31]. These usually intermediate in adhesion interactions among cells and substratum components (substratum adhesion molecules, SAMs). Integrins are well known to promote the internalization of various microorganisms. Viruses and bacteria can be internalized into normally nonphagocytic cells by integrins containing β_1, β_3 and β_5 chains [32].

Except integrins, the selectins group of adhesion molecules, at most participate in this inflammatory process on this certain point. Gastric epithelium expresses the neutrophil intercellular adhesion molecule-1 (ICAM-1, CD54) which binds to LFA-1 (lymphocyte function associated-1, CD11a/CD18) and Mac-1 (CD11b/CD18) as ligands. ICAM-1 is a prominent adhesion molecule that is upregulated in the endothelial surface in active chronic gastritis cases playing a major role in the mediation of leukocyte trafficing into inflammed gastric tissue. Wallace et al demonstrated that monoclonal antibodies directed against CD18 or ICAM-1 reduced the severity of gastric mucosal damage induced by indomethacin in rabbits and rats[33,34]. Their results suggested that β_2 integrins and ICAM-1 may play an important role in the pathogenesis of mucosal damage in the stomach.

It has been shown that the hyperadhessive response by the Hp is dependent on both CD11a/CD18 and CD11b/CD18 on neutrophils and ICAM-1 on endothelial cells. Under unstimulated conditions neutrophils attach to endothelial cells via a CD11a/CD18-ICAM-1 dependent process. However, adhesion of activated neutrophils to endothelial cells involves both CD11a/CD18 and CD11b/CD18 molecules. The prevailing view in the literature is that stimulation of neutrophils with chemotactic agents leads to activation of CD11b/CD18 adhesion molecule on neutrophils.

As was mentioned above, there is a strong correlation between protracted stomach infection by Hp and the pathogenesis of gastritis and gastroduodenal ulcer as well as of ulcer recurrence by reinfection. More recently, Hp infection has been associated to an increased risk of developing gastric adenocarcinoma and MALT lymphomas. Infected by the bacterium individuals are in a nine fold higher risk for gastric cancer development.

Several mechanisms have been suggested by which

Hp infection might lead to gastric cancer. Directly and indirectly affecting epithelial cells function and interventing in the immune inflammation response, Hp influences the rate of epithelial cell proliferation and induces intracellular signaling events counteracting to protein kinase C effects. Thus, the bacterium may initiate an early step in the gastric carcinogenesis and/or may be an interesting cocarcinogenic factor.

Low-grade B cell lymphomas of mucosa-associated lymphoid tissue (MALT) typically arise in mucosal sites that do not contain organized lymphoid tissue. The emergence of the lymphoma is, however, almost always preceded by a chronic inflammatory state that leads to the accumulation of the lymphoid tissue. In the stomach, the most common site of MALT lymphomas, organized lymphoid tissue with the characteristics of MALT is accumulated secondary to Hp infection. The development of gastric MALT lymphoma has been shown by several studies. Gastric MALT lymphomas tend to remain localized to the site of origin for long periods. When they occasionally spread, they preferentially involve other mucosal sites, such as the intestine and curiously the spleen. These observations imply that mechanisms controlling normal mucosal lymphocyte traffic may also be operational in MALT lymphomas.

Hp stains isolated from patients suffering of severe gastritis and gastroduodenal ulcers almost invariably express a cytotoxin (VacA) causing cell vacuolation and a toxin-associated antigen (Cag A) marker of a 40 kb pathogenicity island. Cag A is the major antigen in HP seropositive patients and it is related to the induction of IL-8 in vivo. Activated Vac A alters the permeability of epithelial monolayers via modification of transmembrane protein complexes that mediate cell-to-cell adhesion.

It was recently found that efficient adherence of Hp A5 to cultured cells requires active bacterial protein synthesis and viable target cells. This efficient adherence did not seem to involve the host cell receptor Le^b [35]. The ability of Hp to adhere to gastric cells is believed to play a central role in infection of human stomach on fixed gastric tissue, Le^b and other fucosylated blood group antigens were shown to function as receptor for Hp attachment[35]. Bab A was recently shown to be the adhesion of Hp responsible for bacterial binding to these fucosylated blood group antigens expressed on fixed gastric tissue[36]. Most cultured cells, however, do not express or express very low levels Le^b, suggesting that the efficient adherence to AGS gastric cell line cells and other human gastric cell lines is caused by an interaction with receptors other than Le^b. Integrins, E-cadherin, and CD66 have been shown to act as ligands for bacteria such yersinia, listeria, and naisseria, allowing both adherence and subsequent internalization[37].

In addition to Hp well recognized role as a mediator of gastritis, peptic ulcer, gastric adenocarcinoma, and MALT lymphoma of the stomach, this bacterium has also been implicated in the pathogenesis of cardiovascular diseases[38]. This observation supports the view that Hp may exert some of its effects on the gastric mucosa through an action on the vascular supply.

In conclusion, the pathophysiology of stomach colonization by Hp as well as the disease entities caused by this bacterium, have not been fully elucidated. More data are essential in understanding the role of adhesion molecules and other mediators in the development of chronic active gastritis, peptic ulcer disease, MALT lymphoma, and gastric adenocarcinoma.

Περίληψη

Χαραλαμπόπουλος Κ, Παπαλιμναίου Β, Αγνάντη ΝΙ. Παθογενετικοί μηχανισμοί ενεχόμενοι στη λοίμωξη του στομάχου από Helicobacter Pylori.
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Το gram αρνητικό, σπειροειδές και βλεφαριδωτό ελικοβακτηρίδιο του πυλωρού, της οικογενείας campylobacter, αποικεί το γαστρικό βλεννογόνο και προκαλεί χρόνια ενεργό γαστρίτιδα τύπου Β, καθώς και πεπτικό έλκος. Είναι το συχνότερο αίτιο γαστρίτιδας του άντρου και έλκους του δωδεκαδακτύλου. Επιπλέον ενοχοποιείται στην πρόκληση αδενοκαρκινώματος του στομάχου, ατροφίας του βλεννογόνου καθώς και στην δημιουργία του χαμηλού βαθμού λεμφώματος εκ Β κυττάρων, του σχετιζομένου με τον βλεννογόνιο λεμφοειδή ιστό (MALT λέμφωμα). Η επαναλοίμωξη του πεπτικού έλκους συσχετίζεται με την επαναλοίμωξη με το βακτηρίδιο αυτό, μετά προηγουμένη του εκρίζωση με κατάλληλα αντιβιοτικά. Το ελικοβακτηρίδιο του πυλωρού σε αντίθεση με άλλα παθογόνα μικρόβια του γαστρεντερικού σπανιότατα και μόνο διηθεί τον γαστρικό βλεννογόνο, προκαλεί όμως την κλασσική ιστολογική εικόνα με την χαρακτηριστική συσσώρευση των κοκκιοκυττάρων. Αντιγόνα που σταθερά ανευρίσκονται σε ορισμένα στελέχη του ελικοβακτηριδίου του πυλωρού όπως η ουρεάση, η λιποπολυσακχαρίδη, οι φλατζελίνες Α και Β, οι προσκολλητίνες και η πρωτεΐνη που ενεργοποιεί τα ουδετερόφιλα, καθώς και αντιγόνα που ευρίσκονται σε ορισμένα μόνο στελέχη αυτού, όπως οι πρωτεΐνες cag A, vac A , bab A2 και άλλες, διαδραματίζουν ενδιαφέροντα ρόλο στην όλη ανοσολογική απόκριση του οργανισμού , στην απόπτωση και στη μεταβίβαση του σήματος. Οι παθοφυσιολογικοί μηχανισμοί πρόκλησης των νοσολογικών οντοτήτων που προκαλούνται από τον αποικισμό του στομάχου με το εν λόγω βακτηρίδιο δεν είναι επακριβώς διευκρινισμένοι. Μόρια προσκόλλησης, ιντερλευκίνες και άλλοι μεσολαβητές της φλεγμονής , όπως ο TNFa , συμμετέχουν στη φλεγμονώδη διαδικασία. Στο παρόν άρθρο ανασκόπησης συζητώνται με σχετική λεπτομέρεια οι παθοφυσιολογικοί αυτοί μηχανισμοί.

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