Journal of Microbiology, Immunology and Infection (2017) 50, 4–9

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

REVIEW ARTICLE

Modulation of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis by *Helicobacter pylori* in immune pathogenesis of gastric mucosal damage

Hwei-Fang Tsai [a,b], **Ping-Ning Hsu** [c,d,*]

[a] *Department of Internal Medicine, Taipei Medical University Shuang Ho Hospital, Taipei, Taiwan*
[b] *Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan*
[c] *Graduate Institute of Immunology, College of Medicine, National Taiwan University, Taipei, Taiwan*
[d] *Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan*

Received 1 March 2015; received in revised form 20 December 2015; accepted 17 January 2016
Available online 29 January 2016

KEYWORDS
apoptosis;
chemokine;
FLIP;
Helicobacter pylori;
TRAIL

Abstract *Helicobacter pylori* infection is associated with chronic gastritis, peptic ulcer, gastric carcinoma, and gastric mucosa-associated lymphoid tissue lymphomas. Apoptosis induced by microbial infections is implicated in the pathogenesis of *H. pylori* infection. Enhanced gastric epithelial cell apoptosis during *H. pylori* infection was suggested to play an important role in the pathogenesis of chronic gastritis and gastric pathology. In addition to directly triggering apoptosis, *H. pylori* induces sensitivity to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis in gastric epithelial cells. Human gastric epithelial cells sensitized to *H. pylori* confer susceptibility to TRAIL-mediated apoptosis via modulation of death-receptor signaling. The induction of TRAIL sensitivity by *H. pylori* is dependent upon the activation of caspase-8 and its downstream pathway. *H. pylori* induces caspase-8 activation via enhanced assembly of the TRAIL death-inducing signaling complex through downregulation of cellular FLICE-inhibitory protein. Moreover, *H. pylori* infection induces infiltration of T lymphocytes and triggers inflammation to augment apoptosis. In *H. pylori* infection, significant increases in $CCR6^{+}$ $CD3^{+}$ T cell infiltration in the gastric mucosa was observed, and the CCR6 ligand, CCL20 chemokine, was selectively expressed in inflamed gastric tissues. These mechanisms initiate chemokine-mediated T lymphocyte trafficking into inflamed epithelium and induce mucosal injury during *Helicobacter* infection. This article will review recent findings on the interactions of *H. pylori* with host-epithelial signaling pathways and events involved in the initiation of gastric pathology, including gastric inflammation and mucosal damage.

* Corresponding author. Graduate Institute of Immunology, College of Medicine, National Taiwan University, 1 Jen-Ai Road, Section 1, Taipei 100, Taiwan.
E-mail address: phsu8635@ntu.edu.tw (P.-N. Hsu).

http://dx.doi.org/10.1016/j.jmii.2016.01.002

Helicobacter pylori infection and apoptosis in gastric epithelial cells

Helicobacter pylori is a common human pathogen that infects over half of the world population and is associated with duodenal and peptic ulcer diseases. The clinical consequences range from asymptomatic gastritis to peptic ulceration and gastric malignancy.[1,2] The outcome of the infection is determined by interactions among *H. pylori* virulence factors, host gastric mucosal factors, and the environment. However, the mechanisms by which host factors cause disease remain unclear. Apoptosis induced by microbial infections is implicated in the pathogenesis of *H. pylori* infection, and enhanced gastric epithelial cell apoptosis during *H. pylori* infection was suggested to play an important role in the pathogenesis of chronic gastritis and gastric pathology.[3–7] Direct cytotoxicity, as well as inflammatory responses, occurs in gastric mucosa cells.[5,8–10] *H. pylori* vacuolating (VacA) toxin induces gastric epithelial cell apoptosis, but cytotoxin-associated gene A (CagA) attenuates apoptosis in gastric epithelial cells. Bacterial virulent factors may contribute directly to apoptosis in epithelial cells, whereas the induction of sensitivity to death-receptor mediated apoptosis by *H. pylori* is independent of *H. pylori* virulent factors VacA and CagA,[6] suggesting that immune factors, in addition to bacterial factors, are also important in determining the degree of gastric mucosa damage during *H. pylori* infection.

It was demonstrated that T helper type 1 (Th1) cells selectively increased during *H. pylori* infection.[11–14] Th1 cytokines, such as interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α), can increase the release of proinflammatory cytokines, augmenting apoptosis induced by *H. pylori*.[10] *H. pylori* infection could also induce gastric mucosa damage by increasing expression of Fas in gastric epithelial cells, leading to gastric epithelial cell apoptosis through Fas/Fas ligand (FasL) interaction with infiltrating T cells.[9,15] These findings suggest a role for immune-mediated apoptosis of gastric epithelial cells during *H. pylori* infection. Additionally, *H. pylori* directly triggers cell death by cytotoxins after interacting with gastric epithelial cells.[16,17] Furthermore, *H. pylori* translocates CagA into gastric epithelial cells by Type IV secretion, inducing intracellular protein phosphorylation and dysregulating signal transduction pathways within host cells.[18–21] In addition to directly triggering apoptosis, it is possible that *H. pylori* induces sensitivity to apoptosis in gastric epithelial cells via modulation of apoptosis signaling.

H. pylori modulate tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis in gastric epithelial cells

TNF-related apoptosis-inducing ligand (TRAIL; also called Apo2L) is a novel TNF superfamily member with strong homology with FasL that is capable of inducing apoptosis in a variety of transformed cell lines *in vitro*,[22,23] but usually not in normal primary cells. T cells can kill target cells via TRAIL/TRAIL-receptor interaction,[24,25] indicating that TRAIL might serve as a cytotoxic effector molecule in activated T cells *in vivo*. These findings suggested that TRAIL/TRAIL-receptor interaction is involved in the interaction between infiltrating T cells and gastric epithelium during *H. pylori* gastritis. Recent studies demonstrated that human gastric epithelial cells sensitized to *H. pylori* confer susceptibility to TRAIL-mediated apoptosis, suggesting a role for immune-mediated apoptosis in gastric epithelial cells by infiltrating T cells during *Helicobacter* infection.[6,14,26] The induction of TRAIL sensitivity by *H. pylori* is dependent upon bacterial cell contact, irrespective of expression of *H. pylori* virulent factors.[6]

TRAIL-induced apoptosis occurs through a caspase signaling cascade, and resistance to TRAIL is controlled by intracellular regulators of apoptosis. Crosslinking of the TRAIL receptors leads to the formation of a death-inducing signaling complex (DISC)[27] assembled by the death-adaptor protein Fas-associated death-domain protein (FADD) and caspase-8 and -10.[28–30] Activated caspase-8 is generated after DISC formation, and initiates apoptosis-inducing caspase signaling cascade. Previous studies demonstrated that TRAIL-induced apoptosis could be enhanced by *Helicobacter* and hepatitis C virus core proteins[6,31]; however, the mechanisms leading to microbe-induced TRAIL sensitivity remain unclear. *H. pylori*-induced sensitivity to TRAIL-mediated apoptosis in gastric epithelial cells is dependent upon activation of the caspase-8 downstream pathway for conveyance of death signals to mitochondria, resulting in activation of mitochondrial pathways and removing resistance to apoptosis. *H. pylori* also induces sensitivity to TRAIL-mediated apoptosis by regulation of FLICE-inhibitory protein (FLIP) and assembly of DISC, which initiates caspase activation[26] and promotes apoptosis, thereby providing insight into the pathogenesis of gastric damage during *Helicobacter* infection (Figure 1). Modulation of host-cell apoptosis by bacterial interaction adds a new dimension to immune pathogenesis associated with *Helicobacter* infection.

Chemokine-mediated lymphocyte trafficking of T lymphocytes in gastric inflammation during *H. pylori* infection

During *H. pylori* infection, the degree of apoptosis induced in the stomach is affected by the inflammatory response. *H. pylori* infection induces a T cell response, as well as a number of inflammatory mediators, including cytokines and chemokines.[7,11,14,32] These infiltrating T cells can then target and destroy gastric cells via TRAIL/TRAIL-receptor interaction. In addition to its role in inducing apoptosis by

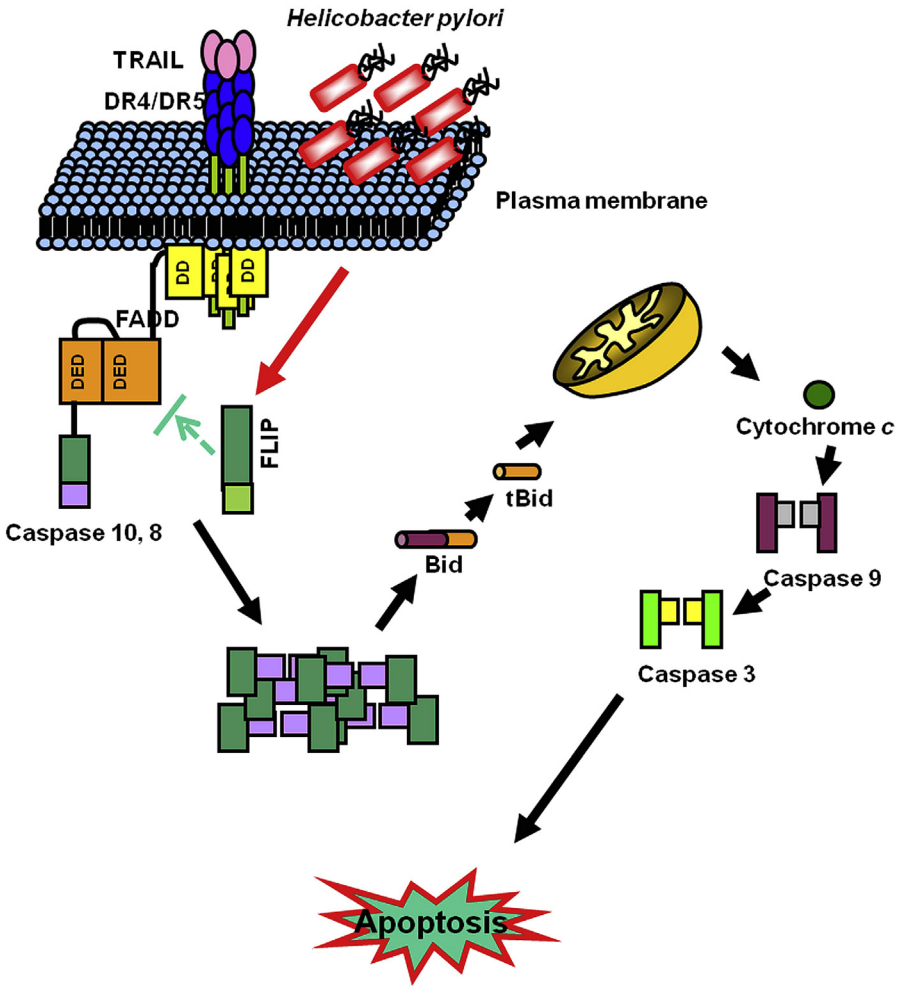

Figure 1. *Helicobacter pylori* modulates TRAIL-mediated apoptosis in gastric epithelial cells. *H. pylori* enhances assembly of TRAIL death inducing signaling complex (DISC) through downregulation of FLIP after TRAIL engagement, to activate caspase 8 cleavage, and to convey the death signal to mitochondria via cleavage of Bid, leading to activation of mitochondrial pathway and breaking the apoptosis resistance. DED = death effector domain; DD = death domain; DR4 = death receptor 4; DR5 = death receptor 5; FADD = Fas-associated death-domain protein; FLIP = FLICE-inhibitory protein; TRAIL = tumor necrosis factor-related apoptosis-inducing ligand.

binding to death receptors, TRAIL can directly stimulate T cells by binding to TRAIL receptors and transducing a reverse signal to T cells in conjunction with T cell receptor engagement, resulting in T cell proliferation and augmenting IFN-γ secretion.[33–35] Therefore, these results support a functional role of TRAIL in *H. pylori*-induced apoptosis. Moreover, the degree of apoptosis during *H. pylori* infection may also be linked to the associated inflammatory response. Therefore, in addition to *H. pylori* virulence, mucosal damage may also be affected by the inflammatory response induced by *H. pylori* within the gastric epithelium.

Inflammation of the gastric mucosa develops in response to host immune reaction against pathogens. The stimulation of epithelial cells by *H. pylori* contributes to neutrophil and lymphocyte recruitment. As described, the features of *H. pylori*-induced inflammatory immune response are orchestrated by sequential elaboration of proinflammatory cytokines, including interleukin (IL)-10, IFN-γ, TNF- α, and IL-1β. Accordingly, factors involved in regulating cytokine responses may confer susceptibility to or protection against *H. pylori*—associated diseases. These results indicate that immune reaction and inflammation mediators associated with *H. pylori* plays an important role in the pathogenesis of *H. pylori*-associated diseases. Among T cells responding to *H. pylori* infection, gastric-infiltrating T cells are mostly $CD45RO^{+}CD69^{+}CD4^{+}$T cells, indicating an accumulation of activated memory $CD4^{+}$ T cells during *Helicobacter* infection.[14] Recent reports indicated that Th1 and Th17 responses were induced during *H. pylori* infection,[11,14,32] and that levels of IFN-γ and TNF-α increased in the gastric mucosa during *H. pylori* infection, augmenting *H. pylori*-induced apoptosis.[5,6,10] These results suggest a role for immune-mediated apoptosis in gastric epithelial cells by infiltrating T cells during *Helicobacter* infection. However, the induction of immune responses and the immunopathogenic mechanism(s) of mucosal inflammation during *H. pylori* infections remain unclear, with chemokines thought to play an important role in this process.[36,37] Chemokines are involved in acute and chronic inflammatory processes by attracting neutrophils, monocytes, and T cells to the site of inflammation via

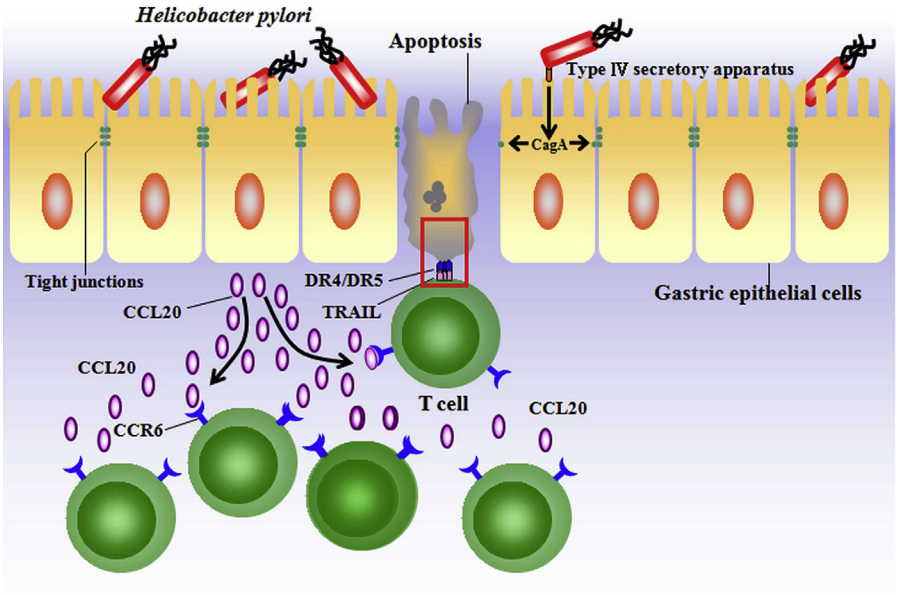

Figure 2. Immune pathogenesis of gastric mucosa damage in *Helicobacter pylori* infection. In the absence of *H. pylori* infection, there are very few infiltrating T cells recruited into the gastric mucosa. When T cells interact with human gastric epithelial cells in the presence of *H. pylori* infection, there are increased CCR6+ activated T cells infiltrated into gastric mucosa via CCL20 induced by *H. pylori*. The infiltrated activated T cells are recruited into gastric mucosa via CCR6, and then induce apoptosis to gastric epithelial cells via TRAIL/TRAIL receptor interaction. CagA = cytotoxin-associated gene A; DR4 = death receptor 4; DR5 = death receptor 5; TRAIL = tumor necrosis factor-related apoptosis-inducing ligand.

their corresponding chemokine receptors.[38,39] Recent reports showed that there are specific chemokines that mediate the homing of lymphocytes in the intestines,[37,40] suggesting that some chemokines may be involved in lymphocyte trafficking in the gut. A set of proinflammatory chemokines are also involved in *H. pylori* gastritis: Gro-α, IL-8, RANTES, IFN-γ-inducible protein-10 (IP-10; CXCL10), a monokine induced by IFN-γ (MIG, CXCL11), and CCL20 (MIP-3α/LARC/exodus).[14,41,42] It was demonstrated that the gastrointestinal epithelium senses invading microorganisms and produces cytokines/chemokines that attract lymphocytes and dendritic cells to the site of inflammation.[43] Recently, it was reported that CCR6 mediates dendritic cell localization, lymphocyte homeostasis, and immune responses in mucosal tissue.[44] CCR6, a specific β-chemokine receptor for CCL20, is selectively expressed on dendritic cells and some memory T cells,[43,45,46] and may play a role in chemokine-mediated lymphocyte trafficking during gastric inflammation. Additionally, CCL20, the ligand of CCR6, is abundantly expressed in mouse and human inflammatory enteric mucosa,[47] and CCL20 production was upregulated in response to *H. pylori* in gastric epithelial cells when there was stimulation by the proinflammatory cytokines IL-1β and TNF-α.[14,48–50] These results implicated the interaction between CCL20 and CCR6 in recruiting $CD45RO^{+}$ memory T cells to sites of inflammation in the gastric mucosa during *Helicobacter* infection (Figure 2).[14]

Conclusion

Human gastric epithelial cells sensitized to *H. pylori* confer susceptibility to TRAIL-mediated apoptosis, and the induction of TRAIL sensitivity by *H. pylori* is dependent upon the activation of caspase-8 and its downstream pathway via enhanced assembly of the TRAIL DISC through down-regulation of cellular FLIP. The degree of mucosal damage is also affected by the inflammatory response induced by *H. pylori* within the gastric epithelium. These results suggest a role for immune-mediated apoptosis and mucosa damage by infiltrating T cells during *Helicobacter* infection. In conclusion, *H. pylori* enhances susceptibility of gastric epithelial cells to TRAIL-mediated apoptosis via modulation of death-receptor signaling. Modulation of host-cell apoptosis by bacterial interaction adds a new dimension to the immune pathogenesis associated with chronic *Helicobacter* infection.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

This work was supported by grants from the National Science Council, Taiwan (NSC98-3112-B-002-047, NSC101-2320-B-038-019-, and NSC 101-2321-B-002-008-).

References

1. Parsonnet J, Friedman GD, Vandersteen DG, Chang Y, Vogelman JH, Orentreich N, et al. *Helicobacter pylori* infection and risk of gastric carcinoma. *N Engl J Med* 1994;**325**:1127–31.
2. Peek RMJ, Blaser MJ. *Helicobacter pylori* and gastrointestinal tract adenocarcinomas. *Nat Rev Cancer* 2002;**2**:28–37.

3. Jones N, Shannon PT, Cutz E, Yeger H, Sherman PM. Increase in proliferation and apoptosis of gastric epithelial cells early in the natural history of *Helicobacter pylori* infection. *Am J Pathol* 1997;**151**:1685—703.
4. Moss S, Calam J, Agarwal B, Wang S, Holt PR. Induction of gastric epithelial apoptosis by *Helicobacter pylori*. *Gut* 1996; **38**:498—501.
5. Rudi J, Kuck D, Strand S, von Herbay A, Mariani SM, Krammer PH, et al. Involvement of the CD95 (APO-1/Fas) receptor and ligand system in *Helicobacter pylori*-induced gastric epithelial apoptosis. *J Clin Investig* 1998;**102**: 1506—14.
6. Wu YY, Tsai HF, Lin WC, Chou AH, Chen HT, Yang JC, et al. *Helicobacter pylori* enhances tumor necrosis factor-related apoptosis-inducing ligand-mediated apoptosis in human gastric epithelial cells. *World J Gastroenterol* 2004;**10**: 2334—9.
7. Tsai HF, Hsu PN. Interplay between *Helicobacter pylori* and immune cells in immune pathogenesis of gastric inflammation and mucosal pathology. *Cell Mol Immunol* 2010;**7**:255—9.
8. Fan XJ, Crowe SE, Behar S, Gunasena H, Ye G, Haeberle H, et al. The effect of class II MHC expression on adherence of *Helicobacter pylori* and induction of apoptosis in gastric epithelial cells: a mechanism for Th1 cell-mediated damage. *J Exp Med* 1998;**187**:1659—69.
9. Jones N, Day A, Jennings HA, Sherman PM. *Helicobacter pylori* induces gastric epithelial cell apoptosis in association with increased Fas receptor expression. *Infect Immun* 1999;**67**: 4237—42.
10. Wagner S, Beil W, Westermann J, Logan RPH, Bock CT, Trautwein C, et al. Regulation of epithelial cell growth by *Helicobacter pylori*: evidence for a major role of apoptosis. *Gastroenterology* 1997;**113**:1836—47.
11. Bamford KB, Fan XJ, Crowe SE, Leary JF, Gourley WK, Luthra GK, et al. Lymphocytes in the human gastric mucosa during *Helicobacter pylori* have a T helper cell 1 phenotype. *Gastroenterology* 1998;**114**:482—92.
12. Elios MM, Manghetti M, De Carli M, Costa F, Baldari CT, Burroni D, et al. T helper 1 effector cells specific for *Helicobacter pylori* in gastric antrum of patients with peptic ulcer disease. *J Immunol* 1997;**158**:962—7.
13. Karttunen R, Karttunen T, Ekre HPT, MacDonald TT. Interferon gamma and interleukin 4 secreting cells in the gastric antrum in *Helicobacter pylori* positive and negative gastritis. *Gut* 1995;**36**:341—5.
14. Wu YY, Tsai HF, Lin WC, Hsu PI, Shun CT, Wu MS, et al. Upregulation of CCL20 and recruitment of CCR6 gastric infiltrating lymphocytes in *Helicobacter pylori* gastritis. *Infect Immun* 2007;**75**:4357—63.
15. Wang J, Fan X, Lindholm C, Bennett M, O'Connoll J, Shanahan F, et al. *Helicobacter pylori* modulates lymphoepithelial cell interactions leading to epithelial cell damage through Fas/Fas ligand interactions. *Infect Immun* 2000;**68**: 4303—11.
16. Kuck D, Kolmerer B, Iking-Konert C, Krammer PH, Stremmel W, Rudi J. Vacuolating cytotoxin of *Helicobacter pylori* induces apoptosis in the human gastric epithelial cell line AGS. *Infect Immun* 2001;**69**:5080—7.
17. Le'Negrate G, Ricci V, Hofman V, Mograbi B, Hofman P, Rossi B. Epithelial intestinal cell apoptosis induced by *Helicobacter pylori* depends on expression of the cag pathogenicity Island phenotype. *Infect Immun* 2001;**69**:5001—9.
18. Asahi BM, Azuma T, Ito S, Ito Y, Suto H, Nagai Y, et al. *Helicobacter pylori* CagA protein can be tyrosine phosphorylated in gastric epithelial cells. *J Exp Med* 2000;**191**:593—602.
19. Higashi H, Tsutsumi R, Muto S, Sugiyama T, Azuma T, Asaka M, et al. SHP-2 tyrosine phosphatase as an intracellular target of *Helicobacter pylori* CagA. *Science* 2002;**295**:683—6.
20. Odenbreit S, Puls J, Sedlmaier B, Gerland E, Fischer W, Haas R. Translocation of *Helicobacter pylori* CagA into gastric epithelial cells by type IV secretion. *Science* 2000;**287**:1497—500.
21. Stein M, Rappuoli R, Covacci A. Tyrosine phosphorylation of the *Helicobacter pylori* CagA antigen after *cag*-driven host cell translocation. *Proc Natl Acad Sci USA* 2000;**97**:1263—8.
22. Griffith TS, Lynch DH. TRAIL: a molecule with multiple receptors and control mechanisms. *Curr Opin Immunol* 1998; **10**:559—63.
23. Wiley SR, Schooley K, Smolak PJ, Din WS, Huang CP, Nicholl JK, et al. Identification and characterization of a new member of the TNF family that induces apoptosis. *Immunity* 1995;**3**: 673—82.
24. Kayagaki N, Yamaguchi N, Nakayama M, Eto H, Okumura K, Yagita H. Type I interferons (IFNs) regulate tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) expression on human T cells: a novel mechanism for the antitumor effects of type I IFNs. *J Exp Med* 1999;**189**:1451—60.
25. Thomas WD, Hersey P. TNF-related apoptosis-inducing ligand (TRAIL) induces apoptosis in Fas ligand-resistant melanoma cells and mediates CD4 T cell killing of target cells. *J Immunol* 1998;**161**:2195—200.
26. Lin WC, Tsai HF, Liao HJ, Tang CH, Wu YY, Hsu PI, et al. *Helicobacter pylori* sensitizes TNF-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis in human gastric epithelial cells through regulation of FLIP. *Cell Death Dis* 2014;**6**:e1109.
27. Walczak H, Sprick MR. Biochemistry and function of the DISC. *Trends Biochem Sci* 2001;**26**:452—3.
28. Bodmer JL, Holler N, Reynard S, Vinciguerra P, Schneider P, Juo P, et al. TRAIL receptor-2 signals apoptosis through FADD and caspase-8. *Nat Cell Biol* 2000;**2**:241—3.
29. Kischkel FC, Lawrence DA, Chuntharapai A, Schow P, Kim KJ, Ashkenazi A. Apo2L/TRAIL-dependent recruitment of endogenous FADD and caspase-8 to death receptors 4 and 5. *Immunity* 2000;**12**:611—20.
30. Sprick MR, Weigand MA, Rieser E, Rauch CT, Juo P, Blenis J, et al. FADD/MORT1 and caspase-8 are recruited to TRAIL receptors 1 and 2 and are essential for apoptosis mediated by TRAIL receptor 2. *Immunity* 2000;**12**:599—609.
31. Chou AH, Tsai HF, Wu YY, Hu CY, Hwang LH, Hsu PI, et al. Hepatitis C virus core protein modulates TRAIL-mediated apoptosis by enhancing Bid cleavage and activation of mitochondria apoptosis signaling pathway. *J Immunol* 2005;**174**: 2160—6.
32. Munari F, Fassan M, Capitani N, Codolo G, Vila-Caballer M, Pizzi M, et al. Cytokine BAFF released by *Helicobacter pylori*-infected macrophages triggers the Th17 response in human chronic gastritis. *J Immunol* 2014;**193**:5584—94.
33. Chou AH, Tsai HF, Lin LL, Hsieh SL, Hsu PI, Hsu PN. Enhanced proliferation and increased IFN-gamma production in T cells by signal transduced through TNF-related apoptosis inducing ligand. *J Immunol* 2001;**167**:1347—52.
34. Tsai HF, Lai JJ, Chou AH, Wang TF, Wu CS, Hsu PN. Induction of costimulation of human CD4 T cells by tumor necrosis factor-related apoptosis-inducing ligand: possible role in T cell activation in systemic lupus erythematosus. *Arthritis Rheum* 2004; **50**:629—39.
35. Huang SC, Tsai HF, Tzeng HT, Liao HJ, Hsu PN. Lipid raft assembly and Lck recruitment in TRAIL costimulation mediates NF-κB activation and T cell proliferation. *J Immunol* 2011;**186**: 931—9.
36. Campbell J, Butcher EC. Chemokines in tissue-specific and microenvironment-specific lymphocyte homing. *Curr Opin Immunol* 2000;**12**:336—41.
37. Dwinell MB, Lugering N, Eckmann L, Kagnoff MF. Regulated production of interferon-inducible T-cell chemoattractants by human intestinal epithelial cells. *Gastroenterology* 2001;**120**: 49—59.

38. Baggiolini M. Chemokines and leukocyte traffic. *Nature* 1998; **392**:565—8.
39. Luster AD. Chemokines: chemotactic cytokines that mediate inflammation. *N Engl J Med* 1998;**338**:436—45.
40. Papadakis KA, Prehn J, Nelson V, Cheng L, Binder SW, Ponath PD, et al. The role of thymus-expressed chemokine and its receptor CCR9 on lymphocytes in the regional specialization of the mucosal immune system. *J Immunol* 2000;**165**:5069—76.
41. Wen S, Felley CP, Bouzourene H, Reimers M, Michetti P, Pan-Hammarstrom Q. Inflammatory gene profiles in gastric mucosa during *Helicobacter pylori* infection in humans1. *J Immunol* 2004;**172**:2595—606.
42. Yamaoka Y, Kita M, Kodama T, Sawai N, Tanahashi T, Kashima K, et al. Chemokines in the gastric mucosa in *Helicobacter pylori* infection. *Gut* 1998;**42**:609—17.
43. Baba M, Imai T, Nishimura M, Kakizaki M, Takagi S, Hieshima K, et al. Identification of CCR6, the specific receptor for a novel lymphocyte-directed CC chemokine LARC. *J Biol Chem* 1997; **272**:14893—901.
44. Cook DN, Prosser DM, Forster R, Zhang J, Kuklin NA, Abbondanzo SJ, et al. CCR6 mediates dendritic cell localization, lymphocyte homeostasis, and immune responses in mucosal tissue. *Immunity* 2000;**12**:495—503.
45. Greaves DR, Wang W, Dairaghi DJ, Dieu MC, Saint-Vis BD, Franz-Bacon K, et al. CCR6, a CC chemokine receptor that interacts with macrophage inflammatory protein 3a and is highly expressed in human dendritic cells. *J Exp Med* 1997;**186**: 837—42.
46. Liao F, Rabin RL, Smith CS, Sharma G, Nutman TB, Farber JM. CC-chemokine receptor 6 is expressed on diverse memory subsets of T cells and determines responsiveness to macrophage inflammatory protein 3 alpha. *J Immunol* 1999;**162**: 186—94.
47. Tanaka Y, Imai T, Baba M, Ishikawa I, Uehira M, Nomiyama H, et al. Selective expression of liver and activation-regulated chemokine (LARC) in intestinal epithelium in mice and humans. *Eur J Immunol* 1999;**29**:633—42.
48. Nishi T, Okazaki K, Kawasaki K, Fukui T, Tamaki H, Matsuura M, et al. Involvement of myeloid dendritic cells in the development of gastric secondary lymphoid follicles in *Helicobacter pylori*-infected neonatally thymectomized BALB/c mice. *Infect Immun* 2003;**71**:2153—62.
49. Tomimori K, Uema E, Teruya H, Ishikawa C, Okudaira T, Senba M, et al. *Helicobacter pylori* induces CCL20 expression. *Infect Immun* 2007;**75**:5223—32.
50. Yoshida A, Isomoto H, Hisatsune J, Nakayama M, Nakashima Y, Matsushima K, et al. Enhanced expression of CCL20 in human *Helicobacter pylori*-associated gastritis. *Clin Immunol* 2009; **130**:290—7.