Molecular and functional analysis of Helicobacter-induced gastric carcinogenesis

Original title / Originaltitel
Molekulare und funktionelle Analyse des Helicobacter-induzierten Magenadenokarzinoms

Summary / Zusammenfassung
Teilprojekt A
The role of effector and regulatory T-cell populations in the control of Helicobacter infection and the induction of preneoplastic gastric pathology
1. TLR-2-activated B-cells suppress Helicobacter-induced preneoplastic gastric immunopathology by inducing Tr-1 cells in a CD40/CD40L-dependent manner.
B cells regulate autoimmune pathologies and chronic inflammatory conditions such as autoimmune encephalomyelitis and inflammatory bowel disease. The potential counterregulatory role of B cells in balancing pathogen-specific immune responses and the associated immunopathology is less well understood owing to the lack of appropriate persistent infection models. In this paper, we show that B cells have the ability to negatively regulate adaptive immune responses to bacterial pathogens. Using mouse models of infection with Helicobacter felis, a close relative of the human gastrointestinal pathogen H. pylori, we found that B cells activated by Helicobacter TLR-2 ligands induce IL-10–producing CD4+CD25+ T regulatory-1 (Treg-1)–like cells in vitro and in vivo. Treg-1 conversion depends on TCR signaling and a direct T-/B-interaction through CD40/CD40L and CD80/CD28. B cell-induced Treg-1 cells acquire suppressive activity in vitro and suppress excessive gastric Helicobacter-associated immunopathology in vivo. Adoptive cotransfer of MyD88-proficient B cells and Treg-1 cells restores a normal gastric mucosal architecture in MyD88-/- and IL-10-/- mice in a manner that depends on T cellular, but not B cellular, IL-10 production. Our findings describe a novel mechanism of B cell-dependent Treg-1 cell generation and function in a clinically relevant disease model. In conclusion, we demonstrate that the B cell/Treg-1 cell axis is essential for balancing the control of Helicobacter infection with the prevention of excessive Th1-driven gastric immunopathology, promoting gastric mucosal homeostasis on the one hand and facilitating Helicobacter persistence on the other. Sayi et al., Journal of Immunology 2011.
MicroRNAs govern immune responses to infectious agents, allergens, and autoantigens and function by posttranscriptional repression of their target genes. In this paper, we have addressed the role of microRNA-155 (miR-155) in the control of Helicobacter pylori infection of the gastrointestinal tract and the development of H. pylori-induced chronic gastritis and associated gastric preneoplastic pathology. We show that miR-155 is upregulated in the gastric mucosa of experimentally infected mice and that miR-155-/- mice fail to control H. pylori infection as a result of impaired pathogen-specific Th1 and Th17 responses. miR-155-/- mice are also less well protected against challenge infection after H. pylori-specific vaccination than their wild-type (wt) counterparts. As a consequence of their impaired T cell responses to H. pylori, miR-155-/- mice develop less severe infection-induced immunopathology manifesting as chronic atrophic gastritis, epithelial hyperplasia, and intestinal metaplasia. T cells from miR-155-/- mice that are activated by CD3/CD28 cross-linking expand less and produce less IFN-g and IL-17 than wt T cells. Finally, we show in this paper using adoptive transfers that the phenotypes of miR-155/2 mice are likely due to T cell-intrinsic defects. In contrast to wt T cells, miR-155-/- T cells from infected donors do...
not control H. pylori infections in T cell-deficient recipients, do not differentiate into Th1 or Th17 cells, and do not cause immunopathology. In addition, naive miR-155-/- T cells fail to induce chronic Th17-driven colitis in an adoptive transfer model. In conclusion, miR-155 expression is required for the Th17/Th1 differentiation that underlies immunity to H. pylori infection on the one hand and infection-associated immunopathology on the other. Oertli, Engler et al, Journal of Immunology, 2011.

Teilprojekt B
Characterization of the mechanisms of tolerance induction and maintenance
1. Tolerance rather than immunity protects from Helicobacter pylori -induced gastric preneoplasia
Chronic infection with the bacterial pathogen Helicobacter pylori causes gastric disorders ranging from chronic gastritis and gastro-duodenal ulcers to adenocarcinoma. Only a subset of infected individuals will develop overt disease; the large majority remains asymptomatic despite lifelong high-level colonization. This study aims to mechanistically elucidate the differential susceptibility to H. pylori that is found both across and within populations. We have established a C57BL/6 mouse model of H. pylori infection with a strain that is capable of delivering the virulence factor CagA into host cells through the activity of a Cag-pathogenicity island-encoded type IV secretion system. Mice infected at 5-6 weeks of age with CagA+ H. pylori rapidly develop gastritis, gastric atrophy, epithelial hyperplasia and intestinal metaplasia in a type IV secretion system-dependent manner. In contrast, mice infected during the neonatal period with the same strain are protected from preneoplastic lesions. Their protection is due to the development of H. pylori-specific peripheral immunological tolerance, which requires TGF-β signaling and is mediated by long-lived, inducible regulatory T-cells, and which efficiently controls the local CD4+ T-cell responses that trigger premalignant transformation. Tolerance to H. pylori develops in the neonatal period due to a strongly biased Treg to T-effector cell ratio, and is favoured by prolonged low-dose exposure to antigen. Using a novel CagA+ H. pylori infection model, we report here that the development and maintenance of tolerance to H. pylori protects from gastric cancer precursor lesions. The age at initial infection may thus account for the differential susceptibility of infected individuals to H. pylori-associated disease manifestations. Arnold et al., Gastroenterology 2011.

2. The C-terminally encoded, MHC class II-restricted T-cell antigenicity of the Helicobacter pylori virulence factor CagA promotes gastric preneoplasia
Chronic infection with the human bacterial pathogen Helicobacter pylori causes gastritis and predisposes carriers to an elevated gastric cancer risk. Consequently, H. pylori-specific vaccination is widely viewed as a promising strategy of gastric cancer prevention. H. pylori strains harboring the Cag pathogenicity island (PAI) are associated with particularly unfavorable disease outcomes and are often responsible for chronic infection with high-level colonization. We show here using a C57BL/6 mouse model of Cag-A-positive H. pylori infection that the development and maintenance of CagA-specific peripheral tolerance is critical for the prevention of Helicobacter-induced gastritis and preneoplasia. Tolerance to CagA is mediated by the development of CagA-specific regulatory T-cells, which are induced by TLR-2 activation of B-cells. Using a novel infection model, we report here that the age at initial infection may thus account for the differential susceptibility of infected individuals to H. pylori-associated disease manifestations.

Publications / Publikationen
Original Articles
Arnold, I.C., Dehzad, N., Reuter, S., Martin, H., Becher, B., Taube, C. and Müller, A. Neonatal


Hitzler, I., Sayi, A., Kohler, E., Engler, D.B., Koch, K.N., Hardt, W.-D. and Müller, A. Caspase-1 has both pro-inflammatory and regulatory properties in Helicobacter infections, which are differentially mediated by its substrates IL-1β and IL-18. In press, Journal of Immunology.

Reviews


Keywords / Suchbegriffe

Helicobacter pylori, gastric cancer, gastritis, immune tolerance, regulatory T-cells

Project Leadership and Contacts / Projektleitung und Kontakte

Prof. Dr. Anne Müller, PhD (Project Leader)  mueller@imcr.uzh.ch

Funding Source(s) / Unterstützt durch

SNF (Personen- und Projektförderung)

In Collaboration with / In Zusammenarbeit mit

Prof. Dr. Christian Taube  Netherlands

Prof. Dr. Marianne Quiding-Järbrink  Sweden

Duration of Project / Projektdauer

Nov 2009 to Oct 2012