compensatory regeneration, components of the HCV genome, such as the HCV core protein, may have a direct effect on tumorigenesis, possibly by activating a variety of growth-promoting signal transduction pathways.

Helicobacter pylori

First incriminated as a cause of peptic ulcers, *H. pylori* now has acquired the dubious distinction of being the first bacterium classified as a carcinogen. Indeed, *H. pylori* infection is implicated in the genesis of both gastric adenocarcinomas and gastric lymphomas.

The scenario for the development of gastric adenocarcinoma is similar to that of HBV- and HCV-induced liver cancer, as it involves increased epithelial cell proliferation in a background of chronic inflammation. As in viral hepatitis, the inflammatory milieu contains numerous genotoxic agents, such as reactive oxygen species. There is an initial development of chronic gastritis, followed by gastric atrophy, intestinal metaplasia of the lining cells, dysplasia, and cancer. This sequence takes decades to complete and occurs in only 3% of infected patients. Like HBV and HCV, the *H. pylori* genome also contains genes directly implicated in oncogenesis. Strains associated with gastric adenocarcinoma have been shown to contain a "pathogenicity island" that contains cytotoxin-associated A (*CagA*) gene. Although *H. pylori* is noninvasive, *CagA* penetrates into gastric epithelial cells, where it has a variety of effects, including the initiation of a signaling cascade that mimics unregulated growth factor stimulation.

As mentioned earlier, *H. pylori* is associated with an increased risk for the development of gastric lymphomas as well. The gastric lymphomas are of B-cell origin, and because the tumors recapitulate some of the features of normal Peyer's patches, they are often called lymphomas of mucosa-associated lymphoid tissue, or MALTomas (also discussed in Chapters 13 and 17). Their molecular pathogenesis is incompletely understood but seems to involve strain-specific *H. pylori* factors, as well as host genetic factors, such as polymorphisms in the promoters of inflammatory cytokines such as IL-1β and tumor necrosis factor (TNF). It is thought that *H. pylori* infection leads to the appearance of *H. pylori*-reactive T cells, which in turn stimulate a polyclonal B-cell proliferation. In chronic infections, currently unknown mutations may be acquired that give individual cells a growth advantage. These cells grow out into a monoclonal "MALToma" that nevertheless remains dependent on T-cell stimulation of B-cell pathways that activate the transcription factor NF-κB. At this stage, eradication of *H. pylori* by antibiotic therapy "cures" the lymphoma by removing the antigenic stimulus for T cells. At later stages, however, additional mutations may be acquired that cause constitutive NF-κB activation. At this point, the MALToma no longer requires the antigenic stimulus of the bacterium for growth and survival and develops the capacity to spread beyond the stomach to other tissues.

KEY CONCEPTS

Viral and Bacterial Oncogenesis

HTLV-1: a retrovirus that is endemic in Japan, the Caribbean, and parts of South America and Africa that causes adult T-cell leukemia/lymphoma

- HTLV-1 encodes the viral protein Tax, which turns on pro-growth and pro-survival signaling pathways (PI3K/AKT, NF-κB), leading to a polyclonal expansion of T cells.
- After a long latent period (decades), a small fraction of HTLV-1–infected individuals develop adult T-cell leukemia/lymphoma, a CD4+ tumor that arises from an HTLV-1 infected cell, presumably due to acquisition of additional mutations in the host cell genome.

HPV: an important cause of benign warts, cervical cancer, and oropharyngeal cancer

- Oncogenic types of HPV encode two viral oncoproteins, E6 and E7, that bind to Rb and p53, respectively, with high affinity and neutralize their function.
- Development of cancer is associated with integration of HPV into the host genome and additional mutations needed for acquisition of cancer hallmarks.
- HPV cancers can be prevented by vaccination against high-risk HPV types.

EBV: ubiquitous herpesvirus implicated in the pathogenesis of Burkitt lymphomas, B-cell lymphomas in patients with T-cell immunosuppression (HIV infection, transplant recipients), and several other cancers

- The EBV genome harbors several genes encoding proteins that trigger B cell signaling pathways; in concert, these signals are potent inducers of B cell growth and transformation.
- In the absence of T-cell immunity, EBV-infected B cells can rapidly "grow out" as aggressive B-cell tumors.
- In the presence of normal T-cell immunity, a small fraction of infected patients develop EBV-positive B-cell tumors (Burkitt lymphoma, Hodgkin lymphoma) or carcinomas (nasopharyngeal, gastric carcinoma)

Hepatitis B virus and hepatitis C virus: cause of between 70% and 85% of hepatocellular carcinomas worldwide

- Oncogenic effects are multifactorial; dominant effect seems to be immunologically mediated chronic inflammation, hepatocellular injury, and reparative hepatocyte proliferation.
- HBx protein of HBV and the HCV core protein can activate signal transduction pathways that also may contribute to carcinogenesis.

H. pylori: implicated in gastric adenocarcinoma and MALT lymphoma

- Pathogenesis of *H. pylori*-induced gastric cancers is multifactorial, including chronic inflammation and reparative gastric cell proliferation.
- *H. pylori* pathogenicity genes, such as *CagA,* also may contribute by stimulating growth factor pathways.
- Chronic *H. pylori* infection leads to polyclonal B-cell proliferations that may give rise to a monoclonal B-cell tumor (MALT lymphoma) of the stomach as a result of accumulation of mutations.

Clinical Aspects of Neoplasia

Ultimately the importance of neoplasms lies in their effects on patients. Although malignant tumors are of course