CANCER MORTALITY AND PATHOGENS

- 15% of cancer can be attributed to infections and 75% are observed in developing countries (Pisani et al., 1997; Kuper et al., 2000; Raoult D., 2005)
- In France (1998-2002) (invs, 2006)
  - Total number of cancers = 143970
  - Cancer due or associated to pathogens = 18876 (HBV, HCV, HPV, HHV8, EBV, H. pylory) 13.11%(w/o skin, oesophagus, colon, H&N, ATL)

PATHOGENS

- 10^{14} microbes at our mucosals surfaces (commensal and potential pathogen)
- Chronic inflammation are potentially compounded by metabolic alterations and malignant transformation ie chronic gastritis, hepatitis, or colitis and increased risk of primary carcinoma (Kuper et al. 2000)
- Only rarely have specific microbial pathogens been identified as critical and universal causes of a particular chronic inflammation or malignancy
- Other mechanisms rely on persistence (bacteria and viruses) or latency (viruses)

IMMUNE SYSTEM AND PATHOGEN

- Pathogenic microorganisms induce the dramatic activation of both innate and adaptive immunity
- Usually, the adaptive immune system clears the invading offender
- But some pathogen can maintain infection even in presence of strong inflammation and adaptive immune response and persist (bacteria such as M. tuberculosis; viruses such as HCV) or become latent(viruses)

PROTOTYPIC EXAMPLES

- **Bacteria**

  - Gastric carcinomas are due in 50 to 70% of the cases to H. pylori. This bacteria infects 50% of the populations and induces diseases in 10% and cancer in 1%

PROTOTYPIC EXAMPLES

- **Viruses**
  - Most if not all cervical cancer are due to oncogenic HPV. They are due to the transformation mediated by the E6 and E7 proteins which alter cell cycle regulation
  - Hepatitis , fibrosis, cirrhosis and hepatocellular carcinoma are complications of persistent HBV and HCV infections. 50 to 70% of HCC are due to these viruses.

Chronic inflammatory situations associated with neoplasms (adapted from Coossens et Werb, 2002)

PATHOLOGY	NEOPLASM	AETIOLOGIC AGENT
Opisthorchis, Cholangitis	Cholangiosarcoma, colon carcinoma	Liver flukes (Opisthorchis viverrini), bile acids
Chronic cholecystitis	Gall bladder cancer	Bacteria, gall bladder stones
Gastritis/ulcers	Gastric adenocarcinoma, MALT	Helicobacter pylori
Osteomyelitis	Skin carcinoma in draining sinuses	Bacterial infection
Typhoid fever	Hepatobiliary cancer	Salmonella enterica serovar Typhi
Chronic cystitis	Bladder, liver, rectal carcinoma, follicular lymphoma of the spleen	Schistosomiasis

Chronic inflammatory situations associated with neoplasms (adapted from Coossens et Werb, 2002)

PATHOLOGY	NEOPLASM	AETIOLOGIC AGENT
Hepatitis	Hepatocellular carcinoma	Hepatitis B and /or C virus
Tropical spastic paraparesia	ATL	HTLV1
Pelvic inflammatory disease, chronic cervicitis	Ovarian carcinoma, cervical/anal carcinoma	Gonnorhea, chlamydia, HPV
Mononucleosis	B -cell non-Hodgkin's lymphoma, Burkitt lymphoma	Epstein-Barr virus
AIDS	Non-Hodgkin's lymphoma, Squamous cell carcinomas Kaposi sarcoma	HIV, HHV8, HPV, EBV

ADAPTIVE IMMUNE RESPONSE AGAINST PATHOGENS

- Inflammation will shape the adaptive immune response via DC-maturation and migration first to inflamed tissues then to lymphoid organs
- Vigourous T and B cell responses will heal in most instances the viral infection (EBV, CMV) but other viruses may escape (HCV, HIV)
- The effector immune response will be turned off and followed by a persistent T and B memory status
- However, a chronic inflammation may persist. This status is mostly associated with lymphocyte responses
- Lymphocytes in persistent inflammation have an altered functional status (apoptosis, activation markers, altered functions, absence of CD45RA reexpression, overexpression of inhibitory receptors such as PD-1 and cytokines such as IL-10)

Resolution of inflammation

- Resolution of inflammation mediated by cytokines (IL-10 and TGFβ) and lipid mediators.
- Numerous inhibitory receptors are present on macrophages that are regulated by apoptotic cells (CD36, αvβ5integrin, C1q, phosphatydilserine receptor, Mer tyrosine kinase, Axl and Tyro3) , CD200L (CD200) , macrophage stimulating protein (RON)
- Presence of T memory cell and clearence of pathogen

GENETIC HOST FACTORS INVOLVED IN PERSISTENT INFLAMMATION

- TNF and IL-1a (gastric carcinoma and H. pylory; Peek et Blaser, 2002)
- TLR 1, 6 and 10 (prostate cancer; Sun et al, 2005)
- IL-10 ko mice develop inflammatory bowel disease and colorectal cancer (Kuhn et al, 1993)
- NOD mutations

PATHOGENS, INFLAMMATION AND CANCER INITIATION AND PROMOTION

- cancers develop from "subthreshold neoplastic states" caused by viral or chemical carcinogens (Initiation, Peyton Rous).
- Initiation, involves DNA alterations, is irreversible and can persist in otherwise normal tissue indefinitely until the occurrence of « Promotion ».
- Promotion can result from exposure of initiated cells to
  - chemical irritants,
  - factors released at the site of wounding,
  - partial organ resection,
  - hormones or
  - chronic irritation and inflammation

CANCER AND INFLAMMATION

- Persistent infections within the host induce chronic inflammation.
- Leukocytes induce DNA damage in proliferating cells (reactive oxygen and nitrogen species).
- These species react to form peroxynitrite, a mutagenic agent.
- Repeated tissue damage and regeneration of tissue induces with DNA alterations such as point mutations, deletions, or rearrangements.
- p53 mutations are seen at frequencies similar to those in tumours in chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease.

WHY DO ONLY A SUBSET OF INFECTED SUBJECTS DEVELOP CANCER?

- While many types of infectious agents are highly prevalent in individuals, only a subset develop associated malignancies and usually after a prolonged latency.
- This may reflect
  - immune suppression and /or dysregulation of the immune response such as chronic inflammation,
  - the necessity of cofactors necessary for promotion or
  - the fact that a neoplasm can develop only if viral infection has targeted a pluripotent progenitor or stem cell (see HPV). Consequently, tumours that develop as a result of infectious agents are almost always monoclonal.

WHY DO ONLY A SUBSET OF INFECTED SUBJECTS DEVELOP CANCER?

- In Rous sarcoma virus infections, inflammation is essential for tumour development and this requirement is mediated by factors such as TGF-beta and inflammatory cytokines.

- Epstein-Barr virus also causes sustained proliferation of B lymphocytes, which, when coupled with a secondary mutation, can result in neoplastic progression and malignant conversion to give rise to Burkitt's lymphoma.

ACQUIRED IMMUNOSUPPRESSION AND CANCER

- TRANSPLANTATION
- AID

INCIDENCE OF CANCER IN IMMUNOSUPPRESSED INDIVIDUALS

- Incidence of cancer in patients transplanted (110395 person/ year Buell et al., 2005)
  - Kaposi 26.44 (Adjusted Relative risk)
  - Liver 4.78
  - Cervix 6.60
  - Vulva 45.60
  - Perinea 36.02
  - Penis and other genital organs 17.81
  - NHL 10.16
  - Cutaneous cancers not evaluated in this study but found in more than 30% of patients

HIV AND CANCER

- KAPOSI SARCOMA
- NHL
- CERVICAL CANCER

- The course of cancer in immunocompromised hosts is generally very aggressive, even though risk factors remain unchanged.

HIV AND CANCER (CDC, Patel et al 2006)

- 59,101 individuals were followed in USA from 1992 to 2002
- Relative risks of three different AIDS-associated malignancies
  - KS (353.7)
  - NHL (28.7)
  - cervical cancer (17)

HIV AND CANCER (Patel et al 2006)

- Seven different non-AIDS-associated malignancies were also higher among HIV-infected individuals:
  - anal cancer (18.3),
  - Hodgkin's disease (17.5),
  - liver cancer (4.5),
  - testicular cancer (3.3),
  - melanoma (2.1),
  - oropharyngeal cancer (2.0)
  - lung cancer (1.6)

- In contrast, the rates of both breast cancer and prostate cancer seemed to be reduced among HIV-infected individuals, while no differences in the rates of renal and colorectal cancer were observed between the two populations.

ESCAPE MECHANISMS AND ADAPTIVE IMMUNITY AGAINST HIV AND HCV

PATHOGENS' STRATEGIES TO EVADE OF SUBVERT IMMUNE ATTACK

- HPV
- HHV8 disappeance of anti-HHV8 effector T cells
- HCV
- H. pylory

HPV' STRATEGIES TO EVADE OF SUBVERT IMMUNE ATTACK

- Low antigen load, non secreted proteins, no viremia, no cytopathic effect
- Inhibition of immune system (E7 binds IRF3, E6 inhibits Jak-Stat activation, E6 inhibits IL-18, E5 inhibits MHC class II maturation)
- Decreased APC numbers in the tissues
- Decreased Th1 and increased Treg

Helicobacter pylori STRATEGIES TO EVADE OR SUBVERT IMMUNE ATTACK

- Evasion of innate responses
  - Prevention of NO production by inducing argianse production
  - Inhibition of phagocytosis
- Evasion to adaptive immunity
  - VacA secreted protein inhibits Ca mobilization and calcineurin activity
  - VacA inhibits peptide processing by converting the late endosomal compartment to large acidic vacuoles
- Inflammatory responses
  - H. pylory LPS and flagellin have reduced potential to activate TLR4 and TLR5 (depends on Cag pathogenicity island)

PREVENTION OF PATHOGENS' ASSOCIATED CANCERS

- VACCINATION (HBV, HPV)
- PATHOGEN SCREEN IN INJECTED AND TRANSPLANTED PRODUCTS
- STERILISATION
- PREVENTION (STI)
- FOOD PATHOGEN CONTROL
- SCREENING OF PATIENTS WITH HIV AND UNDERGOING IMMUNOSUPRESSION