Multi-step Tumorigenesis

In the survival of favoured individuals and races, during the constantly-recurring struggle for existence, we see a powerful and ever-acting form of selection.

Charles Darwin
1859

Does cancer progression proceed like Darwinian evolution and selection?

What is the evidence for multi-step carcinogenesis?

What drive the progression of cancer?

How many independent steps are needed to Develop a cancer?

Cooperative and complementary oncogenes in cell transformation and cancer development
Cancer Stem cells

Tumor initiator and tumor promoter

Genetic and epigenetic changes

Diversity of cancer cells genomes

Inflammation and cancer

Epidemiological evidence for multi-step, time limiting carcinogenesis
Age dependent increase of cancer incidence

Discussion: Does this phenomenon indicate
1) requirement of age-dependent time limiting events or
2) age-related susceptibility to cancer occurrence?

Number of events needed for developing a cancer

Figure 11.3  The Biology of Cancer (© Garland Science 2007)
Fact: cancer death rate = (age of diagnosis)^5

Conclusions:

cancer occurrence requires 5 + 1 independent time limiting events.

Each event needs 10 – 15 years.
Cigarettes smoking and lung cancer

About 35 years lag between marked increase of cigarettes smoking and the onset of large number of lung cancer. Why?

Histopathological evidence for progressive cancer development
Intestinal adenoma and adjacent carcinoma

Evidence 1: Continuous adenoma to carcinoma transition
Evidence 2: Polypectomy reduces colon cancer

Histopathological alterations of the human colon

Figure 11.8a The Biology of Cancer (© Garland Science 2007)
A good example of histopathological progression of cancer

FAP (Familial adenomatous polyposis)
Apc mutation

Apc mutation increases polyps and risk of colon cancer

Polypectomy reduces colorectal cancer

Figure 11.8b The Biology of Cancer (© Garland Science 2007)
Familial adenomatous polyposis (FAP)

Apc+/Apc-

Wnt/beta-catenin signaling
**Apc in beta-catenin signaling**

- Wnt
- Frizzled
- Dishevelled
- axin
- GSK-3β
- β-catenin
- nuclear membrane
- Tcf/Lef

**Time scale of multi-step tumorigenesis of tumors at various sites**

<table>
<thead>
<tr>
<th>Site</th>
<th>NORMAL</th>
<th>INITIATED</th>
<th>PRE-CANCER</th>
<th>CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>5–20 years</td>
<td>adenoma</td>
<td>5–15 years</td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>tobacco use 4–10 years</td>
<td>dysplastic oral leukoplakia</td>
<td>6–8 years</td>
<td></td>
</tr>
<tr>
<td>Cervix</td>
<td>CIN 1 9–13 years</td>
<td>CIN 3/CIS</td>
<td>10–20 years</td>
<td></td>
</tr>
<tr>
<td>Lung (smokers)</td>
<td>20–40 pack-years</td>
<td>DCIS 6–10 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>atypical hyperplasia</td>
<td>PIN 3–15 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>20 years</td>
<td>PIN ≥10 years</td>
<td>latent cancer</td>
<td></td>
</tr>
</tbody>
</table>

**Definitions:**
- CIN: Cervical intraepithelial neoplasia
- DCIS: Ductal carcinoma in situ
- PIN: Prostatic intraepithelial neoplasia
What is the driving force for cancer progression?

The need for cancer cells to survive the stress from their microenvironment

What endow the cancer cells the ability to evolve and prevail?

The genetic and epigenetic changes that enable cancer cells to survive and growth

Result: Darwinian evolution and selection

Colon tumor progression and LOH in various chromosome

5q21 = Apc

17p13 = p53

Bert Vogelstein (Johns Hopkins Univ): genomic analysis of different stages of colon cancer

Figure 11.9  The Biology of Cancer (© Garland Science 2007)
Tumor suppressor genes and oncogenes in colon carcinoma progression

**Figure 11.10** The Biology of Cancer (© Garland Science 2007)

![Diagram showing tumor suppressor genes and oncogenes in colon carcinoma progression]

- **Unknown gene**
- **17p13**

- 90%
- 40-50%
- 60%
- 50-70%

15% probability for this exact pathway
meaning: many other alternative possibilities

Other genes involved in colon cancer

- Tyrosine kinase genes: 15%
- PI3 kinase gene 110Kd subunit: 30%
- DPC4/MADH4: Smad4: 15%
- Type 2 TGFbeta receptor: 12%
- B-raf (Thr/Ser Protein kinase): often in polyps
  (mutually exclusive from ras)
Figure 11.11a  The Biology of Cancer © Garland Science 2007

Genes involved in colon cancer

90%

APC
Less variable

Genes involved in colon cancer

Variable gene mutations

TKs
B-raf
K-ras
PI3K

Gene mutation, LOH, promoter methylation

Barrett’s esophageal carcinoma

Gene mutation, LOH, promoter methylation

Figure 11.11b  The Biology of Cancer © Garland Science 2007
Darwinian evolution and clonal selection

Mutant cells population needs to reach at least one million to attain 2nd mutation

Cancer stem cells
or
Cancer initiator cells
Fluorescence-activated cell sorting (FACS)

Are all cells in a tumor biologically equivalent?

Gao et al 2001

AML: CD34 - 99%  >500,000 cells for tumor formation
    CD34+ : 1%  5,000 cells for tumor formation
Breast cancer cells

For tumor formation in NOD/SCID mice

CD24 low, CD44 high ESA +: <12%  200 cells

CD24 high, C44 high : 88% >20,000 cells
Xenograft model of human breast cancer cells transplantation

![CD24 high site and CD24 low site](image)

**Brain tumor cells**

For tumor formation

- **CD133 +**: <15% 100-1000 cells
- **CD133 -**: >80% >100,000 cells
CD133+ Dark red

Suspension culture

$\text{CD133}^{\text{low}}$: $10^5$ cells $\rightarrow$ no tumors
$\text{CD133}^{\text{high}}$: $10^2$–$10^3$ cells $\rightarrow$ tumors

stem cells

OR

post-mitotic differentiated cells

Figure 11.15 The Biology of Cancer (© Garland Science 2007)

Figure 11.16a The Biology of Cancer (© Garland Science 2007)
Cancer stem cells
And clonal succession
Figure 11.18 The Biology of Cancer (© Garland Science 2007)

Clonal diversification due to mutation

Figure 11.20 The Biology of Cancer (© Garland Science 2007)

Comparative genomic hybridization (CGH)

mixed probes and anneal to normal DNA

probes made from

normal DNA and tumor DNA

clones

chromosomes

normal DNA anneals, tumor DNA does not, therefore red signal

both normal DNA and tumor DNA anneal, therefore yellow signal

normal DNA anneals, tumor DNA anneals more, therefore green signal

green:red ratio copy number

deletion

amplification

distance along genome
Human breast cancer

chromos
No.8

Figure 11.21 The Biology of Cancer (© Garland Science 2007)

NSCLC FISH: chromos 11 (green), chromos 17 (pink)

Genetic diversification of tumor cells

Figure 11.19 The Biology of Cancer (© Garland Science 2007)
Body mass and life time cancer risk

Bumblebee
Bat: 1.5 g

Life span:
Approx: 2 yr

High metabolic rate
Mammalian body size and relative risk of gene mutation and cell transformation

**Blue whale:** 130 tons
Life span: 80 years
low metabolic rate

**Bat:** 1.5 g
Life span: 2 years

Risk factor for accumulating mutations of whale vs bat:

Body mass & life span: \( \frac{130 \text{ tons}}{1.5 \text{ g}} \times \frac{80}{2} = 1,000,000,000 \)

Metabolic rate: whale/bat = 1/1000
Overall risk factor of whale/bat = 1,000,000

---

**Burden of gene mutation in human**

**Human body** = \( 3 \times 10^{13} \) cells
Human life span = 80 years = 29,200 days
\( 3 \times 10^{13} / 29,200 \text{ days} = 1 \times 10^9 \text{ cells/day} \)
\( 1 \times 10^9 \text{ mitosis/} 10^{-6} \text{ mutation per mitosis} = 1 \times 10^3 \text{ mutation/day} \)

**Colon:** \( 10^{14} \) cells generated/life
\( 10^{14} / 29,200 \text{ days} = 3.3 \times 10^9 \text{ cells/day} \)
\( 3.3 \times 10^9 / 10^{-6} \text{ mutation rate} = 3.3 \times 10^3 \text{ mutations/day} \)

**Implication:** are we generating cancer cells every day?
Life time mitosis:

Mouse: $10^{11}$

Human: $10^{16}$

Cancer risk factor: human / mouse = 100,000

Cooperative and complementary oncogenes

• Normal cells are quite resistant to transformation.

• Transformation of normal cells usually requires collaboration of two or more complementary oncogenes
Hyperplasia, but not cancerous

β-galactosidase-positive
K-ras oncogene active

Leukemia in identical twins

<table>
<thead>
<tr>
<th>Country</th>
<th>Age at Diagnosis (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chile</td>
<td>1, 2, 3, 4, 5, 6</td>
</tr>
<tr>
<td>UK</td>
<td>2, 4, 6, 7, 9, 10</td>
</tr>
<tr>
<td>Guatemala</td>
<td>3, 8, 9, 10</td>
</tr>
<tr>
<td>Switzerland</td>
<td>6, 7, 8</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>7, 8</td>
</tr>
<tr>
<td>Japan</td>
<td>8, 9</td>
</tr>
<tr>
<td>Brazil</td>
<td>9, 10, 13</td>
</tr>
<tr>
<td>UK</td>
<td>10, 11, 13</td>
</tr>
<tr>
<td>Netherlands</td>
<td>11, 12</td>
</tr>
<tr>
<td>Brazil</td>
<td>13</td>
</tr>
<tr>
<td>UK</td>
<td>14, 15, 16, 17</td>
</tr>
<tr>
<td>Czech Rep.</td>
<td>18</td>
</tr>
<tr>
<td>Pakistan</td>
<td>19</td>
</tr>
</tbody>
</table>

- pro-B ALL/MLL
- common (pre-B) ALL
- T-ALL/NHL
- AML
- TEL/AML1 positive

Conclusion: Single genetic lesion is insufficient to cause cancer
Collaboration of two oncogenes in cell transformation

\[ \text{myc or E1A} \quad \text{myc or E1A} \quad \text{ras} \]

Tumorigenic conversion of primary embryo fibroblasts requires at least two cooperating oncogenes.

Land, Parada and Wenberg 1983 Nature

- Mitotic promoting, transformation
- Survival, anti-apoptosis, immortalization

Table 11.1 Examples of collaborating oncogenes \textit{in vitro} and \textit{in vivo}

<table>
<thead>
<tr>
<th>“ras-like” oncogene(^a)</th>
<th>“myc-like” oncogene(^a)</th>
<th>Target cell or organ</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{In vitro} transformation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>\textit{ras}</td>
<td>\textit{myc}</td>
<td>transfected rat embryo fibroblasts (REFs)</td>
</tr>
<tr>
<td>\textit{ras}</td>
<td>\textit{E1A}</td>
<td>transfected rat kidney cells</td>
</tr>
<tr>
<td>\textit{ras}</td>
<td>\textit{SV40 large T}</td>
<td>transfected REFs</td>
</tr>
<tr>
<td>\textit{Notch-1}</td>
<td>\textit{E1A}</td>
<td>transfected rat kidney cells</td>
</tr>
<tr>
<td>\textit{In vivo} tumorigenesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>\textit{middle T}</td>
<td>\textit{large T}</td>
<td>polyomavirus-induced murine tumors</td>
</tr>
<tr>
<td>\textit{mil (= raf)}</td>
<td>\textit{myc}</td>
<td>MH2 avian leukemia virus chicken tumors</td>
</tr>
<tr>
<td>\textit{erbB}</td>
<td>\textit{erbA}</td>
<td>avian erythroblastosis virus chicken tumors</td>
</tr>
<tr>
<td>\textit{pim1}</td>
<td>\textit{myc}</td>
<td>mouse leukemia virus tumors</td>
</tr>
<tr>
<td>\textit{abl}</td>
<td>\textit{myc}</td>
<td>mouse leukemia virus tumors</td>
</tr>
<tr>
<td>\textit{Notch-1/2}</td>
<td>\textit{myc}</td>
<td>thymomas in transgenic mice</td>
</tr>
<tr>
<td>\textit{bcl-2}</td>
<td>\textit{myc}</td>
<td>follicular lymphomas in transgenic mice</td>
</tr>
</tbody>
</table>

\(^a\)The terms “ras-like” and “myc-like” refer to functional classes rather than genes encoding components of a common signaling pathway. “ras-like” oncogenes tend to encode components of cytoplasmic signaling cascades, while “myc-like” oncogenes tend to encode nuclear proteins.
### Table 11.2 Physiologic mechanisms of oncogene collaboration

<table>
<thead>
<tr>
<th>Oncogene pair</th>
<th>Cell type</th>
<th>Mechanisms of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>ras + SV40 large T</td>
<td>rat Schwann cells</td>
<td>ras: proliferation + proliferation arrest. Large T: prevents proliferation arrest and reduces mitogen requirement.</td>
</tr>
<tr>
<td>ras + E1A</td>
<td>mouse embryo fibroblasts</td>
<td>ras: proliferation and senescence. E1A: prevents senescence.</td>
</tr>
<tr>
<td>erbB + erbA</td>
<td>chicken erythroblasts</td>
<td>erbB: induces GF-independent proliferation. erbA: blocks differentiation.</td>
</tr>
<tr>
<td>TGF-α + myc</td>
<td>mouse mammary epithelial cells</td>
<td>TGF-α: induces proliferation and blocks apoptosis. myc: induces proliferation and apoptosis.</td>
</tr>
<tr>
<td>v-sea + v-ski</td>
<td>avian erythroblasts</td>
<td>v-sea: induces proliferation. v-ski: blocks differentiation.</td>
</tr>
<tr>
<td>bcl-2 + myc</td>
<td>rat fibroblasts</td>
<td>bcl-2: blocks apoptosis.</td>
</tr>
<tr>
<td>raf + myc</td>
<td>chicken macrophages</td>
<td>raf: induces growth factor secretion. myc: stimulates proliferation.</td>
</tr>
<tr>
<td>src + myc</td>
<td>rat adrenocortical cells</td>
<td>src: induces anchorage and serum independence. myc: prolongs proliferation.</td>
</tr>
</tbody>
</table>

*In each pair, the first oncogene encodes a cytoplasmic oncoprotein while the second oncogene encodes a nuclear oncoprotein.*

---

### Collaboration of two Oncogenes in tumor formation

![Collaboration of two Oncogenes in tumor formation](image-url)

---

**Figure 11.24a** The Biology of Cancer (© Garland Science 2007)
Figure 11.24a part 1 of 2  The Biology of Cancer (© Garland Science 2007)

Figure 11.24a part 2 of 2  The Biology of Cancer (© Garland Science 2007)
Discussion:

The *myc* and *ras* double transgenic mice did not develop tumors soon after birth, instead, the tumors were seen with great delay.

Despite *myc* and *ras* are able to transform normal fibroblasts *in vitro*, additional mutations must be required for the tumor development *in vivo*. 
Normal cells can suppress transformation

Isolated REF (ras) cells $\rightarrow$ colony

Normal cells + REF (ras) cells $\rightarrow$ no colony

Primary human cells are particularly resistant to transformation

In vitro exp showed 5 genes or their related substitutes are needed to transform diploid human cells.
Alteration of 5 gene pathways are needed to transform diploid human cells

<table>
<thead>
<tr>
<th>pathway</th>
<th>Ras</th>
<th>pRb</th>
<th>p53</th>
<th>telomeres</th>
<th>PP2A</th>
</tr>
</thead>
<tbody>
<tr>
<td>genes/agents used to deregulate pathway</td>
<td>ras</td>
<td>CDK4 + D1</td>
<td>DN p53</td>
<td>hTERT myc + SV40 LT</td>
<td>SV40 sT sometimes: myc Akt/PI3K</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SV40 LT</td>
<td>SV40 LT</td>
<td></td>
<td>B56 shRNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HPV E7</td>
<td>HPV E6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cancer development needs initiation and promotion

Tumor initiator
&
Tumor promoter
Tumor initiation: mutation, oncogenes activation

Tumor progression: additional mutations, epigenetic changes, gene activation, suppressor gene inactivation

Tumor initiator: ex chemical carcinogens, ex benzo pyrene (BP), 3-methyl cholanthrene (3MC) dimethylbenza(a)anthracene (DMBA)

Tumor promoter: ex 12-O-tetradecanoylphorbol-13-acetate (TPA or PMA); toxin, mitogens, sex hormones, and inflammatory agents
Cancer initiation and promotion has been best learnt from mouse skin tumor model

**Induction of mouse skin tumor**

Figure 11.28  *The Biology of Cancer* (© Garland Science 2007)
Figure 11.28 part 1 of 2  The Biology of Cancer (© Garland Science 2007)

Figure 11.28 part 2 of 2  The Biology of Cancer (© Garland Science 2007)
Initiation and promotion of mouse epidermal carcinoma

Figure 11.29  The Biology of Cancer (© Garland Science 2007)
Genes and proteins involved in mouse skin carcinogenesis

Figure 11.29 part 2 of 2 The Biology of Cancer (© Garland Science 2007)

Figure 11.30 The Biology of Cancer (© Garland Science 2007)
Mechanism of TPA-mediated molecular signaling

Cellular toxin could be a cancer promoter
Kostmann syndrome: mutant neutrophils specific elastase $\rightarrow$ neutropenia

Endogenous sex hormones could function as cancer promoter
Sex hormone as tumor promoter

LH (international units/ml)

FSH (international units/ml)

Progesterone (ng/ml)

 Estradiol (pg/ml)

Figure 11.33a  The Biology of Cancer (© Garland Science 2007)

% of cells incorporating 3H-thymidine

Natural

OC user

Figure 11.33b  The Biology of Cancer (© Garland Science 2007)
Effect of estrogen exposure on breast cancer

• Increase menstrual cycles per life increases risk.
• 20% decrease in risk per year of delay in menarche
• Earlier menopause in identical twins decreases risk.
• Menopause before age 36 decreases risk by 90%
• Postmenopause women with breast cancer have 15% higher estrogen.

Mitogenic agents could be tumor promoter by increasing proliferation of initiated cells and further mutation of cancer cooperating gene(s).
Chronic inflammation often serves to promote tumor progression.

TGFbeta1-/-, Rag2-/- mouse intestine

Mice kept in germ free condition
TGFbeta1-/-, Rag2-/- mouse intestine

infected with \textit{Helicobacter hepaticus}

Figure 11.34b  The Biology of Cancer (© Garland Science 2007)

Human ulcerative colitis→ chronic inflammation→ colon cancer

Lymphocyte infiltration

Figure 11.34c  The Biology of Cancer (© Garland Science 2007)
Gallbladder carcinoma associated with gallstones causing chronic inflammation
Control Keratin 5-PKC alpha

TPA treatment resulted in neutrophil infiltration in PKC transgenic mouse skin

Mdr-/- transgenic → increase bile acid → chronic liver inflammation → dysplastic

Mdr: multi-drug resistant gene

Anti-inflamm drug

Figure 11.36, Figure 11.37a: The Biology of Cancer (© Garland Science 2007)
TNF alpha knockdown displayed only 5 to 10% tumor compared to DMBA plus TPA treated mice.

Chronic liver inflammation acts via TNFalpha and NF-kBeta to cause HCC

- Loss of Mdr function
- Chronic liver inflammation by bile
- Recruitment of inflammatory cells into liver stroma
- Release of TNF-α by inflammatory cells and endothelial cells

TNF-α

Anti-TNF-α antibody

STROMA

TNF receptor of hepatocytes

IKK

NF-κB:IkB

NF-κB

NF-κB

TNF-α (more inflammation)

Cyclin D1, Myc (mitogenesis)

Anti-apoptotic genes

Dysplastic hepatocyte nodules

Hepatocellular carcinoma

Figure 11.37b  The Biology of Cancer (© Garland Science 2007)
Anti-inflammatory such as aspirin and sulindac reduce cancer rate

Aspirin studies:
Aspirin use for 15 years: decreases lung, colon and breast cancer

Aspirin use for 7 years: decreases pancreatic cancer

Aspirin use resulted in 40% reduction of stomach cancer in individuals infected with \textit{H pylori}, but not in the uninfected individuals.

Aspirin binds to and inhibits COX2, and thus reduces inflammation.

However, aspirin could cause gastrointestinal side effect including bleeding.

Cox2, an inflammatory molecule, is an important anti-cancer target
Cox2

Figure 11.38a  The Biology of Cancer (© Garland Science 2007)

Figure 11.38b  The Biology of Cancer (© Garland Science 2007)
mT transgenic mammary carcinoma

**TUNEL assay (apoptosis)**

- **solvent control**
- **5 mg/kg celecoxib** (Cox2 inhibitor)
- **10 mg/kg celecoxib**
- **20 mg/kg celecoxib**
PCNA staining (proliferation)

solvent control

5 mg/kg celecoxib

10 mg/kg celecoxib

20 mg/kg celecoxib

Human colon hyperplastic polyp immuno stained for COX2
COX2 staining in more advanced polyps

Figure 11.40b  The Biology of Cancer (© Garland Science 2007)

Apc⁻/⁻ mouse polyps immunostaining; cytokeratin(blue) epithelial; Vimentin (green) stroma; COX2 (yellow)

Figure 11.40c  The Biology of Cancer (© Garland Science 2007)
Epithelial cells, not the stroma, stained + for COX2

Apc-/- transgenic

solvent control

prostaglandin E$_2$ (150 μg)
Inflammation signaling pathways

Various types of inflammatory stimuli lead to the recruitment of inflammatory cells and endothelial cells. TNF-α acts on the epithelium to activate the TNF receptor, which in turn activates IKK, leading to NF-κB activation. NF-κB can also activate COX-2, which in turn leads to the synthesis of prostaglandins H2 and E2. These prostaglandins can inhibit the loss of contact inhibition, anchor in an independent manner to promote proliferation, and increase E-cadherin expression. COX-2 is also induced by other factors such as TPA and PKC-α.

**Table 11.3: Known or suspected human tumor promoters and their sites of action**

<table>
<thead>
<tr>
<th>Agent or process</th>
<th>Cancer site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormones</td>
<td></td>
</tr>
<tr>
<td>Estrogen</td>
<td>endometrium</td>
</tr>
<tr>
<td>Estrogen and progesterone</td>
<td>breast</td>
</tr>
<tr>
<td>Ovulation</td>
<td>ovary</td>
</tr>
<tr>
<td>Testosterone</td>
<td>prostate</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives, anabolic steroids</td>
<td>liver</td>
</tr>
<tr>
<td>Analgesics</td>
<td>renal pelvis</td>
</tr>
<tr>
<td>Diuretics</td>
<td>kidney</td>
</tr>
<tr>
<td>Infectious agents</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B/C viruses</td>
<td>liver</td>
</tr>
<tr>
<td>Schistosoma haematobium—blood fluke</td>
<td>bladder</td>
</tr>
<tr>
<td>Schistosoma japonicum—blood fluke</td>
<td>colon</td>
</tr>
<tr>
<td>Clonorchis sinensis—liver fluke</td>
<td>biliary tract</td>
</tr>
<tr>
<td>Helicobacter pylori—bacterium</td>
<td>stomach</td>
</tr>
<tr>
<td>Malarial parasites</td>
<td>B cell</td>
</tr>
<tr>
<td>Tuberculosis bacillus</td>
<td>lung</td>
</tr>
<tr>
<td>Chemical agents</td>
<td></td>
</tr>
<tr>
<td>Betel nut, lime</td>
<td>oral cavity</td>
</tr>
<tr>
<td>Chewing tobacco</td>
<td>oral cavity</td>
</tr>
<tr>
<td>Bile</td>
<td>small intestine</td>
</tr>
<tr>
<td>Salt</td>
<td>stomach</td>
</tr>
<tr>
<td>Acid reflux</td>
<td>esophagus</td>
</tr>
<tr>
<td>Physical or mechanical trauma</td>
<td></td>
</tr>
<tr>
<td>Asbestos</td>
<td>mesothelium, lung</td>
</tr>
<tr>
<td>Gallstones</td>
<td>gallbladder</td>
</tr>
<tr>
<td>Coarsely ground corn</td>
<td>stomach</td>
</tr>
<tr>
<td>Head injury</td>
<td>meninges</td>
</tr>
<tr>
<td>Chronic irritation/inflammation</td>
<td></td>
</tr>
<tr>
<td>Tropical ulcers</td>
<td>skin</td>
</tr>
<tr>
<td>Chronic ulcerative colitis</td>
<td>colon</td>
</tr>
<tr>
<td>Chronic cystitis</td>
<td>bladder</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>pancreas</td>
</tr>
</tbody>
</table>

Figure 11.42  The Biology of Cancer (© Garland Science 2007)

Table 11.4 Links between inflammation and cancer pathogenesis

<table>
<thead>
<tr>
<th>Links between Inflammation and Cancer Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Many inflammatory conditions predispose to cancer</td>
</tr>
<tr>
<td>Cancers arise at sites of chronic inflammation</td>
</tr>
<tr>
<td>Functional polymorphisms of cytokine genes are associated with cancer susceptibility and severity</td>
</tr>
<tr>
<td>Distinct populations of inflammatory cells are detected in many cancers</td>
</tr>
<tr>
<td>Extent of tumor-associated macrophage infiltrate correlates with prognosis</td>
</tr>
<tr>
<td>Inflammatory cytokines are detected in many cancers; high levels are associated with poor prognosis</td>
</tr>
<tr>
<td>Chemokines are detected in many cancers; they are associated with inflammatory infiltrate and cell motility</td>
</tr>
<tr>
<td>Deletion of cytokines and chemokines protects against carcinogens, experimental metastases, and lymphoproliferative syndrome</td>
</tr>
<tr>
<td>Inflammatory cytokines are implicated in the action of non-genotoxic liver carcinogens</td>
</tr>
<tr>
<td>The inflammatory cytokine tumor necrosis factor is directly transforming in vitro</td>
</tr>
<tr>
<td>Long-term NSAID use decreases mortality from colorectal cancer</td>
</tr>
</tbody>
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Table 11.4  The Biology of Cancer (© Garland Science 2007)
Does the initial mutated oncogene needed for maintenance of cancer?

Study using mouse transgenic models with different oncogenes gave dubious results: Tumor decreased upon inhibition of the oncogene, but later tumor outgrowth became independent of the initial oncogene.

**Tributes of cancer cells**

1. Reduced dependence on exogenous mitogenic growth factors
2. Acquired resistance to growth-inhibitory signal, ex TGFbeta
3. Immortalized cell proliferation
4. Reduced susceptibility to apoptosis
5. Ability to neoangiogenesis
6. Acquisition of invasive and metastatic ability
7. Ability to evade immune system
8. Acquisition of genome instability
The Hallmarks of Cancer

Sustaining proliferative signaling
Resisting cell death
Inducing angiogenesis
Enabling replicative immortality
Evading growth suppressors
Activating invasion and metastasis

Emerging Hallmarks and Enabling Characteristics

Emerging Hallmarks
Deregulating cellular energetics
Avoiding immune destruction
Genome instability and mutation
Tumor-promoting Inflammation

Enabling Characteristics

Hanahan and Weinberg 2011
The Cells of the Tumor Microenvironment

Hanahan and Weinberg, 2011

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Hallmarks and therapeutic Targeting of Cancer

Hanahan and Weinberg, 2011