

Acute and Chronic Inflammation

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INFLAMMATION

Inflammation is a **normal response** of the body to protect tissues from infection, injury or disease.

The inflammatory response begins with the production and release of chemical agents by cells in the infected, injured or diseased tissue. These agents cause redness, swelling, pain, heat and loss of function.

Inflamed tissues generate additional signals that recruit leukocytes to the site of inflammation. Leukocytes destroy any infective or injurious agent, and remove cellular debris from damaged tissue.

This inflammatory response usually promotes healing but, **if uncontrolled, may become harmful.**

The inflammatory response can be either acute or chronic.

Acute inflammation typically lasts only a few days. If a wound gets hot, turns red, hurts, and swells, we recognize that inflammation is at work. In this instance, inflammation is a beneficial process, serving to immobilize the area of injury as the rest of the immune system mobilizes to heal.

Inflammation is the first line of defense against injury or infection. The treatment of acute inflammation, where therapy includes the administration of aspirin and other non-steroidal anti-inflammatory agents, provides relief of pain and fever for patients.

In contrast, chronic inflammation lasts weeks, months or even indefinitely and causes tissue damage.

CHRONIC INFLAMMATION

In **chronic** inflammation, the inflammation becomes the problem rather than the solution to infection, injury or disease. Chronically inflamed tissues continue to generate signals that attract leukocytes from the bloodstream.

When leukocytes migrate from the bloodstream into the tissue they amplify the inflammatory response. This chronic inflammatory response can break down healthy tissue in a misdirected attempt at repair and healing.

Diseases characterized by chronic inflammation include, among others:

Crohn's

Lupus

Psoriasis

Diabetes

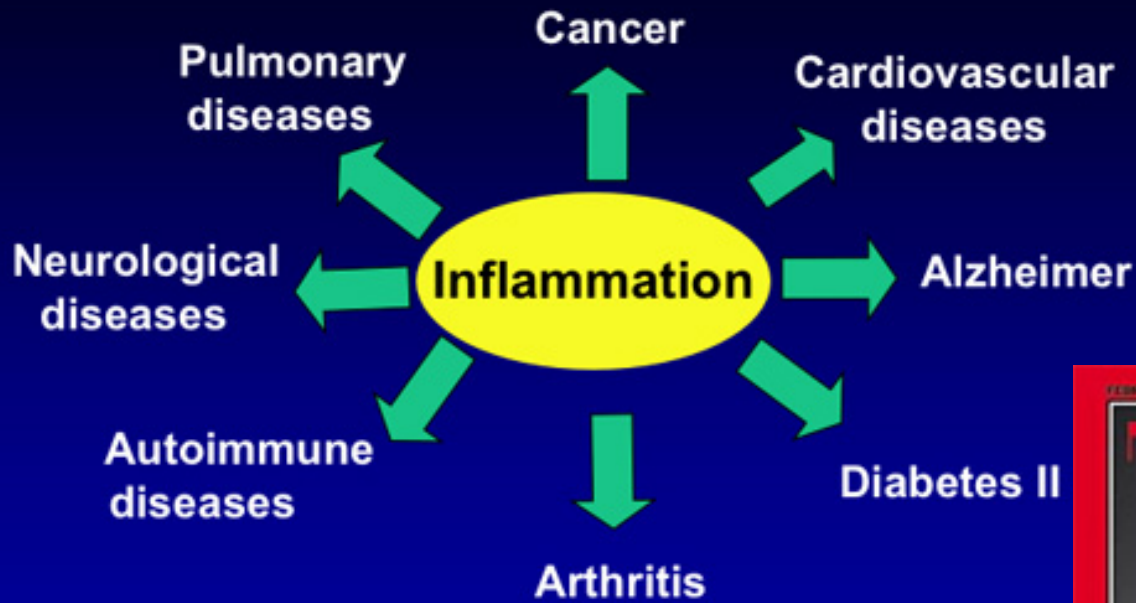
Coronary artery disease (atherosclerosis)

Rheumatoid arthritis

Asthma

Solid organ transplant rejection

Chronic Bronchitis

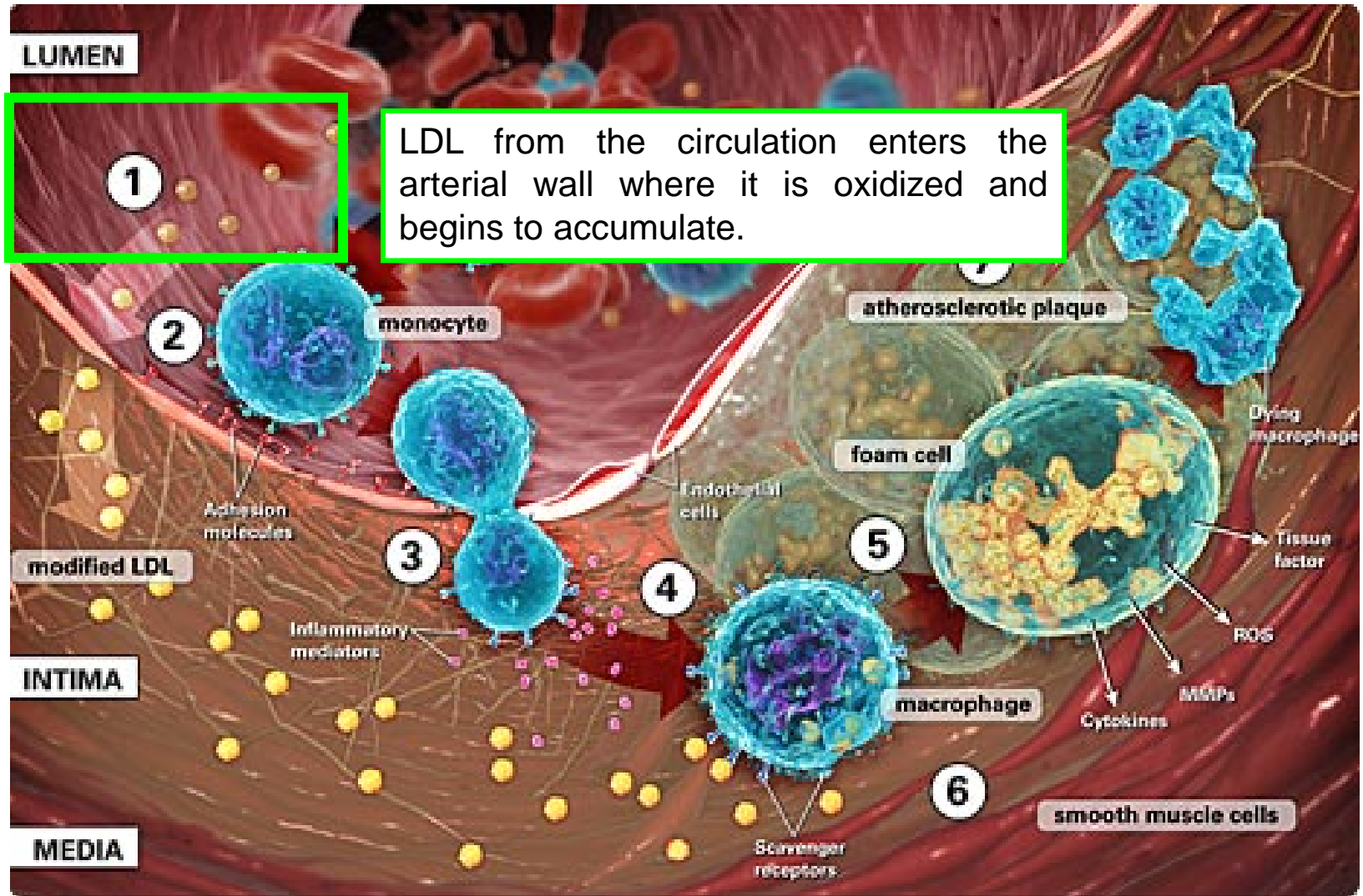


Inflammation and Cardiovascular Disease

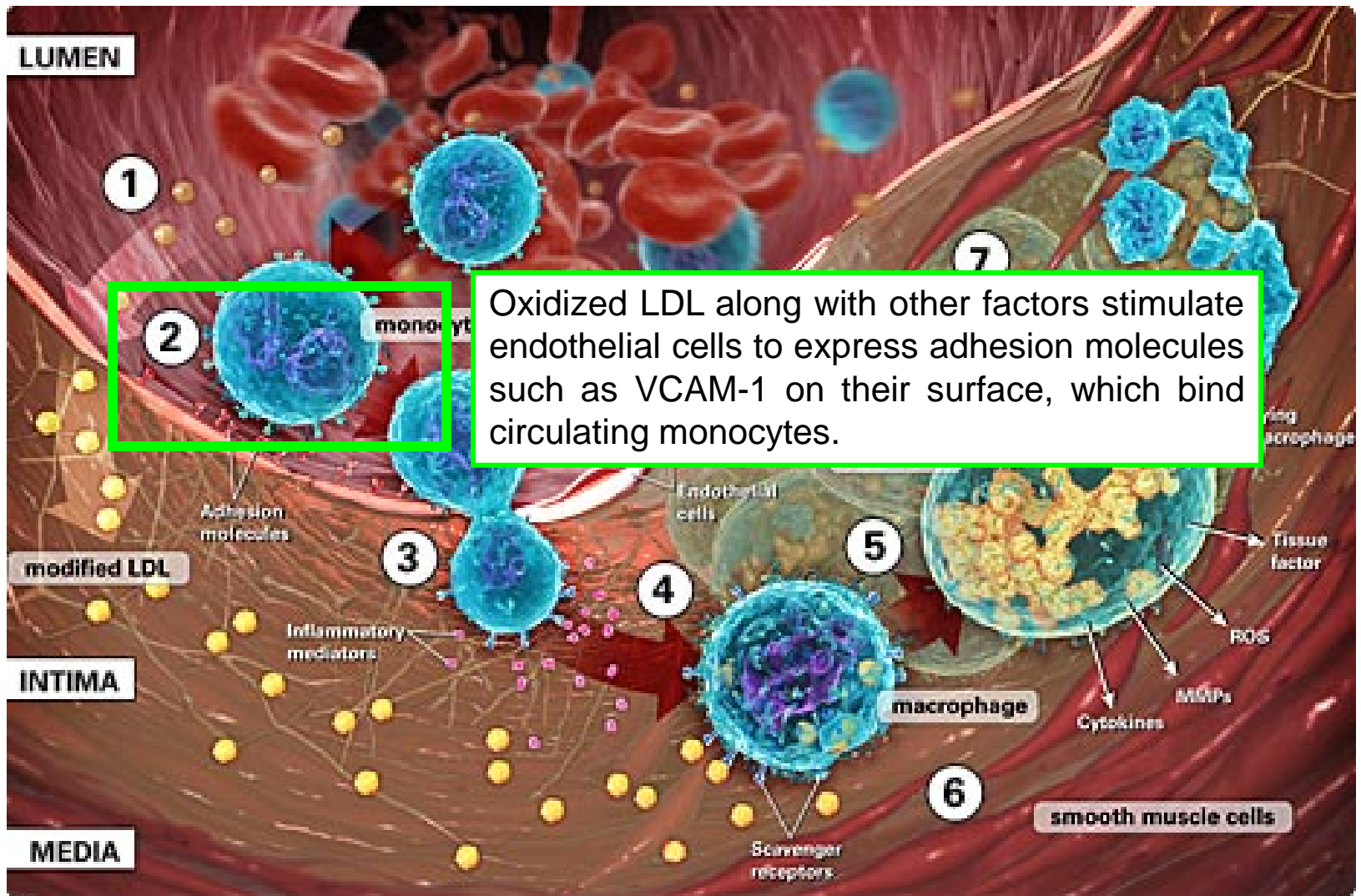
Recent advances in the field of cardiovascular medicine have emphasized the involvement of inflammation in the formation of atherosclerotic plaque.

It has been shown that inflammatory signals at the site of plaque initiation attract monocytes from the circulation into the vascular wall to form lipid-laden foam cells and promote smooth muscle cell proliferation, resulting in plaque progression.

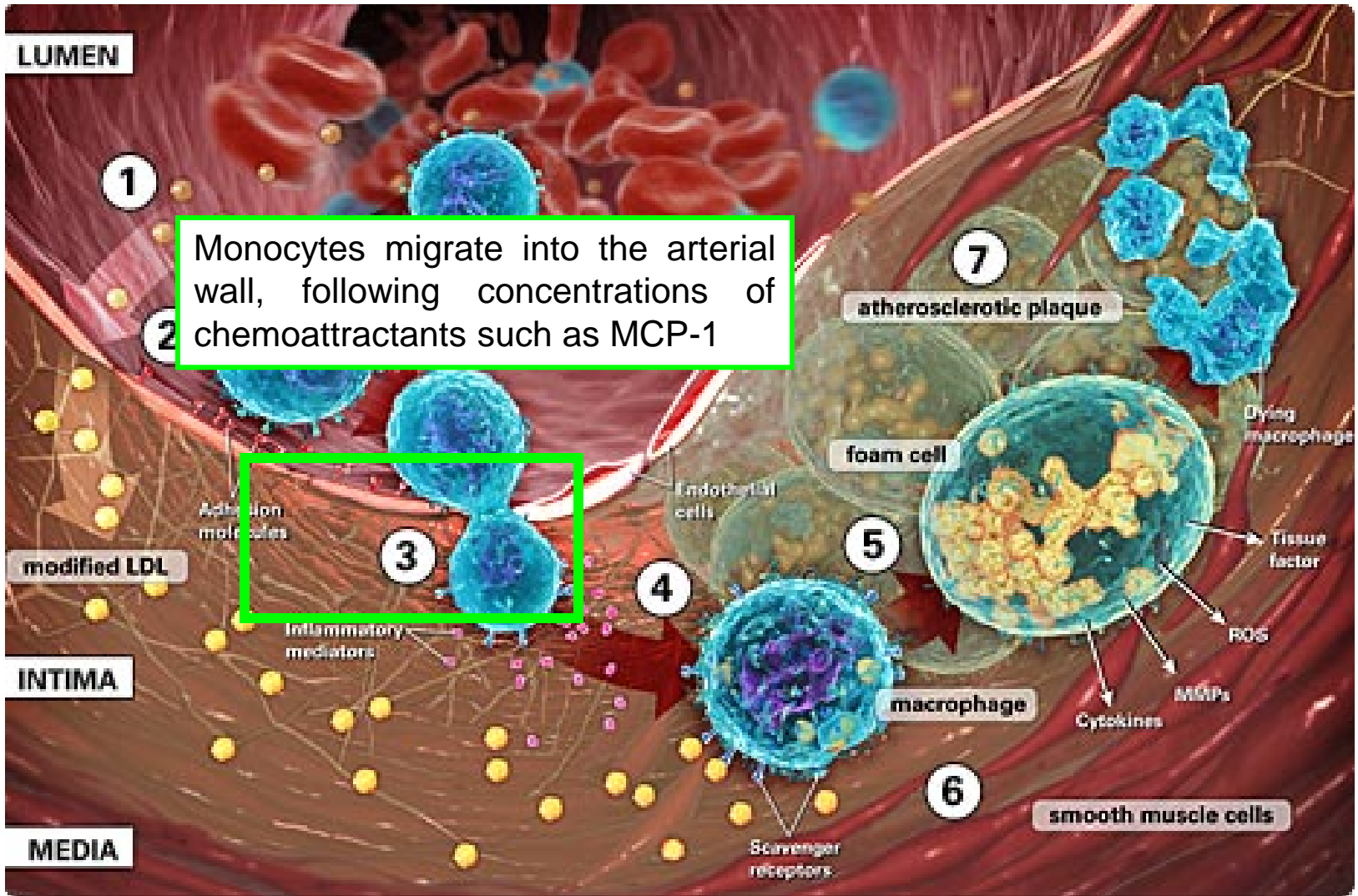
It is for this reason that emerging strategies focus on inhibiting cellular proliferation and pro-inflammatory mediators of monocyte migration.



LDL from the circulation enters the arterial wall where it is oxidized and begins to accumulate.

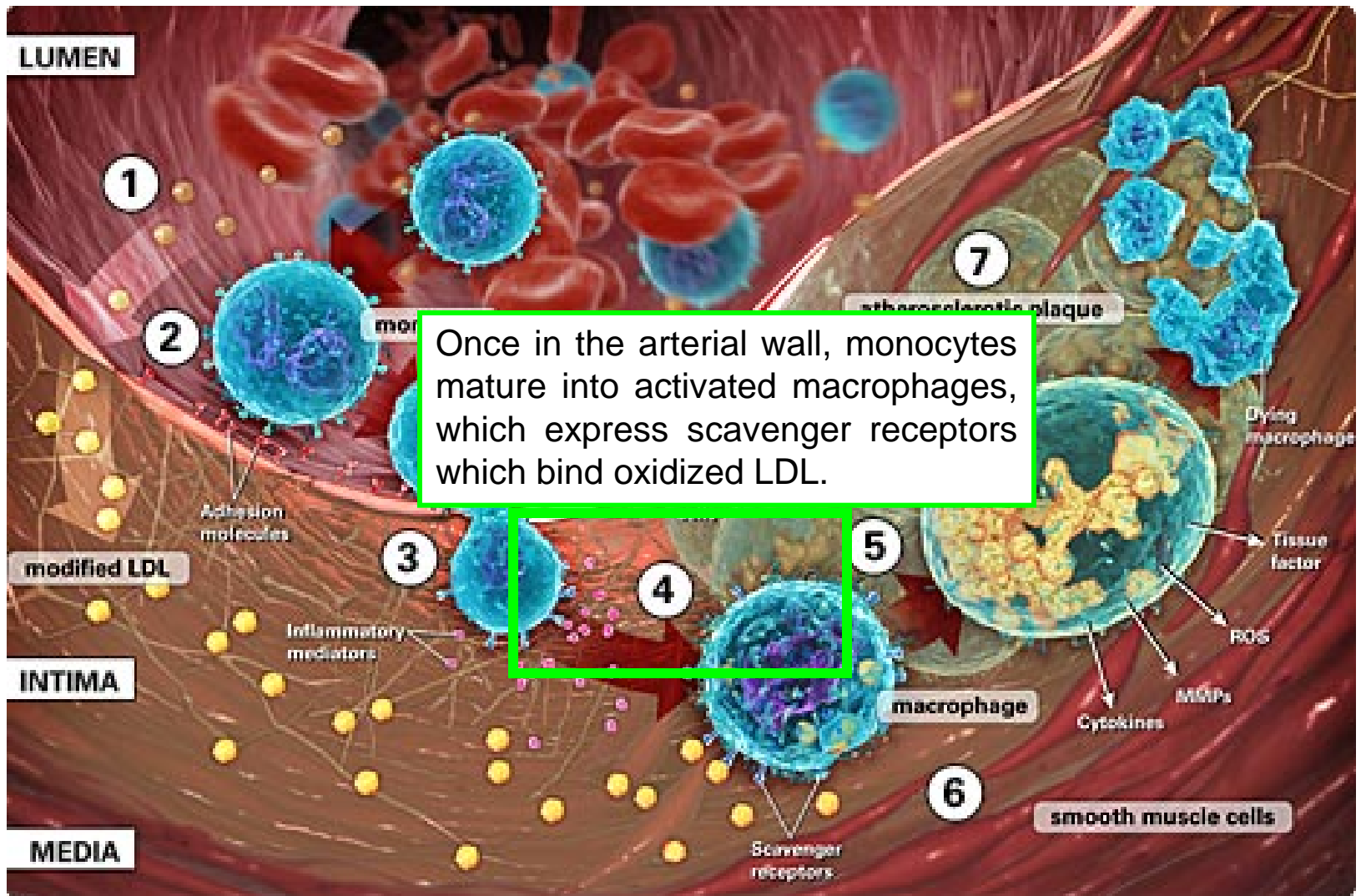


Oxidized LDL along with other factors stimulate endothelial cells to express adhesion molecules such as VCAM-1 on their surface, which bind circulating monocytes.

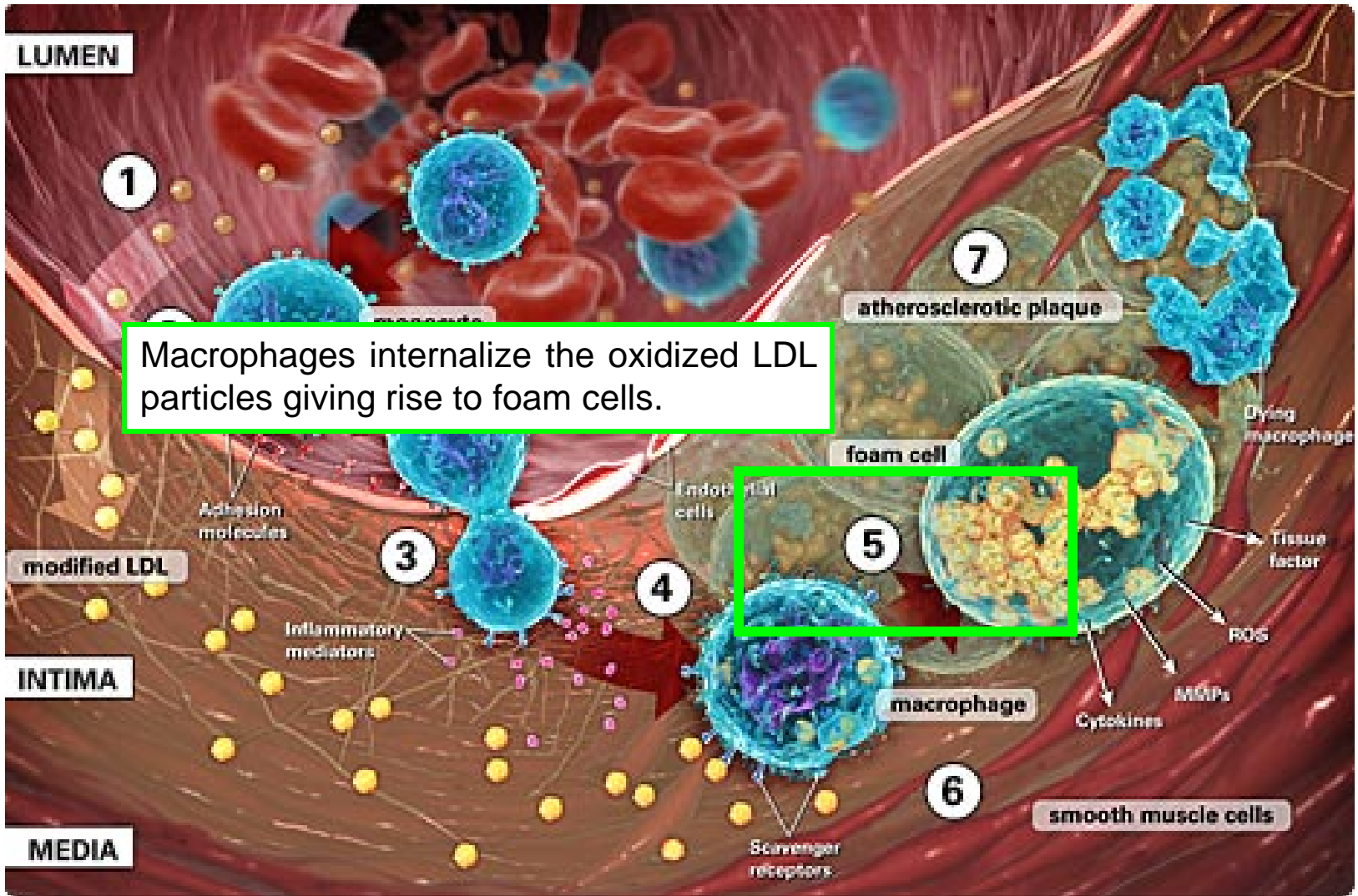


Monocytes migrate into the arterial wall, following concentrations of chemoattractants such as MCP-1

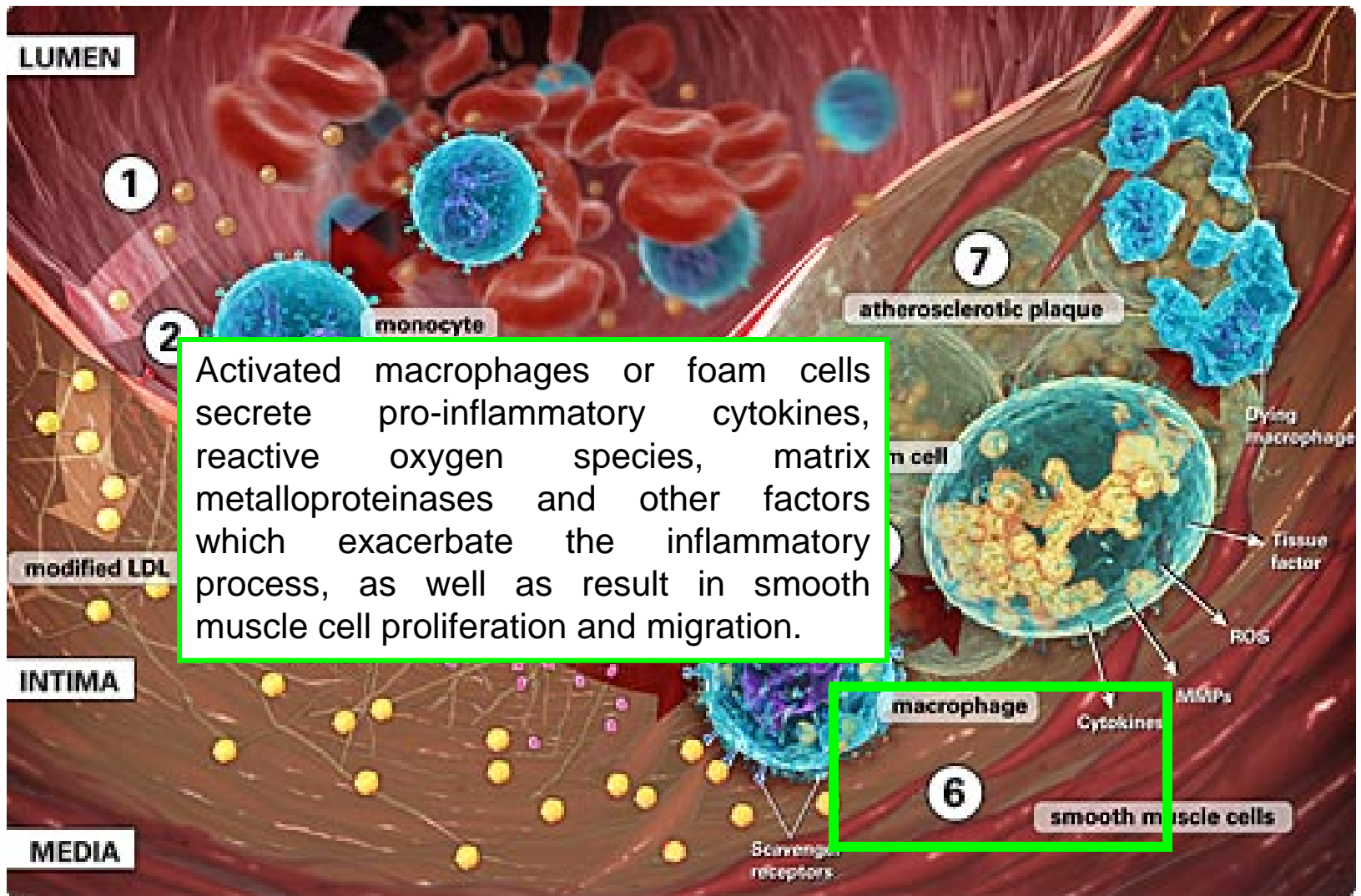
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Once in the arterial wall, monocytes mature into activated macrophages, which express scavenger receptors which bind oxidized LDL.



Macrophages internalize the oxidized LDL particles giving rise to foam cells.



LUMEN

1

Foam cells, dead macrophages, lipids and smooth muscle cells accumulate to form a fatty streak eventually resulting in atherosclerotic plaque.

7

atherosclerotic plaque

modified LDL

Adhesion molecules

3

Inflammatory mediators

INTIMA

4

Endothelial cells

5

foam cell

Dying macrophage

Tissue factor

ROS

Cytokines

MMPs

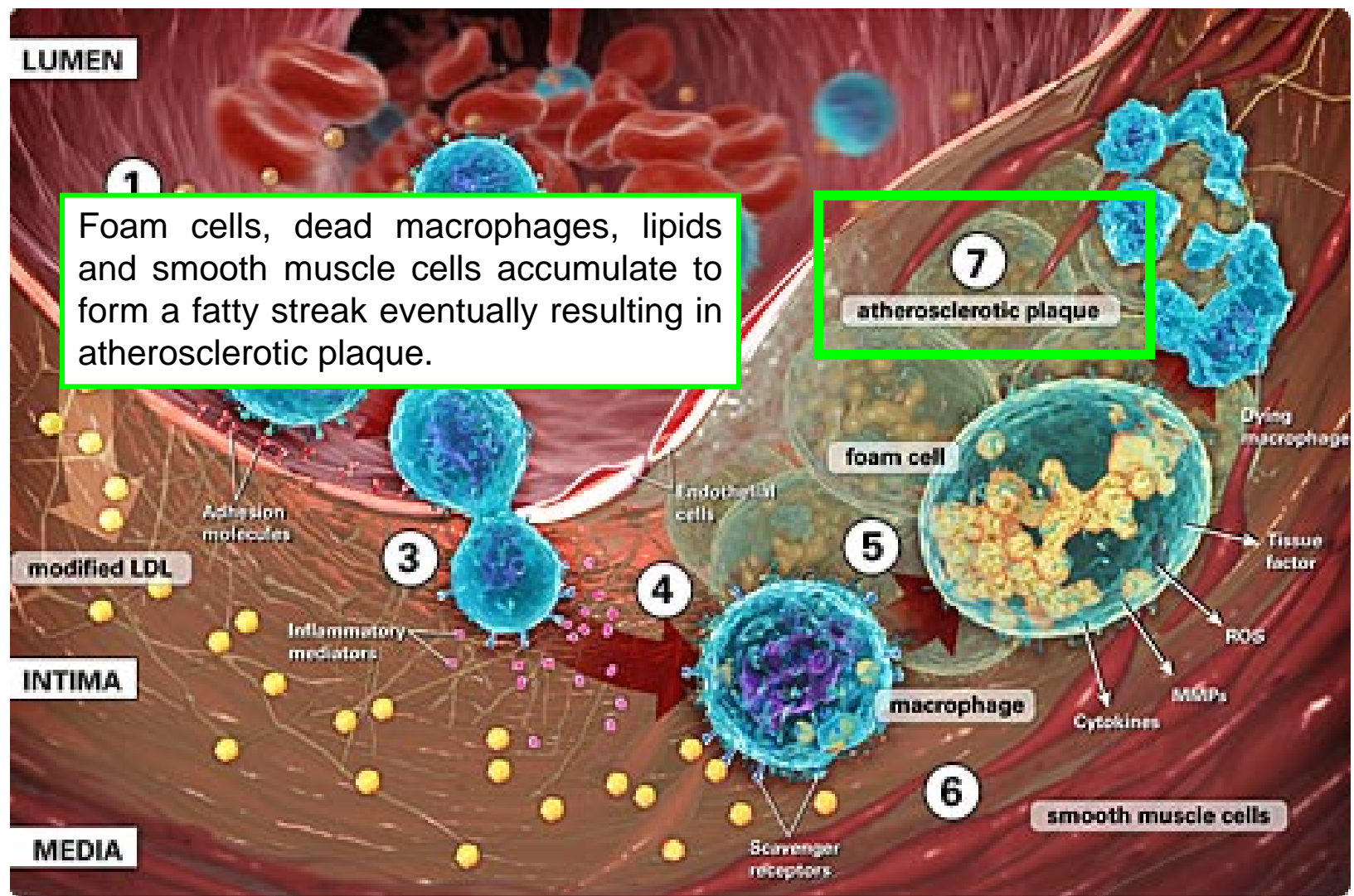
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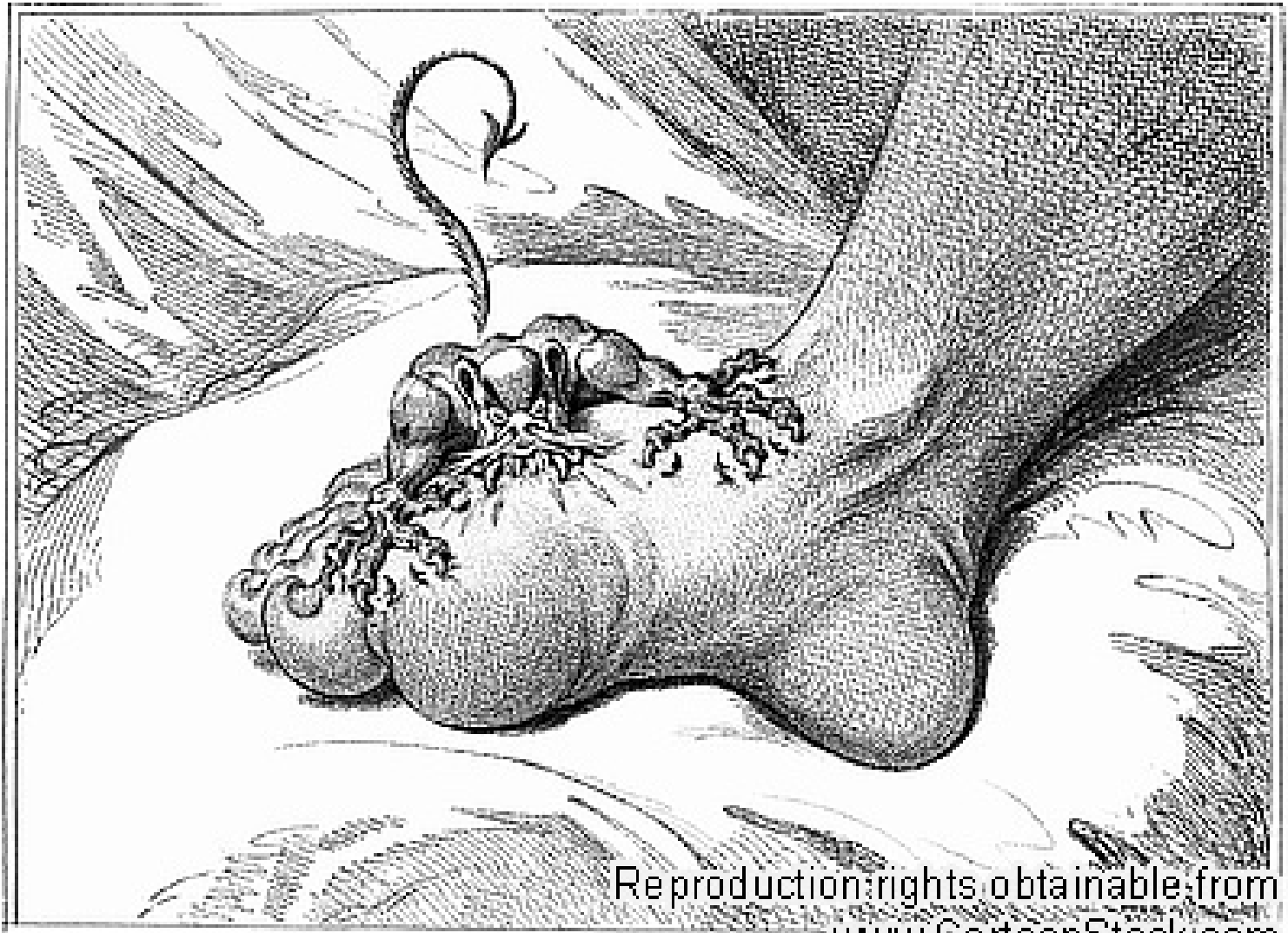
macrophage

smooth muscle cells

Scavenger receptors

MEDIA





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The GODD



Gout is a condition characterized by an abnormal metabolism of uric acid. People with gout either produce too much **uric acid**, or more commonly, their bodies have a problem in removing it.

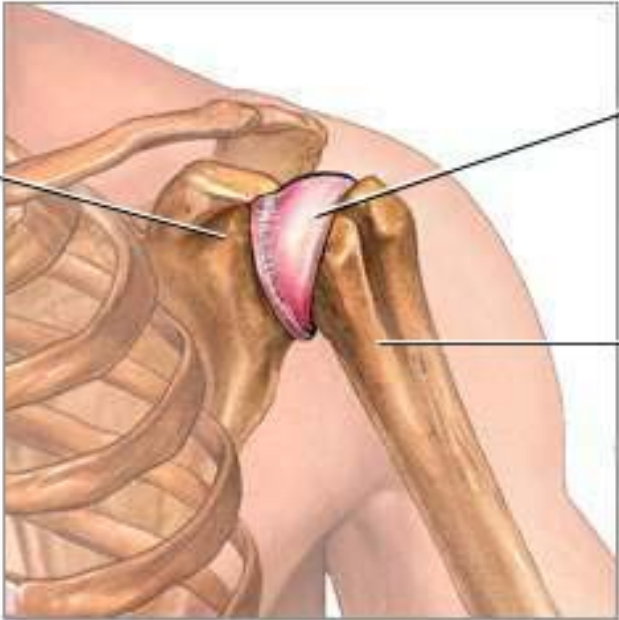
There are a number of possible consequences of this buildup of uric acid in the body, including acute and chronic gouty arthritis, kidney stones, and deposits of uric acid in the skin and other tissues. These crystals can accumulate over the years in the joint and trigger repeated bouts of inflammation. Repeated "attacks" of gouty arthritis can damage the joint and lead to chronic arthritis. Inflammation of the skin caused by gout is characterized by swelling and a smooth appearance to the skin. Gout and pain are synonymous.

Uric acid coming in contact with the high levels of free sodium present in the extracellular environment forms monosodium urate (MSU) crystals. MSU stimulates the NALP3 inflammasome to produce active IL-1 β .

Inflammation is the Root Cause of Joint Pain.

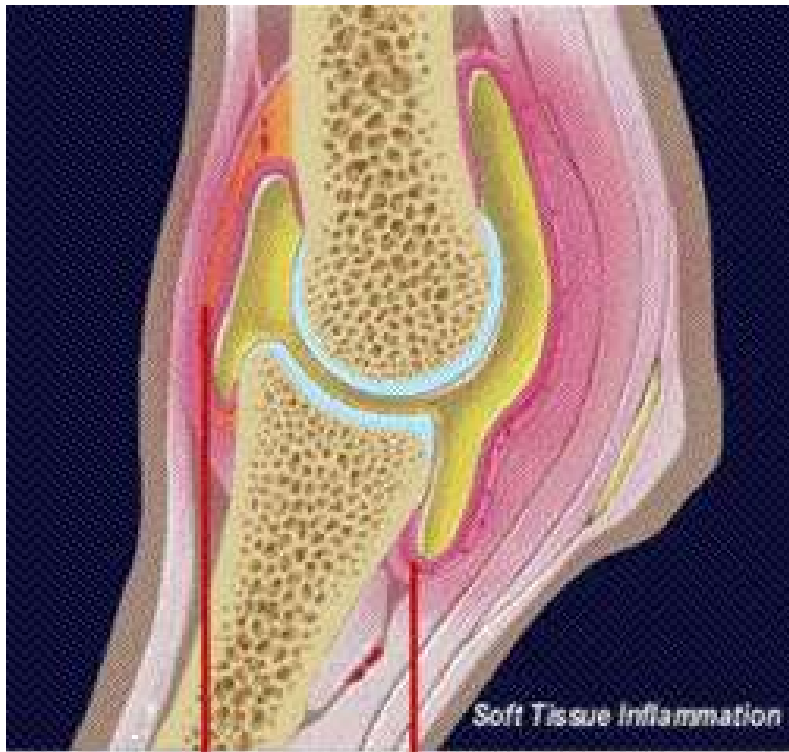


Left scapula



Affected joint capsule

Left humerus



Capsulitis

Synovitis

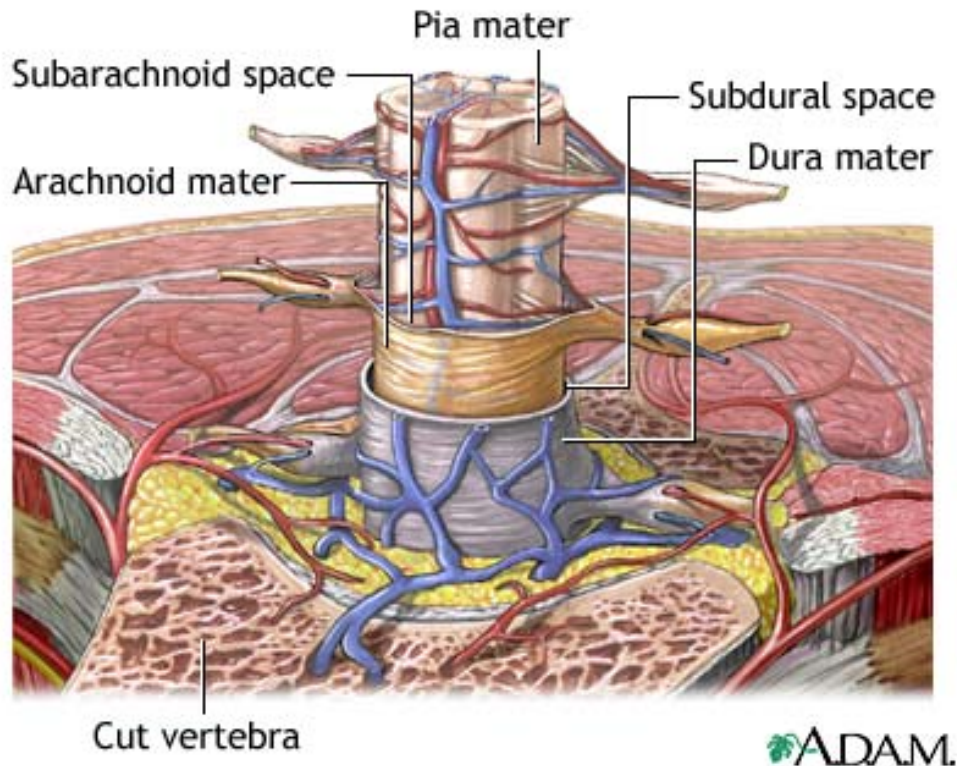
Joint Inflammation:

Repeated trauma or stress to the joint, incurred during everyday use, athletic training, or performance, is often the initiating cause of joint inflammation. The familiar symptoms — *lameness, swelling, and heat* — are usually the result of inflammation in the synovial membrane and joint capsule.

The initial inflammation usually involves only the soft tissue structures of the joint (synovial membrane/joint capsule), and cartilage damage is generally not present at this early stage. The synovial membrane responds to injury by becoming inflamed, a condition referred to as synovitis.

This inflammation allows leukocytes, or white blood cells, which are normally filtered out of the joint, to invade the joint space. The inflamed synovial membrane and the leukocytes release destructive enzymes such as free radicals, cytokines, and prostaglandins, all of which are potentially damaging to the articular cartilage.

Left untreated, or allowed to recur repeatedly (chronic insult), these inflammatory mediators produced by the inflamed joint have a degrading or damaging effect upon the cartilage.



Inflammation in the Brain

The organs of the central nervous system (brain and spinal cord) are covered by 3 connective tissue layers collectively called the meninges. Consisting of the pia mater (closest to the CNS structures), the arachnoid and the dura mater (farthest from the CNS), the meninges also support blood vessels and contain cerebrospinal fluid. These are the structures involved in **meningitis, an inflammation of the meninges**, which, if severe, may become **encephalitis, an inflammation of the brain**.

Chronic inflammation and disease pathogenesis

What molecular mechanisms underlie harmful, excessive stimulation of immune-cell responses?

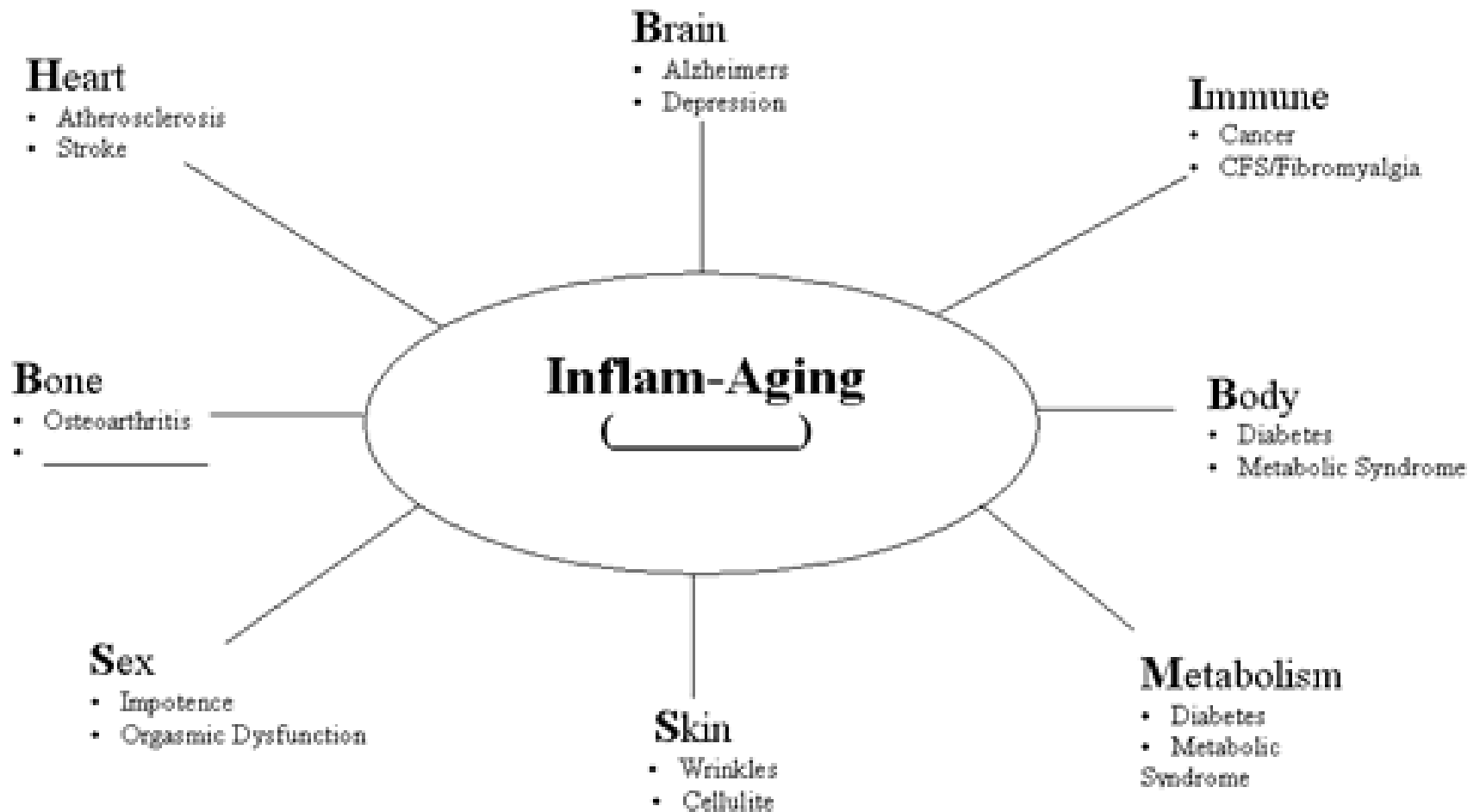
1. Genetic predisposition underlies some disorders, such as pancreatitis, ulcerative colitis and some rheumatoid diseases.
2. Others are associated with infectious pathogens that are able to evade natural tissue immune clearance mechanisms . For example, *Helicobacter pylori*, a gram-negative bacterium, causes chronic gastritis in infected hosts, whereas unresolved infection with *hepatitis B* or *hepatitis C virus* is linked to chronic hepatitis.
3. Unresolved inflammation also results from exposure to toxic factors such as *asbestos* or *smoke*, as well as from ongoing chemical or physical irritation, such as acid-reflux disease or exposure to ultraviolet (UV) light.
4. Mutations and/or genetic polymorphisms in crucial genes that regulate cytokine function, metabolism and leukocyte survival have also been implicated as aetiological factors in chronic inflammation.

During acute inflammation, innate immune cells form the first line of immune defense and regulate activation of adaptive immune responses.

By contrast, during chronic inflammation, these roles can be reversed — adaptive immune responses can cause ongoing and excessive activation of innate immune cells.

In arthritis, for example, activation of T and B lymphocytes results in antibody deposition into affected joints, prompting recruitment of innate immune cells into tissue. Once within the tissue, activation and/or degranulation of mast cells, granulocytes and macrophages, in combination with humoral immune responses, leads to joint destruction. By contrast, whereas acutely activated innate immune cells contribute to efficient T-cell activation, chronically activated innate immune cells can cause T-cell dysfunction through the production of reactive oxygen.

Regardless of the underlying initiating cause, if an infectious or assaulting agent is **inadequately cleared and persists in tissue**, or a tissue is **subjected to ongoing insult and damage that fails to heal** in a timely manner, **host inflammatory responses can persist and exacerbate chronic tissue damage**, which can cause primary organ dysfunction and systemic complications.



Inflammation is the Cause and the Effect of Illness and the Disease of Aging

An inflammatory cascade is initiated in several situations, including infection, trauma, surgery, burns, tissue infarction and advanced cancer.

Locally, the acute inflammatory response includes:
capillary vessel vasodilatation (congestion),
exudation of plasma proteins (oedema),
leukocyte adherence to endothelium,
chemoattraction and local activation of leukocytes,
release of numerous mediators, elimination of foreign substances
(phagocytosis),
elimination of recruited cells (apoptosis) and healing of tissue.

The main components of the **acute inflammatory response** are **cytokines, acute-phase proteins and leukocytes.**

The systemic response following local inflammation is known as the acute-phase response which is marked by fever, increased synthesis of hormones, such as adrenocorticotrophic hormone (ACTH) and hydrocortisone, increased production of white blood cells and production of acute-phase proteins in the liver.

The production of acute -phase proteins is stimulated by the inflammation-associated cytokines, interleukin (IL)-1 β , tumour necrosis factor (TNF)- α , IL-6, interferon (IFN)- γ , transforming growth factor (TGF)- β and IL-8, which are secreted mainly by activated tissue macrophages .

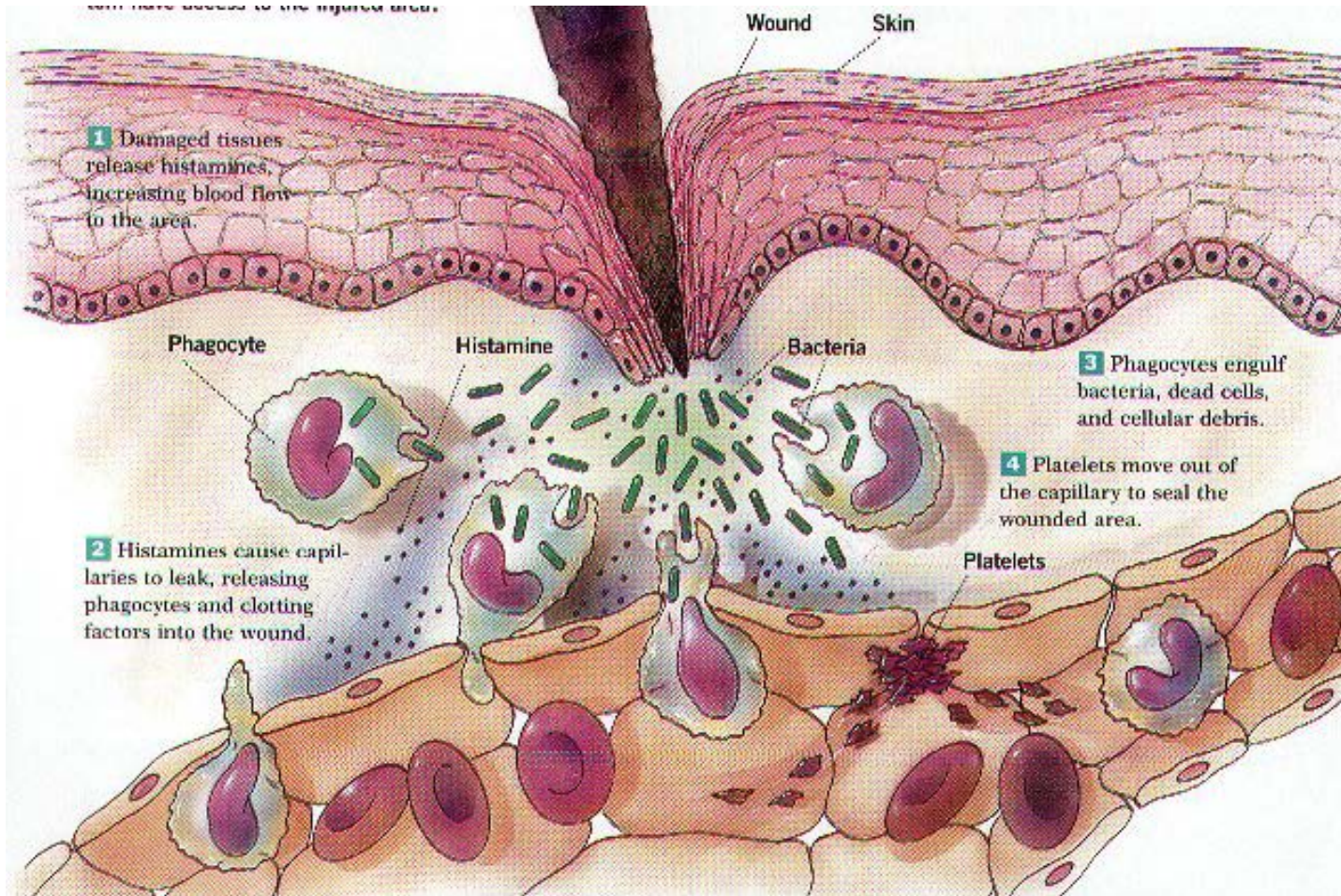
Neutrophils and monocyte/macrophages of the innate immune system are the main effector cells during acute inflammation.

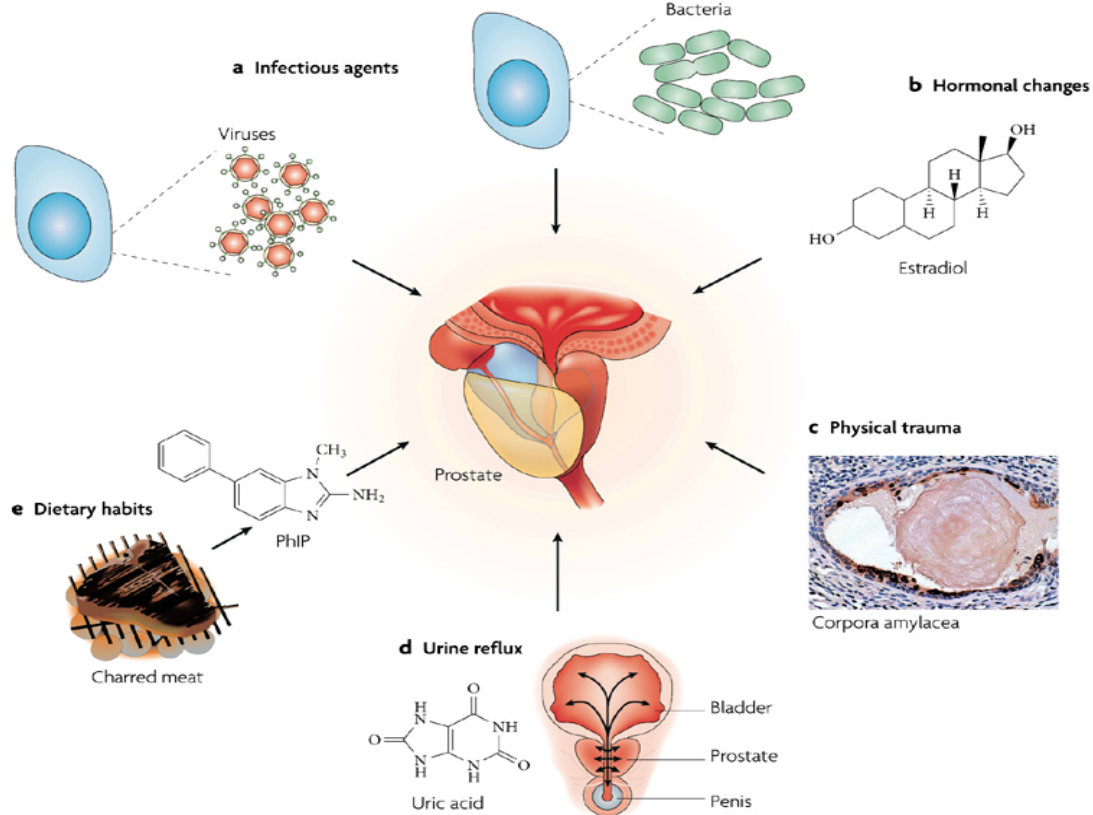
A landmark study showed that people with high levels of C-reactive protein (CRP), one of the cardinal markers of inflammation, were over four times more likely to have heart attacks than those with low CRP levels. Researchers then began to link C-reactive protein, along with other markers of inflammation, to a wide range of chronic diseases, including Alzheimer's disease, arthritis, Parkinson's disease, and even cancer.

Chronic silent inflammation is now accepted as a warning that something is drastically out of balance in a person's overall health.

Inflammatory Process

with more access to the injured area.





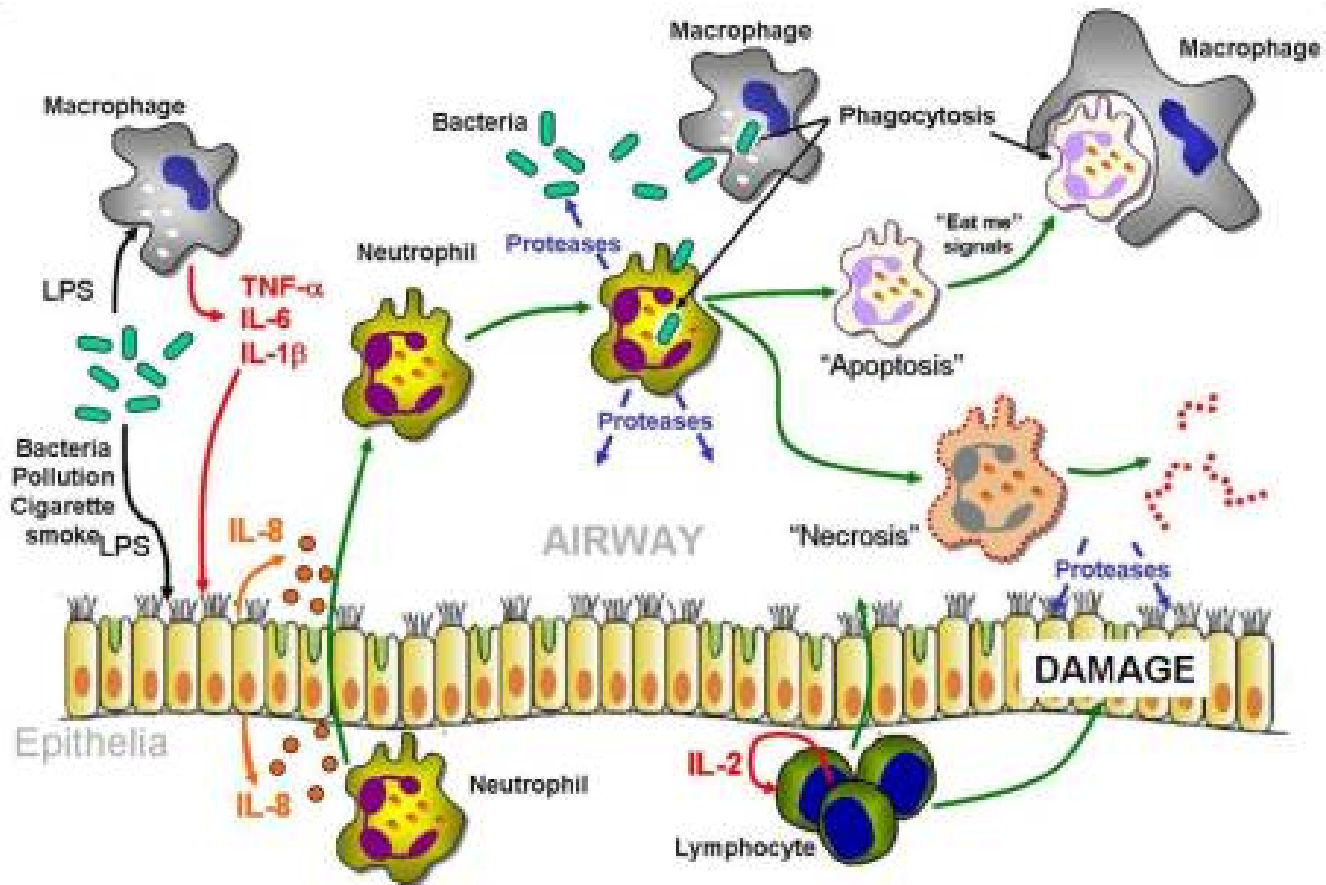
Chronic bacterial prostatitis is a rare recurring infection in which pathogenic bacteria are cultured from prostatic fluid. Viruses, fungi, mycobacteria and parasites can also infect the prostate and incite inflammation. The figure represents two prostate cells infected either by bacteria or viruses.

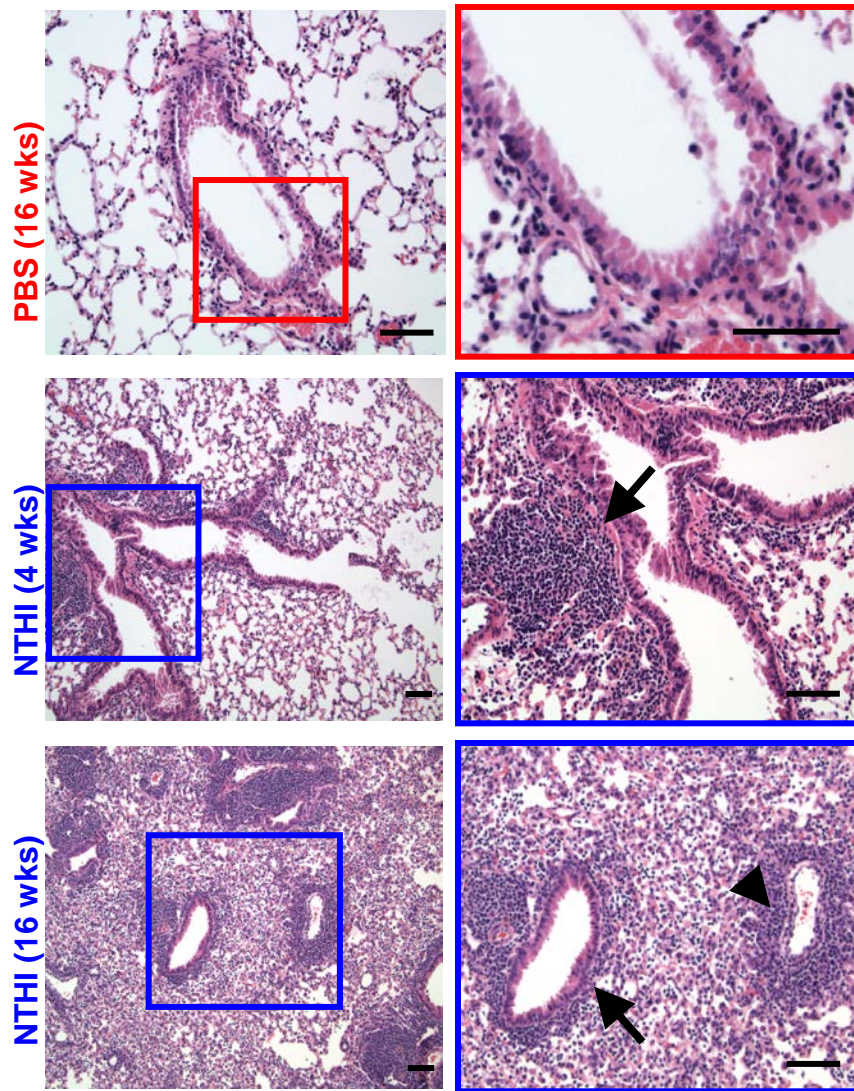
b. Hormones. Hormonal alterations such as oestrogen exposure at crucial developmental junctures can result in architectural alterations in the prostate that produce an inflammatory response.

c Physical trauma. Corpora amylacea can traumatize the prostate on a microscopic level. The figure shows a corpora within a prostatic acinus in which its edges appear to be eroding the epithelium, resulting in an increase in expression of the stress enzyme cyclooxygenase 2 (PTGS2), represented by brown immunostaining. Prostate cell nuclei are visible in violet following haematoxylin staining.

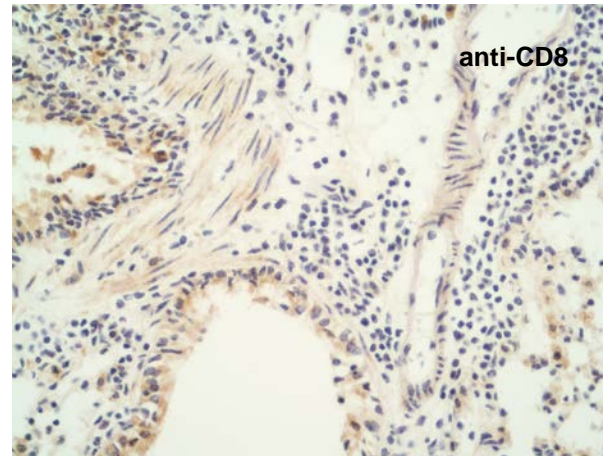
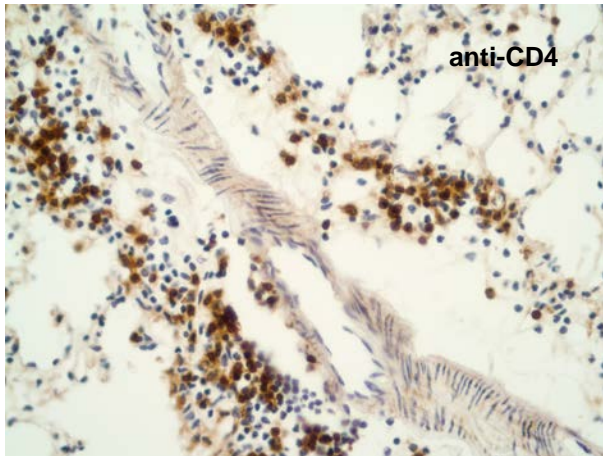
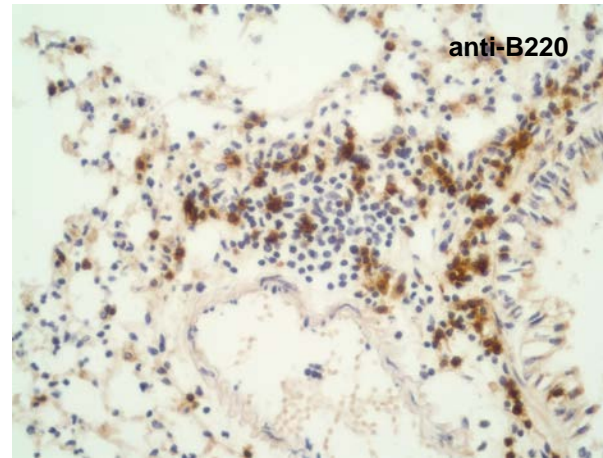
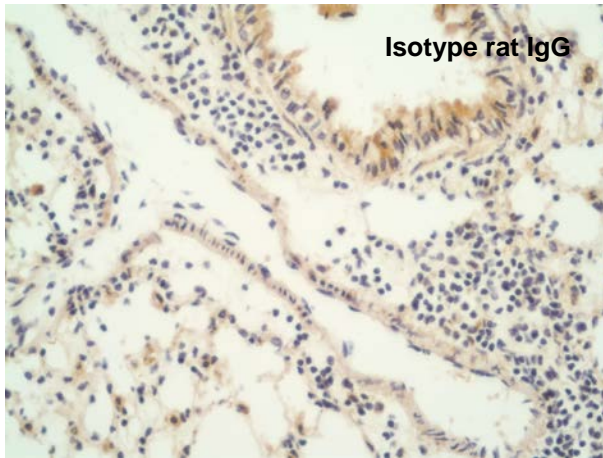
d Urine reflux. Urine that travels up back towards the bladder ('retrograde' movement) can penetrate the ducts and acini of the prostate. Some compounds, such as crystalline uric acid, can directly activate innate inflammatory cells. Although these compounds would not be expected to traverse the prostate epithelium, if the epithelium was already damaged this would facilitate the leakage of these compounds into the stromal space where they would readily activate inflammatory cells.

e Dietary habits. Ingested carcinogens (for example 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), which derives from charred meat.

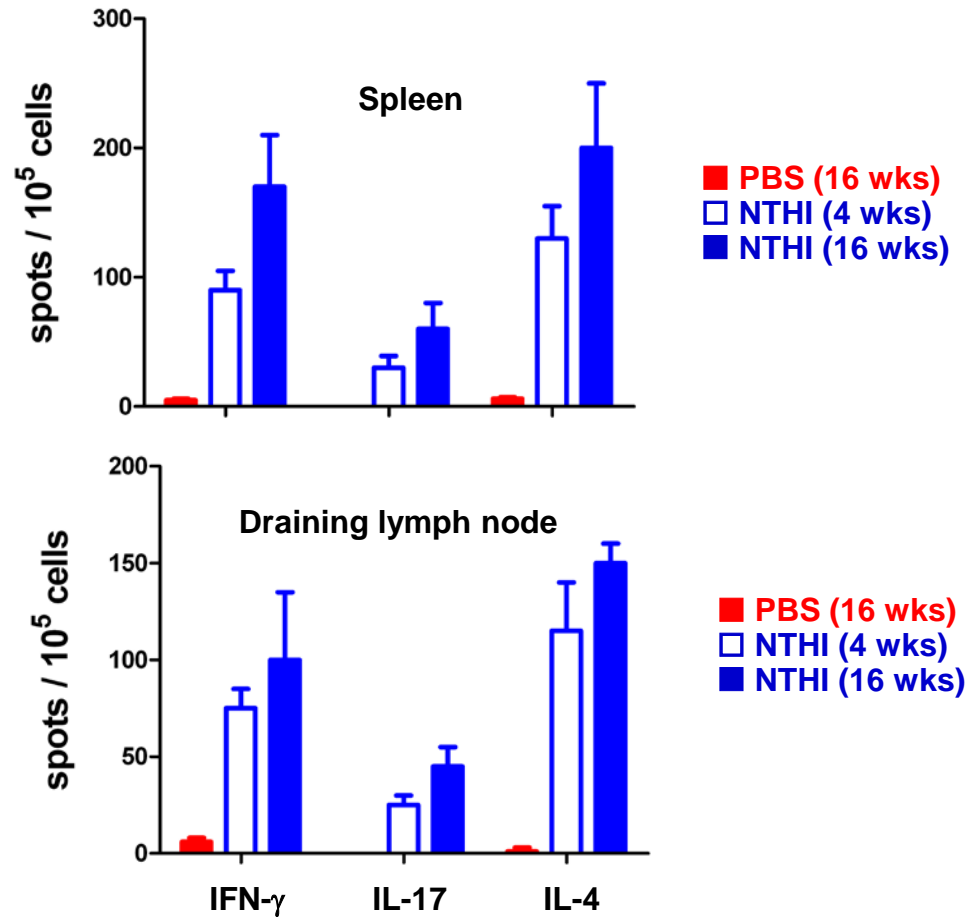




Chronic bronchiolitis (inflammation) in lungs of mice exposed to NTHI (gram negative bacteria) for 4 or 16 consecutive weeks. Lungs were fixed in formalin, embedded in paraffin, and stained with H&E. Lymphocyte cuffing is evident in peribronchial (arrows) and perivascular (arrowheads) spaces of NTHI inflamed lung.



CD4+ T cells and B220+ B cells accumulate in perivascular and peribronchial spaces of lungs in mice exposed to NTHI for 4 weeks. Infiltration patterns assessed by IHC of zinc-fixed lung tissue.



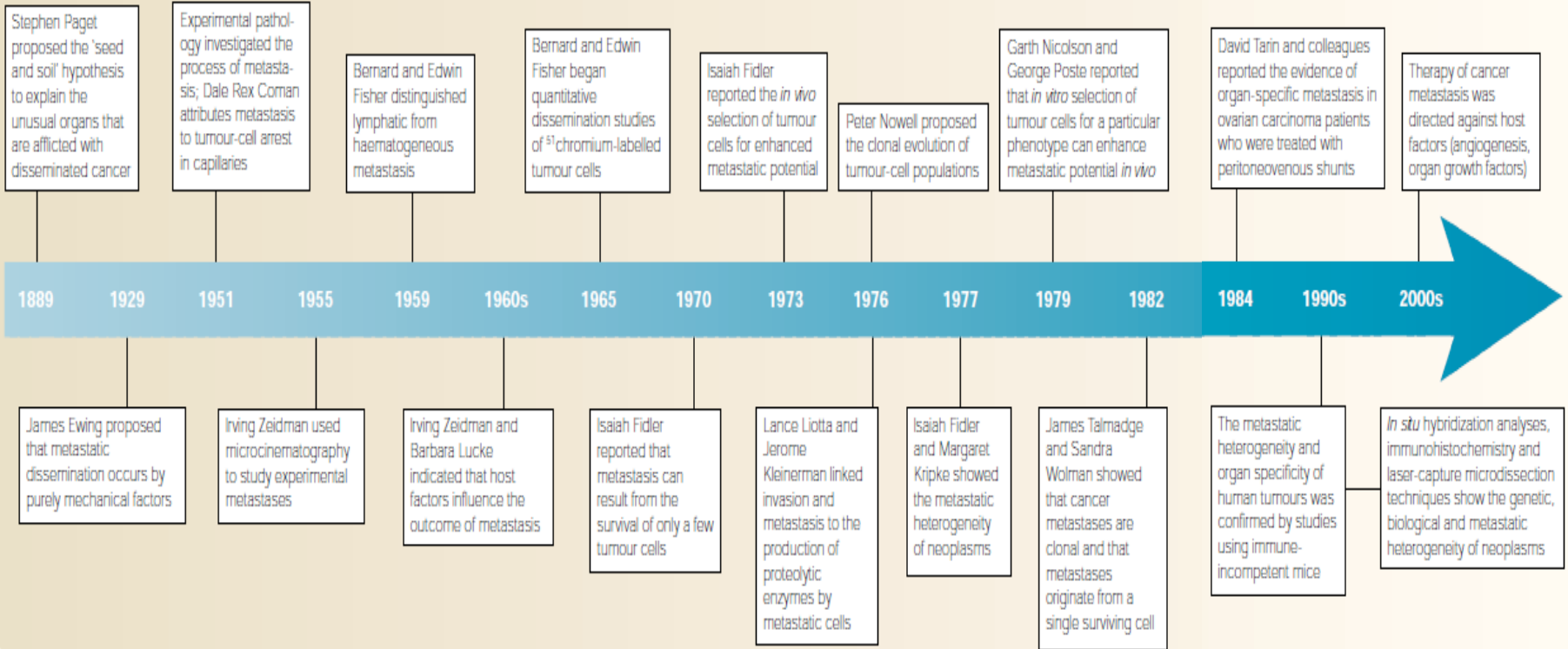
Presence of cytokine secreting antigen-specific T cells in lymphoid organs of mice with chronic inflammation due to bacterial challenge in the lungs. Frequency of cells enumerated by cytokine ELISPOT.

Links between cancer and inflammation were first made in the nineteenth century by the English surgeon **Stephen Paget** who published the seminal “seed and soil “ hypothesis.

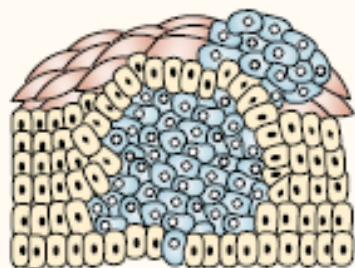
He analyzed 900 autopsy records of patients with primary tumors and noted a ***non-random pattern of metastasis***. This indicated to him that the outcome of metastasis was not due to chance, instead that certain tumor cells “seed” have specific affinity for the milieu of certain organs “soil”.

He concluded that metastases formed only when the **soil and seed were compatible.**

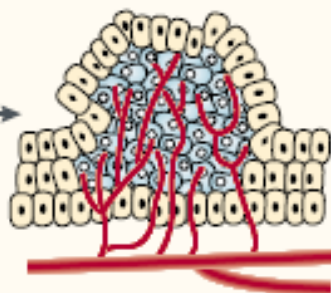
Timeline | Retrospective analysis of the pathogenesis of cancer metastasis



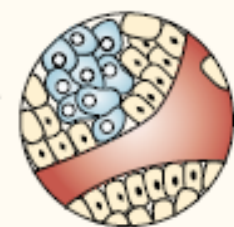
a Primary tumour



b Proliferation/
angiogenesis

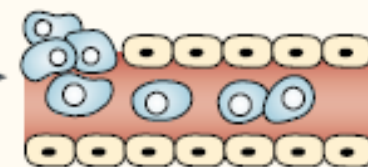


c Detachment/
invasion



Lymphatics,
venules,
capillaries

d Embolism/circulation



Interaction with platelets,
lymphocytes and other
blood components

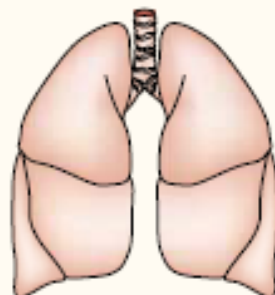
e Extravasation



Adherence to
vessel wall



Arrest in organs



Lung

Transport



Heart

Establishment of a
microenvironment

f
Proliferation/
angiogenesis

Metastasis

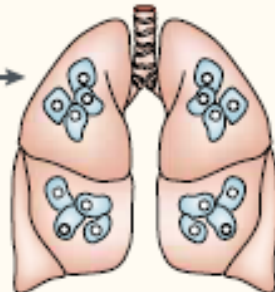


Table 1 | **Regulation of metastasis**

Cell type	Facilitation of metastasis	Inhibition of metastasis
Tumour cells	<ul style="list-style-type: none"> Production of growth factors and their receptors Production of angiogenic factors Motility, invasiveness Aggregation, deformability Specific cell-surface receptors and adhesion molecules 	<ul style="list-style-type: none"> Antigenicity Inhibitors of angiogenesis Cohesion (E-cadherin) Tissue inhibitors of proteolytic enzymes
Host cells	<ul style="list-style-type: none"> Paracrine and endocrine growth factors Neovascularization Platelets and their products Immune cells and their products 	<ul style="list-style-type: none"> Tissue barriers Blood turbulence, endothelial cells Tissue inhibitors of proteolytic enzymes Antiproliferative factors Inhibitors of angiogenesis

The pre-metastatic and metastatic 'niche' model

Temporal evolution for the development of the "soil"

The metastatic niche model suggests that a suitably conducive microenvironment (pre-metastatic niche) must evolve in order for tumor cells to be able to engraft (metastatic niche) and proliferate (micro to macro metastatic) at secondary sites.

i.e. tumor cell does not solely dictate its own fate but that the formation of a *hospitable microenvironment* at the destination site is **ESSENTIAL** to enable the disseminating tumor cell to establish secondary tumors (metastases).

Observation that tumors often arose at sites of chronic inflammation and that inflammatory cells were present in biopsied samples of tumors.

Several lines of evidence from epidemiological studies of patients to molecular studies of genetically modified mice have led to the general acceptance that inflammation and cancer are linked.

The evidence that links cancer and inflammation

- Inflammatory diseases increase the risk of developing many types of cancer (including bladder, cervical, gastric, intestinal, oesophageal, ovarian, prostate and thyroid cancer).
- Non-steroidal anti-inflammatory drugs reduce the risk of developing certain cancers (such as colon and breast cancer) and reduce the mortality caused by these cancers.
- Signalling pathways involved in inflammation operate downstream of oncogenic mutations (such as mutations in the genes encoding RAS, MYC and RET).
- Inflammatory cells, chemokines and cytokines are present in the microenvironment of all tumors in experimental animal models and humans from the earliest stages of development.
- The targeting of inflammatory mediators (chemokines and cytokines, such as TNF- α and IL-1 β), key transcription factors involved in inflammation (such as NF-KB and STAT3) or inflammatory cells decreases the incidence and spread of cancer.
- Adoptive transfer of inflammatory cells or over expression of inflammatory cytokines promotes the development of tumors.

Cancer and inflammation are connected by two pathways: the intrinsic pathway and the extrinsic pathway.

The intrinsic pathway is activated by genetic events that cause neoplasia.

These events include:

- **the activation of various types of oncogene by mutation,**
- **chromosomal rearrangement or amplification,**
- **the inactivation of tumor-suppressor genes.**

Cells that are transformed in this manner produce inflammatory mediators, thereby generating an inflammatory microenvironment in tumors for which there is no underlying inflammatory condition (for example, breast tumors).

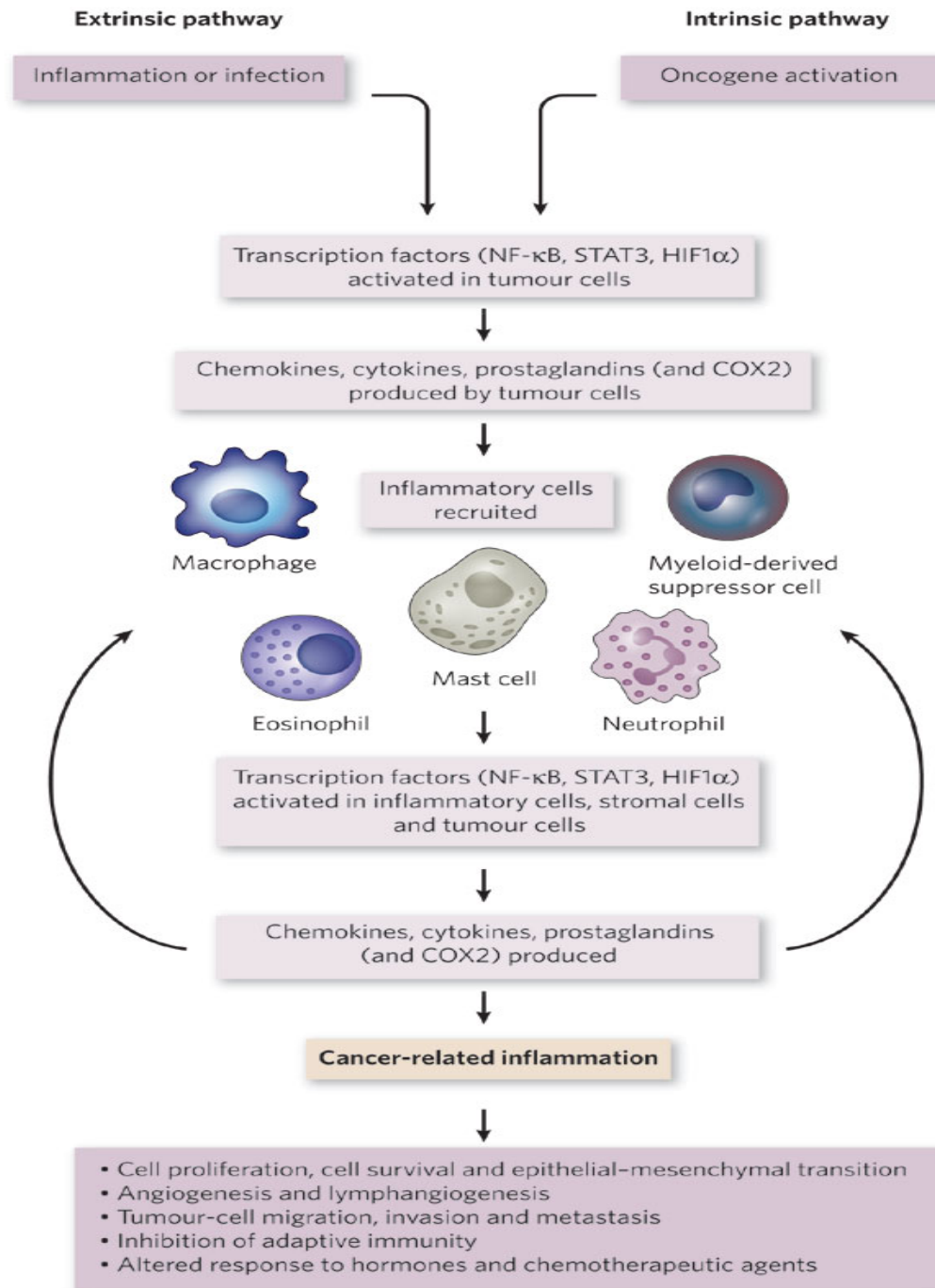
By contrast, in the extrinsic pathway, inflammatory or infectious conditions augment the risk of developing cancer at certain anatomical sites (for example, the colon, prostate and pancreas).

The two pathways converge, resulting in the activation of transcription factors, mainly nuclear factor- κ B (NF κ B), signal transducer and activator of transcription 3 (STAT3) and hypoxia-inducible factor 1 (HIF1), in tumour cells. These transcription factors coordinate the production of inflammatory mediators, including cytokines and chemokines, as well as the production of cyclooxygenase 2 (COX2) (which, in turn, results in the production of prostaglandins).

These factors recruit and activate various leukocytes, most notably cells of the myelomonocytic lineage.

The cytokines activate the same key transcription factors in inflammatory cells, stromal cells and tumor cells, resulting in more inflammatory mediators being produced and a cancer-related inflammatory microenvironment being generated.

Smouldering cancer-related inflammation has many tumor-promoting effects.



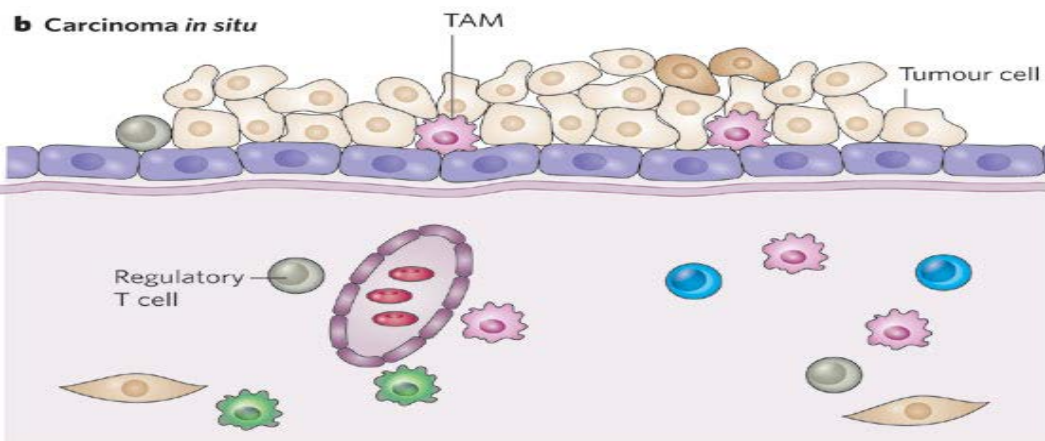
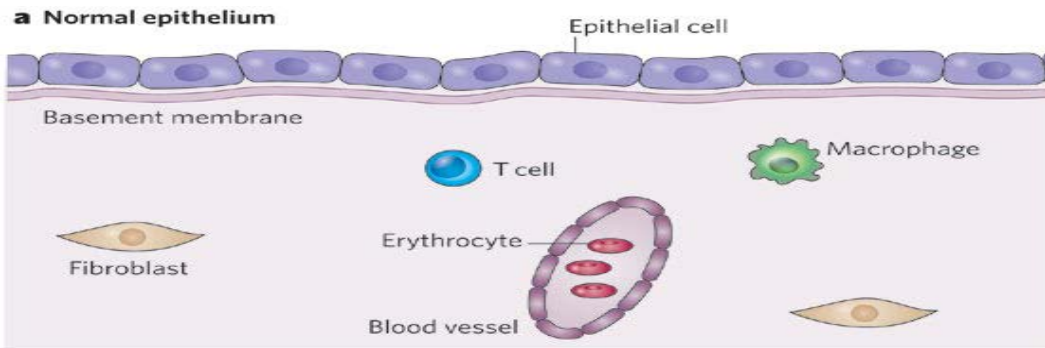
**Mantovani et al
Nature 2008.**

Chronic inflammatory conditions associated with neoplasms

Pathologic condition	Associated neoplasm(s)	Aetiologic agent
Asbestosis, silicosis	Mesothelioma, lung carcinoma	Asbestos fibres, silica particles
Bronchitis	Lung carcinoma	Silica, asbestos, smoking (nitrosamines, peroxides)
Cystitis, bladder inflammation	Bladder carcinoma	Chronic indwelling, urinary catheters
Gingivitis, lichen planus	Oral squamous cell carcinoma	
Inflammatory bowel disease, Crohn's disease, chronic ulcerative colitis	Colorectal carcinoma	
Lichen sclerosus	Vulvar squamous cell carcinoma	
Chronic pancreatitis, hereditary pancreatitis	Pancreatic carcinoma	Alcoholism, mutation in trypsinogen gene on Ch. 7
Reflux oesophagitis, Barrett's oesophagus	Oesophageal carcinoma	Gastric acids
Sialadenitis	Salivary gland carcinoma	
Sjögren syndrome, Hashimoto's thyroiditis	MALT lymphoma	
Skin inflammation	Melanoma	Ultraviolet light
Cancers associated with infectious agents		
<i>Opisthorchis, Cholangitis</i>	Cholangiosarcoma, colon carcinoma	Liver flukes (<i>Opisthorchis viverrini</i>), bile acids
Chronic cholecystitis	Gall bladder cancer	Bacteria, gall bladder stones
Gastritis/ulcers	Gastric adenocarcinoma, MALT	<i>Helicobacter pylori</i>
Hepatitis	Hepatocellular carcinoma	Hepatitis B and/or C virus
Mononucleosis	B-cell non-Hodgkin's lymphoma, Burkitt's lymphoma,	Epstein-Barr Virus
AIDS	Non-Hodgkin's lymphoma, squamous cell carcinomas, Kaposi's sarcoma	Human immunodeficiency virus, human herpesvirus type 8
Osteomyelitis	Skin carcinoma in draining sinuses	Bacterial infection
Pelvic inflammatory disease, chronic cervicitis	Ovarian carcinoma, cervical/anal carcinoma	Gonorrhoea, chlamydia, human papillomavirus
Chronic cystitis	Bladder, liver, rectal carcinoma, follicular lymphoma of the spleen	Schistosomiasis

Modified from refs 29, 67. MALT, mucosa-associated lymphoid tissue.

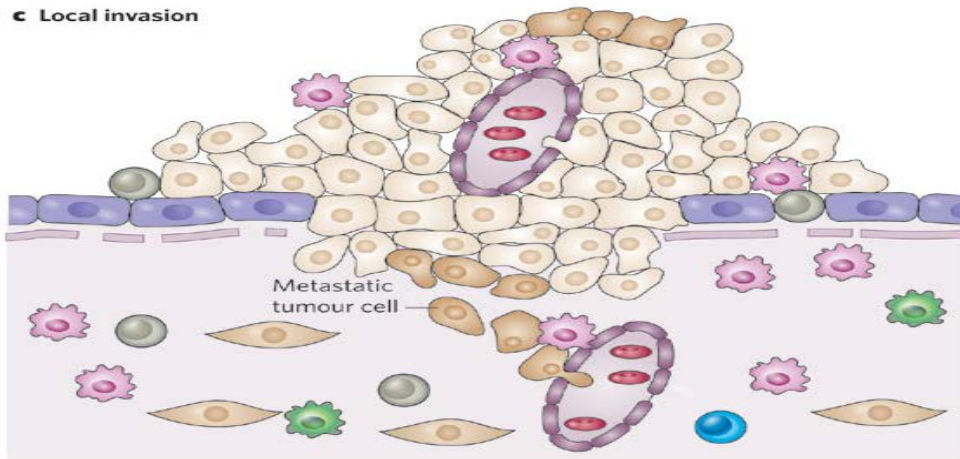
Coussens and Werb, Nature 2002.



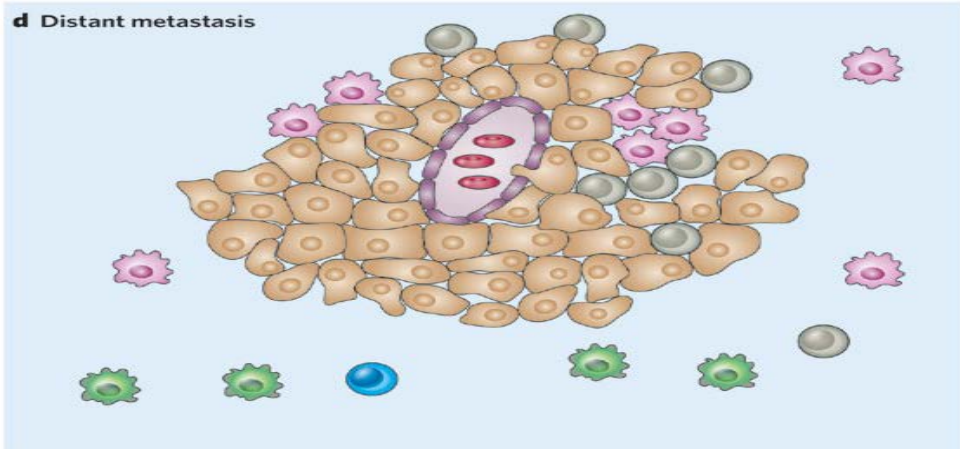
a, Normal epithelium. The proliferation of epithelial cells and the homeostatic trafficking of leukocytes in the epithelium is regulated by autocrine and paracrine chemokine- and cytokine-mediated signalling.

b, Carcinoma *in situ*. The extrinsic (inflammatory) pathway and the intrinsic (oncogenic) pathway induce the production of chemokines and cytokines. These factors attract a tumour-promoting infiltrate (which contains, for example, TAMs and regulatory T cells, as shown here), and they also promote angiogenesis. The expression of chemokine receptors can be induced on initiated cells (that is, early tumour cells). These receptors then aid in tumour-cell survival and might be necessary (but are not sufficient) for invasion across the basement membrane. Both autocrine and paracrine networks of cytokines and chemokines are involved in these processes.

c Local invasion



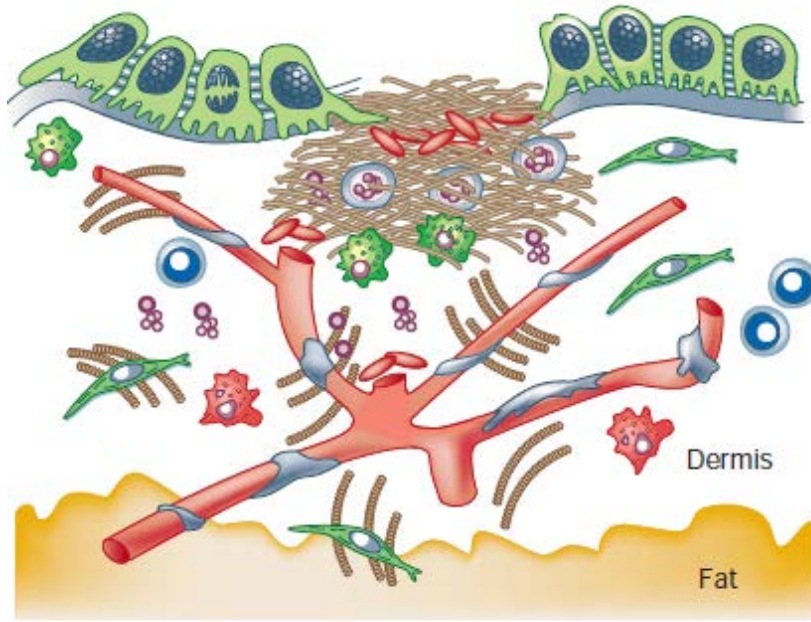
d Distant metastasis



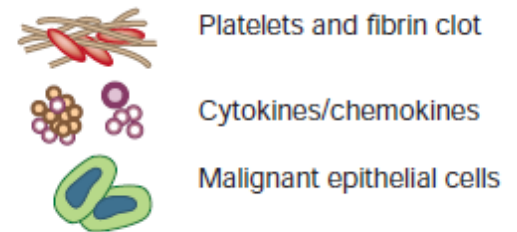
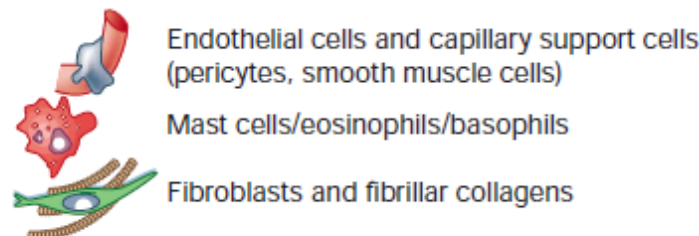
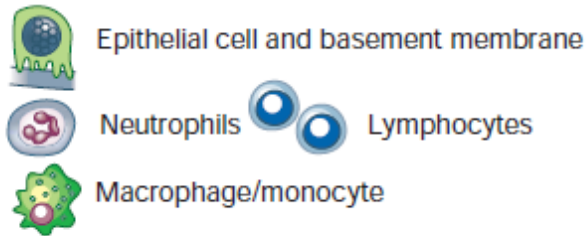
c, Local invasion. The chemokines and cytokines continue to attract and modulate a tumour-promoting infiltrate. They also promote angiogenesis and control tissue remodelling (for example, changes in the basement membrane). Operating in paracrine and autocrine loops, these factors induce the expression of genes associated with survival, invasion and migration in cells that have enough oncogenic changes to allow them to invade the basement membrane. The chemokines and cytokines are also involved in the intravasation of tumour cells into blood vessels and in lymphatic spread.

d, Distant metastasis. The autocrine and paracrine chemokine- and cytokine-mediated signalling promotes the survival of malignant cells in distant organs, again attracting a tumour-promoting infiltrate and stimulating angiogenesis

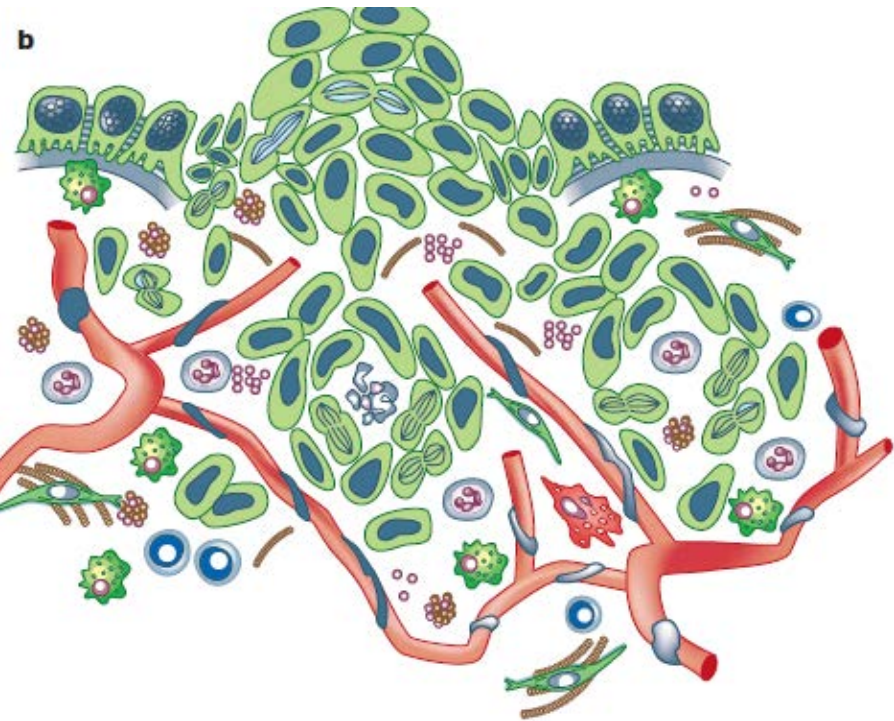
a



Wound healing versus invasive tumour growth. a, Normal tissues have a highly organized and segregated architecture. Epithelial cells sit atop a basement membrane separated from the vascularized stromal (dermis) compartment. Upon wounding or tissue assault, platelets are activated and form a haemostatic plug where they release vasoactive mediators that regulate vascular permeability, influx of serum fibrinogen, and formation of the fibrin clot. Chemotactic factors such as transforming growth factor-[beta] and platelet-derived growth factor, derived from activated platelets, initiate granulation tissue formation, activation of fibroblasts, and induction and activation of proteolytic enzymes necessary for remodelling of the extracellular matrix (for example, matrix metalloproteinases and urokinase-type plasminogen activator). In combination, granulocytes, monocytes and fibroblasts are recruited, the venous network restored, and re-epithelialization across the wound occurs. Epithelial and stromal cell types engage in a reciprocal signalling dialogue to facilitate healing. Once the wound is healed, the reciprocal signalling subsides.



b








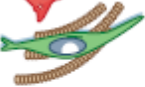




b. Invasive carcinomas are less organized. Neoplasia-associated angiogenesis and lymphangiogenesis produces a chaotic vascular organization of blood vessels and lymphatics where neoplastic cells interact with other cell types (mesenchymal, haematopoietic and lymphoid) and a remodelled extracellular matrix, many reciprocal interactions occur in parallel.

Neoplastic cells produce an array of cytokines and chemokines that are mitogenic and/or chemoattractants for granulocytes, mast cells, monocytes/macrophages, fibroblasts and endothelial cells.

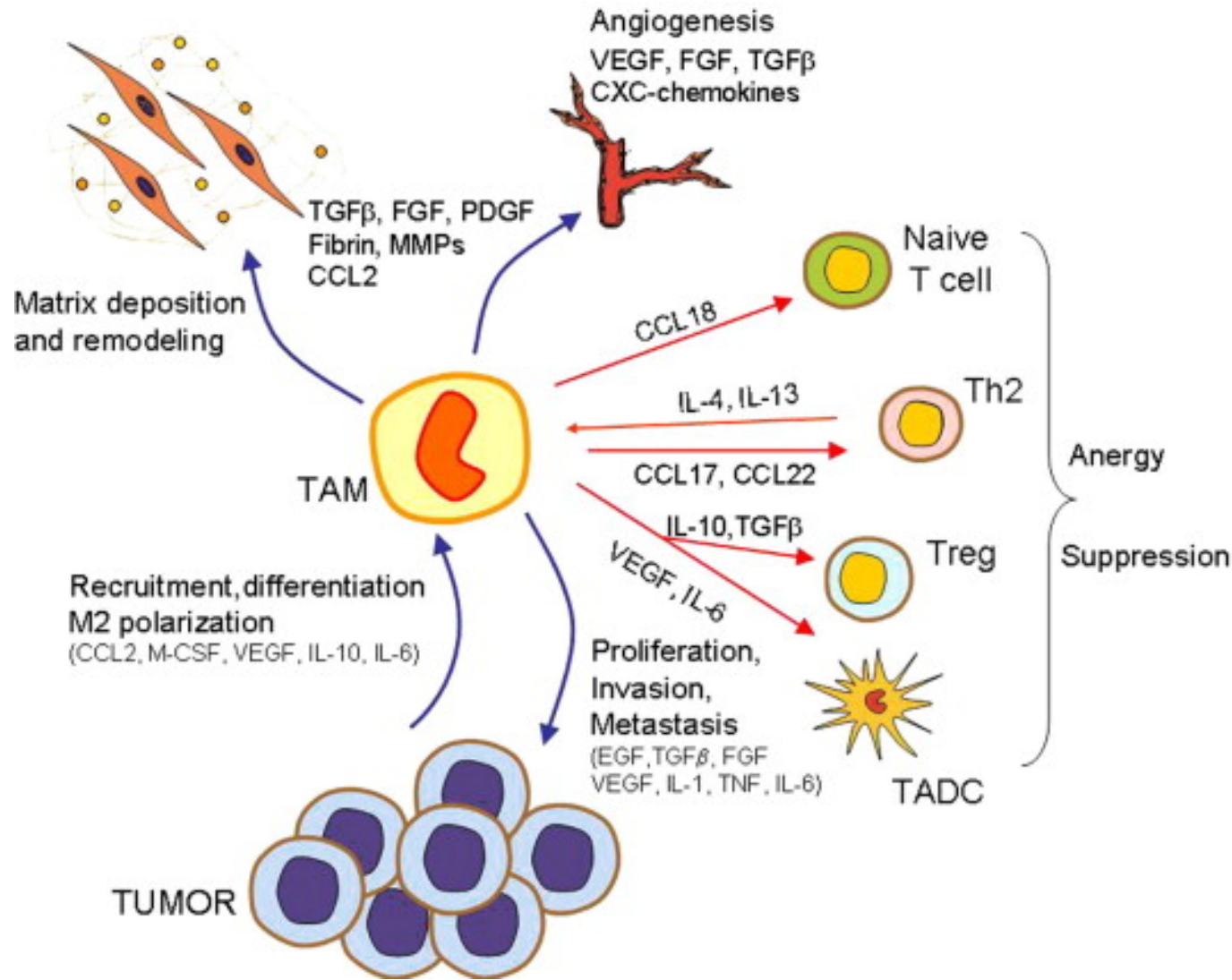
In addition, activated fibroblasts and infiltrating inflammatory cells secrete proteolytic enzymes, cytokines and chemokines, which are mitogenic for neoplastic cells, as well as endothelial cells involved in neoangiogenesis and lymphangiogenesis.

These factors potentiate tumour growth, stimulate angiogenesis, induce fibroblast migration and maturation, and enable metastatic spread via engagement with either the venous or lymphatic networks.

	Epithelial cell and basement membrane		Endothelial cells and capillary support cells (pericytes, smooth muscle cells)		Platelets and fibrin clot
	Neutrophils		Mast cells/eosinophils/basophils		Cytokines/chemokines
	Lymphocytes		Fibroblasts and fibrillar collagens		Malignant epithelial cells
	Macrophage/monocyte				

Pro-tumoral functions of TAM

- **Production of growth and survival factors for tumor cells**
e.g. EGF, IL-6, CXCL8
- **Production of angiogenic factors**
e.g. EGF, FGF, VEGF, PDGF, TGF β , ELR+ chemokines
- **Degradation of extra-cellular matrix and tissue remodelling activity**
e.g. Expression and release of MMPs, uPA, deposition of fibrin and collagen
- **Suppression of adaptive immune responses**
e.g. Production of immunosuppressive mediators, e.g. IL-10, PGE2, TGF β
Low or absent immunostimulatory cytokines, e.g IL-12
Release of chemokines CCL17, CCL18 and CCL22 recruiting T cell subsets devoid of cytotoxic ability (Th2, T naïve and Treg)



Protumoral functions of tumor-associated macrophages (TAM) and interplay with tumor cells. Tumor-derived chemotactic factors (CC-chemokines, eg. CCL2), M-CSF and VEGF actively recruit blood monocytes at the tumor site, where they differentiate to resident macrophages. Several TAM products directly stimulate the growth of tumor cells (e.g. EGF, FGF, cytokines). TAM also contribute to the angiogenic switch by releasing angiogenic factors (VEGF, FGF, TGF β , chemokines) and to the degradation and remodeling of the matrix with metalloproteases, MMPs. Inhibition of anti-tumor responses is achieved by the secretion of immunosuppressive cytokines, like IL-10 and TGF β , and by selective recruitment of naïve T cells, via the chemokine CCL18, and of Th2 and Treg, via the chemokines CCL17 and CCL22.

Sica et al Cancer Letters, 2008.