# V11: Tumor microenvironment

A tumor is not simply a group of cancer cells, but rather a heterogeneous collection of infiltrating and resident host cells, secreted factors and extracellular matrix.

Tumor cells stimulate significant molecular, cellular and physical changes within their host tissues to support tumor growth and progression.

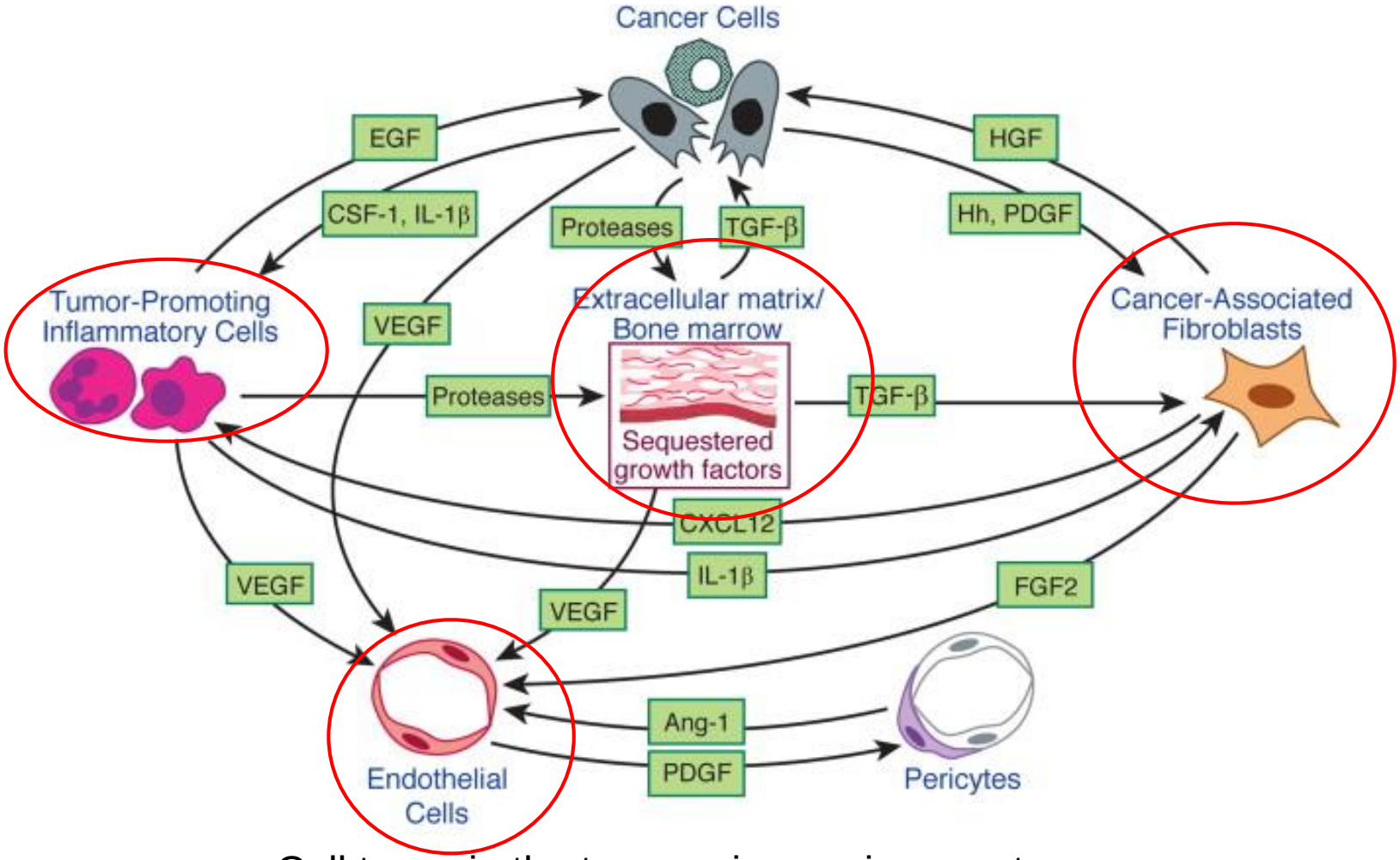
An emerging tumor microenvironment is a complex and continuously evolving entity.

The composition of the tumor microenvironment varies between tumor types, but hallmark features include immune cells, stromal cells, blood vessels, and extracellular matrix.

It is believed that the “tumor microenvironment is not just a silent bystander, but rather an active promoter of cancer progression”.

Anderson & Simon,
Current Biology 30, R921–R925, (2020)

# Cell types in the tumor microenvironment

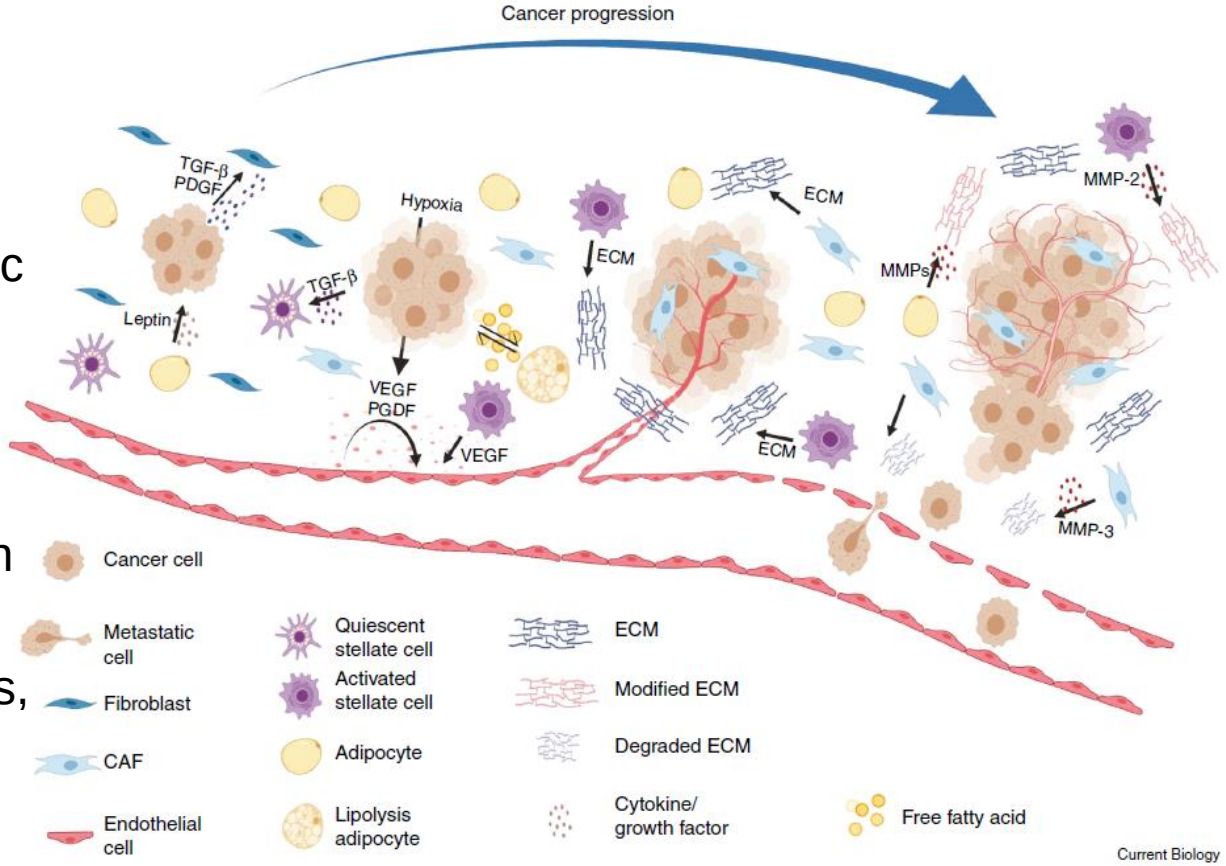



Cell types in the tumor microenvironment communicate by cellular signaling.

Hanahan & Weinberg, *Cell* **144**, 646–674 (2011)

# Tumor microenvironment

In the tumor microenvironment, stromal cells from neighboring tissue and cancer cells are in a dynamic relationship promoting the cancer progression.




The stromal cell composition varies between tumor types but includes endothelial cells, fibroblasts, adipocytes and stellate cells.

The tumor microenvironment orchestrates angiogenesis, proliferation, invasion and metastasis through the secretion of growth factors and cytokines.



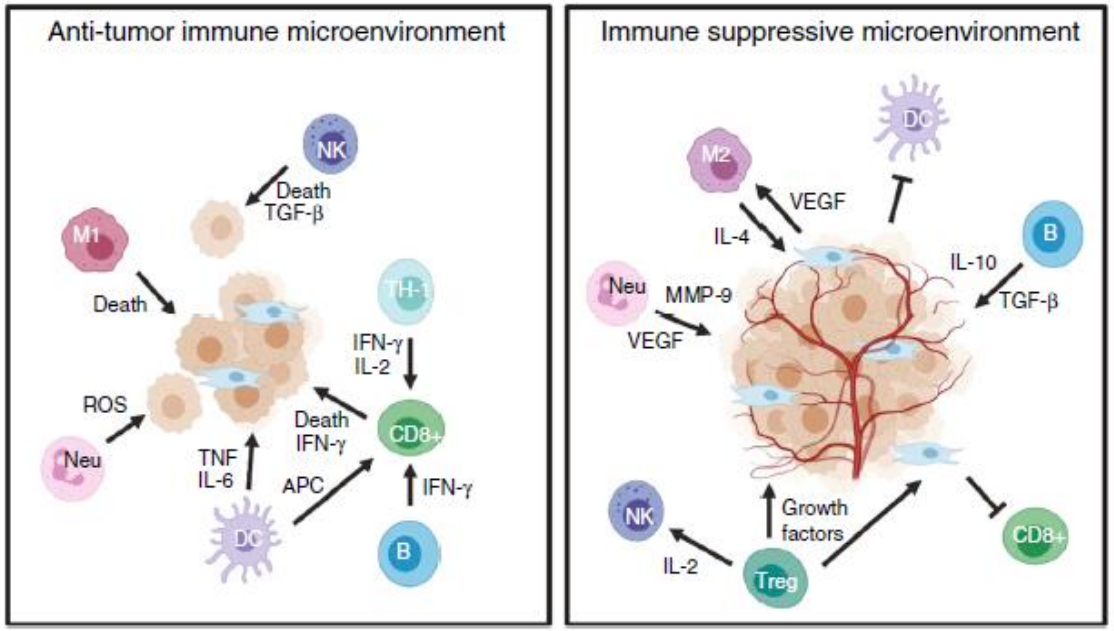
Anderson & Simon, Cellular Programs
Current Biology 30, R921–R925 (2020)

# Tumor microenvironment (II)

Early in tumor growth, a dynamic and reciprocal relationship develops between cancer cells and components of the tumor microenvironment that supports cancer cell survival, local invasion and metastatic dissemination.

To overcome a hypoxic (low oxygen supply) and acidic microenvironment, the tumor microenvironment coordinates a program that promotes **angiogenesis** to restore oxygen and nutrient supply and remove metabolic waste.

Tumors become infiltrated with diverse adaptive and innate immune cells that can perform both pro- and antitumorigenic functions.



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# Immune cells

Immune cells are critical components of the tumor microenvironment.

Persistent **inflammation** due to chronic infection is a common mechanism underlying tumor formation in several types of cancer, including colorectal, hepatocellular and cervical cancer.

Broadly, immune cells fall into 2 categories: adaptive immune cells and innate immune cells.

**Adaptive immunity** is activated by exposure to specific antigens and uses an **immunological memory** to ‘evaluate’ the threat and enhance immune responses.

T cells, B cells and natural killer (NK) cells belong to the adaptive immune response.

**Innate immunity** is a non-specific defense mechanism that comes into play within hours of a foreign antigen entering the body.

Cells that carry out an innate immune response include macrophages, neutrophils and dendritic cells.

Anderson & Simon,
Current Biology 30, R921–R925 (2020)

# Landscape of immune cells

The immune landscape within the tumor microenvironment falls into three main categories: immune infiltrated, immune excluded, and immune silent.

In an **immune infiltrated tumor**, immune cells (such as cytotoxic T cells) are homogeneously distributed throughout the tumor indicating an active immune response.

Alternatively, some tumors are classified as **immune excluded**.

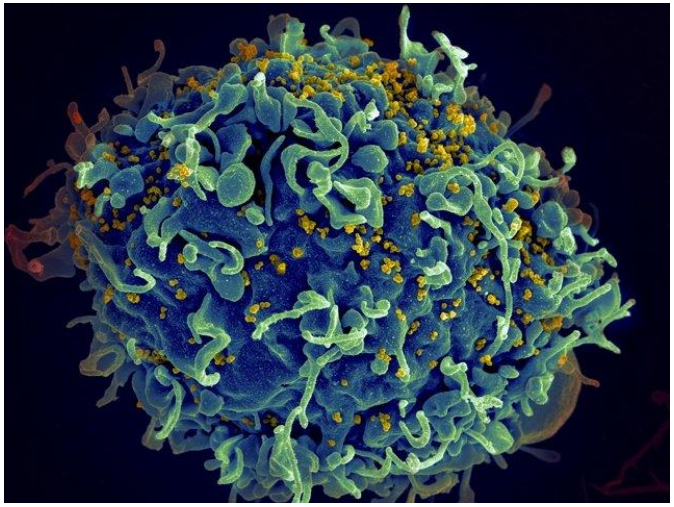
In these cases T cells are only located at the periphery of the tumor and have not infiltrated the tumor microenvironment.

Finally, some tumors are categorized as '**immune silent**' and completely lack immune cell infiltrates, indicating no immune response to the tumor.

Anderson & Simon,
Current Biology 30, R921–R925 (2020)

# Immune cells: regulatory T-cells

Regulatory T cells (Tregs) are normally required to suppress inflammatory responses and control autoimmunity.



In the context of the tumor microenvironment, Tregs are ubiquitous and promote tumor development and progression by dampening anti-tumor immune responses..

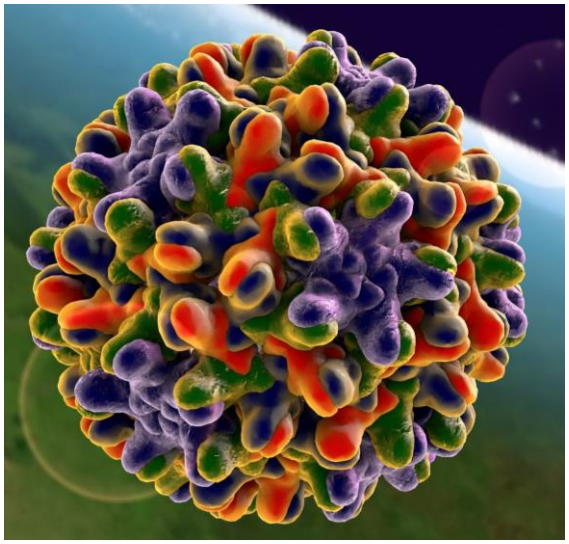
E.g. Tregs secrete the cytokine interleukin 2 (IL-2), which modulates NK cell homeostasis and function.

Additionally, Tregs directly support the survival of cancer cells through the secretion of growth factors, and indirectly through interaction with stromal cells such as fibroblasts and endothelial cells.

Anderson & Simon,
Current Biology 30, R921–R925 (2020)
Picture: blog.hemacare.com

# T cells (I)

Each T cell develops its own T-cell receptor (TCR) that recognizes a specific antigen. Within the tumor microenvironment, there are several distinct populations of T cells that influence tumorigenesis.



**Cytotoxic T cells** (CD8+) (abbreviated as CTLs) detect abnormal tumor antigens expressed on cancer cells and target them for destruction.

The presence of CTLs in the tumor microenvironment is often associated with a **positive prognosis** in cancer patients.

CTLs kill tumor cells and suppress angiogenesis through the secretion of interferon gamma (IFN-γ).

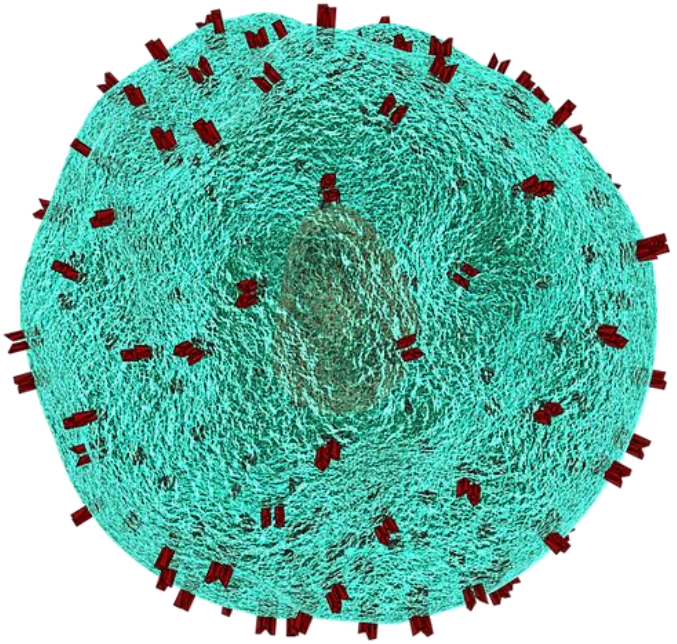
Anderson & Simon,
Current Biology 30, R921–R925 (2020)
Picture: blog.hemacare.com

# T cells (II)

CD4+ T cells differentiate into a variety of subtypes and thus coordinate a wide range of immune responses within the context of the tumor microenvironment.

T helper 1 (Th-1) cells are proinflammatory CD4+ T cells that support CD8+ cells through the secretion of IL-2 and IFN-γ.

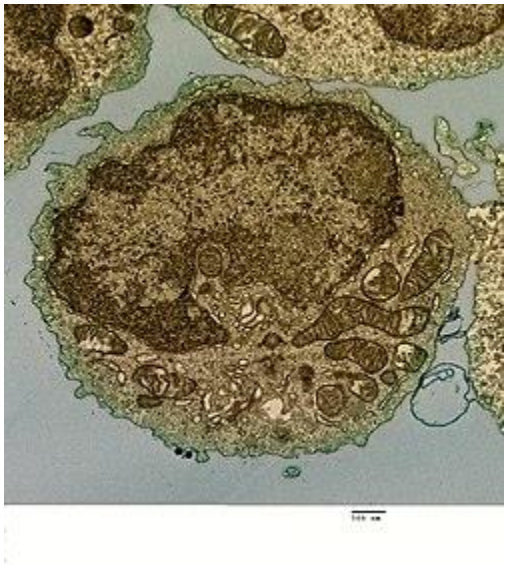
Increased levels of Th-1 cells within the tumor microenvironment are also associated with **positive outcomes** in many types of cancer.



Anderson & Simon,
Current Biology 30, R921–R925 (2020)
Picture: pixabay.com

# B cells

B cells, also known as B lymphocytes, are a type of white blood cell of the lymphocyte subtype.



The antitumorigenic roles of B cells include antigen-presentation to T cells, anti-tumor antibody production and secretion of cytokines, like IFN-γ, that promote cytotoxic immune responses.

Alternatively, B cells can have protumor effects.

Their presence in the tumor microenvironment can be predictive of **poor outcome** in bladder cancer, prostate cancer, and renal cell carcinoma.

Similar to Tregs, regulatory B cells promote tumor aggression through production of cytokines (including IL-10 and transforming growth factor beta (TGF-β)) that promote immune suppressive phenotypes in macrophages, neutrophils, and cytotoxic T cells.

Anderson & Simon,
Current Biology 30, R921–R925 (2020)
Picture: Wikipedia.org

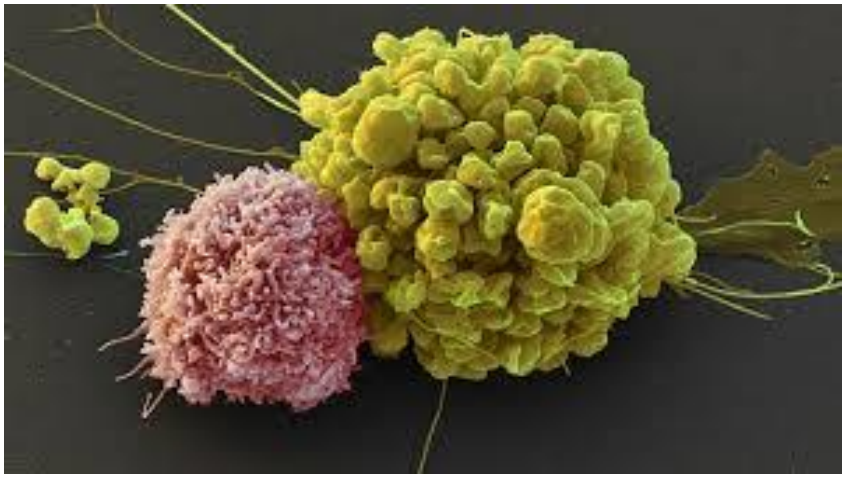
# Natural killer cells

Natural killer cells typically patrol the bloodstream, seeking out virally infected host cells and tumor cells.

Functionally, natural killer cells can be broken down into two classes, those that directly participate in cell-mediated killing of tumor cells and those that secrete inflammatory cytokines.

Natural killer cells are highly efficient at killing tumor cells within the circulation and can participate in blocking metastasis, but they are less efficient at killing within the tumor microenvironment.

NK cell (left) attacks cancer cell (right)



Anderson & Simon,
Current Biology 30, R921–R925 (2020)
Picture: https://nature.com

# Macrophages

Macrophages are critical components of the innate immune system that modulate immune responses through pathogen phagocytosis and antigen presentation.

In addition, macrophages are critical in wound healing and tissue repair.

Monocyte derived macrophages can be categorized as either

**- inflammatory M1 macrophages**, which phagocytize and kill cells, or

**- immune-suppressive M2 macrophages**, which participate in wound healing.

Both classes of macrophages can be found within a tumor. Yet, the tumor microenvironment promotes the M2 phenotype through hypoxia and the secretion of cytokines (such as IL-4) to support tumor growth and progression.

Certain tumor types can be heavily infiltrated with macrophages, which can comprise up to 50% of a tumor's mass.

Typically, high macrophage infiltration is associated with **poor patient prognosis** in many types of cancer, such as breast, lung, and gastric cancers.

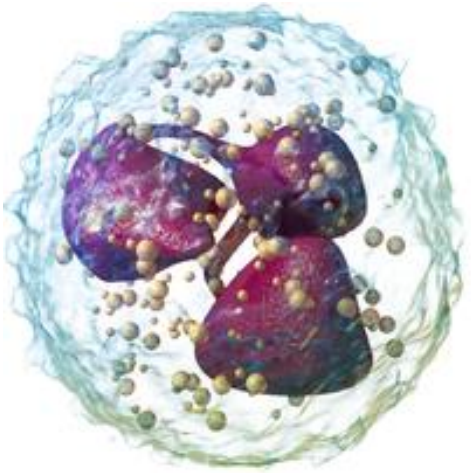
Often, macrophages are found to surround blood vessels in the tumor microenvironment where they secrete vascular endothelial growth factor (VEGF) and induce new blood vessel formation.

Anderson & Simon,
Current Biology 30, R921–R925 (2020)

# Neutrophils

Neutrophils make up to 70% of circulating leukocytes and provide the first line of defense against many pathogens.

In the context of cancer, neutrophils can act to either suppress or promote tumor growth, depending on tumor type and stage of development.



Neutrophils contain a nucleus divided into 2–5 lobes.

As a tumor begins to grow, neutrophils are recruited to the tumor microenvironment and promote inflammation through release of cytokines and reactive oxygen species that promote tumor cell apoptosis.

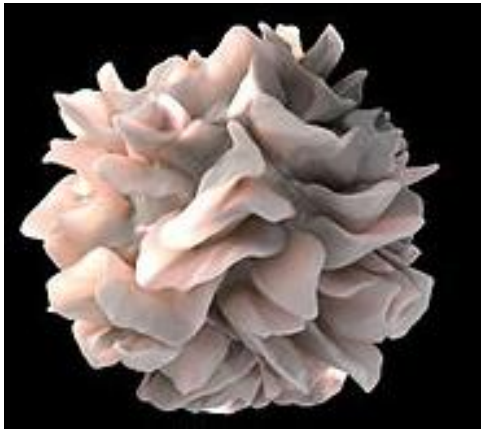
Later in tumor development, neutrophils promote tumor growth through modification of the extracellular matrix, releasing VEGF and producing matrix metalloprotease (MMP)-9 to stimulate angiogenesis and, ultimately, tumor progression and local invasion.

Anderson & Simon,
Current Biology 30, R921–R925 (2020)
picture: Wikipedia.org

# Dendritic cells

Dendritic cells play a critical role in the immune system: they recognize, capture and **present antigens** to T cells at secondary lymphoid organs (such as lymph nodes).

Such antigens could e.g. result from pathogen infection.



The fate of dendritic cells in the tumor microenvironment is shaped by cues that promote either an anti-tumor immune response or tolerance.

Dendritic cells are inherently programmed to have an anti-tumorigenic function in the body, but the tumor microenvironment can co-opt dendritic cells to support tumor progression.

Specifically, cytokines secreted from the tumor microenvironment trigger dendritic cells to tolerate the presence of tumor cells and block the induction of an immune response.

Anderson & Simon, Current Biology 30, R921–R925 (2020) Picture: Sriram Subramaniam, National Cancer Institute (NCI) and Donny Bliss, National Library of Medicine (NLM).

# Stromal cells

Cancer cells recruit supporting cells from nearby endogenous tissue stroma to promote critical steps in tumor formation.

Stromal cell composition can vary significantly between tumor types and include vascular endothelial cells, fibroblasts, adipocytes and stellate cells.

Once recruited to the tumor microenvironment, stromal cells secrete many factors that influence angiogenesis, proliferation, invasion, and metastasis.

Anderson & Simon,
Current Biology 30, R921–R925 (2020)

# Endothelial cells (I)

Vascular endothelium is a thin monolayer of endothelial cells that help to orchestrate the formation of blood vessels.

Vascular endothelium separates circulating blood from tissues. Besides, it also delivers water and nutrients, maintains metabolic homeostasis, carries immune cells and participates in the formation of new blood vessels.

During the initial stages of tumor development, cancer cells rely on passive diffusion for gas exchange and the transport of nutrients.

Once tumors reach 1–2 $mm^3$ in volume, insufficient oxygen and a build-up of metabolic waste results in the tumor microenvironment becoming hypoxic and acidic.

To overcome this, tumors must develop their own blood supply.

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# Endothelial cells (II)

Specifically, hypoxia-inducible factors initiate blood vessel sprouting by **instructing endothelial cells to secrete proangiogenic factors** such as platelet derived growth factor (PDGF), epidermal growth factor (EGF) and VEGF.

VEGF stimulates migration of endothelial cells to form new blood vessel lumens.

Endothelial cells are also critical in promoting cancer cell migration, invasion and metastasis. They are highly plastic in nature and can change cell fate.

During tumor progression, endothelial cells undergo what is called the '**endothelial–mesenchymal transition**' (EMT) to become **cancer-associated fibroblasts** (CAFs).

This transition is organized by TGF-β and bone morphogenetic protein (BMP), and leads to loss of cell-to cell connections, detachment and elongation, enhanced migration and loss of endothelial properties.

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# Endothelial cells (III)

Cancer associated fibroblasts are critical in stimulating migration and invasion of tumor cells.

Metastasis is a multistep process that involves translocation of cancer cells from the primary tumor microenvironment to distant locations.

Tumor cells must first escape the primary tumor site and enter the vasculature in a process known as **intravasation**.

During intravasation, tumor cells adhere to endothelial cells and this interaction changes the endothelial barrier, allowing tumor cells to migrate between two endothelial cells.

In addition, blood vessels formed in the tumor microenvironment are usually immature and lack proper cell-to-cell connections, enabling cancer cells to transverse the vasculature.

Anderson & Simon,
Current Biology 30, R921–R925 (2020)

# Cancer associated fibroblasts (I)

Cancer-associated fibroblasts (CAFs) are a major component of the tumor stroma and play a critical role in facilitating crosstalk between cancer cells and tumor microenvironment (see also https://www.nature.com/articles/s41568-019-0238-1).

CAFs are often (not always) derived from fibroblasts.

Upon injury, fibroblasts that normally reside within tissues can become reversibly induced to form **myofibroblasts**, which actively participate in wound healing.

Myofibroblasts are activated by TGF-β signaling and develop characteristics important in wound healing, such as proliferation, contractile properties, secretory phenotypes and ECM formation.

Tumors have been termed ‘wounds that never heal’.

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# Cancer associated fibroblasts (II)

In the tumor microenvironment, cancer and stromal cells secrete factors such as TGF-β, PGDF, and fibroblast growth factor 2 (FGF2) to convert fibroblasts into CAFs.

A build-up of CAFs within the tumor microenvironment is often associated with **poor prognosis** in many cancer types.

Despite this association, CAFs have been shown to both promote and restrain tumorigenesis.

Within the tumor microenvironment, CAFs produce the majority of extracellular components, including growth factors, cytokines and extracellular matrix components.

CAFs shape the tumor microenvironment in 4 main ways:

tumor proliferation and metastasis, neoangiogenesis, ECM remodeling and immunosuppression.

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# Cancer associated fibroblasts (III)

In tumors of epithelial origin, the epithelial– mesenchymal transition (EMT) is a critical step in metastasis. During EMT, epithelial cells lose cell polarity and cell-to-cell adhesions and gain migratory and invasive phenotypes.

CAFs control metastasis by secreting TGF-β, which is required for the EMT and angiogenesis.

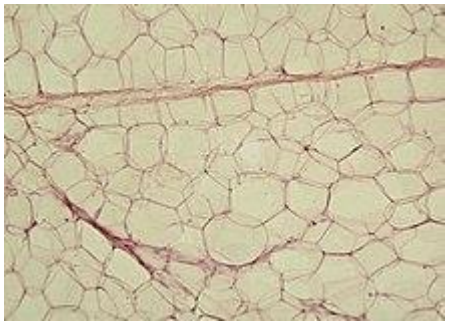
To facilitate migration of cancer cells through the tumor microenvironment, cancer-associated fibroblasts secrete the matrix metallo protease MMP-3, which degrades E-cadherin to promote cancer cell invasion → MMPs are candidate drug targets.

The ECM is also an important source of VEGF, which can be released by MMP-13 to promote angiogenesis.

In general, cancer-associated fibroblasts promote an immunosuppressive phenotype through the production of immune-modulatory chemokines and cytokines.

Anderson & Simon,
Current Biology 30, R921–R925 (2020)

# Adipocytes



Adipocytes are specialized cells within the body that regulate energy balance and are responsible for storing excess energy as fat.

Adipocytes exert their effects on the tumor microenvironment through secretion of metabolites, enzymes, hormones, growth factors and cytokines.

Within the context of the tumor microenvironment, adipocytes are in a dynamic and reciprocal relationship with tumor cells to support tumor progression.

Breast tissue is largely composed of white adipose tissue; therefore, adipocytes are a critical player in the breast cancer tumor microenvironment.

Anderson & Simon,
Current Biology 30, R921–R925 (2020)
Picture: Wikipedia.org

# Non-cellular components: extracellular matrix (ECM)

The ECM is composed of collagen, fibronectin, elastin, and laminin.

It is an important molecular component of the tumor microenvironment.

The ECM provides a physical scaffold for cells and plays a key role in promoting tumor cell dissemination.

Solid tumors contain large ECM deposits that constitute up to 60% of tumor mass. Large **collagen deposits**, together with a high percentage of fibroblast infiltration, result in desmoplasia, which is strongly linked to **poor patient prognosis**.

Many cells within the tumor microenvironment secrete components of the ECM, although cancer-associated fibroblasts are the predominant source.

MMPs are proteases that break down extracellular matrix proteins and are critical in remodeling the ECM to promote tumor progression and metastasis.

The ECM is a depot for cytokines and growth factors, which are released by proteases like the MMPs. E.g., the ECM can be a deposit for proangiogenic factors, like VEGF, FGF, PDGF, TGF-β.



Anderson & Simon,
Current Biology 30, R921–R925 (2020)

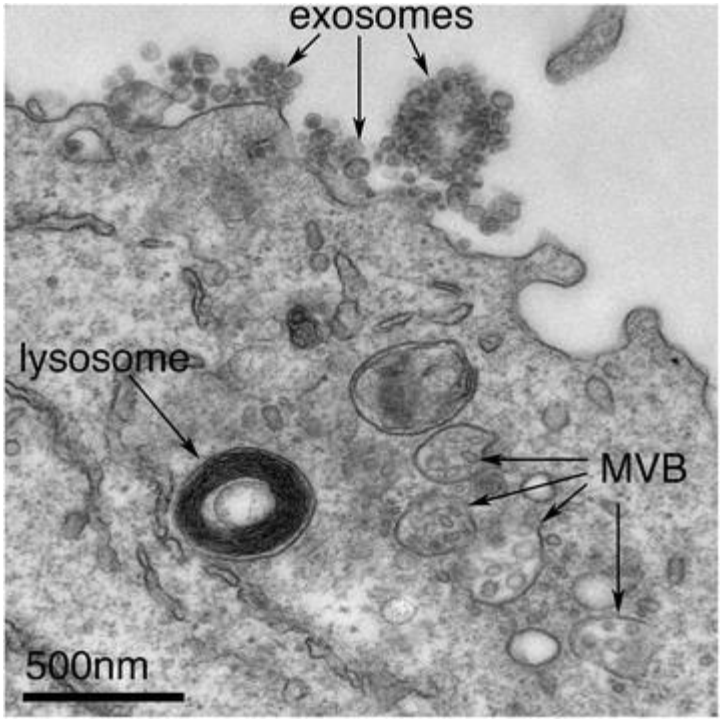
# Extracellular components: exosomes

Exosomes are **microvesicles** that range in size from 30–200 nm.

Their contents reflect the cells from which they were derived, including protein, RNA, DNA and lipids.

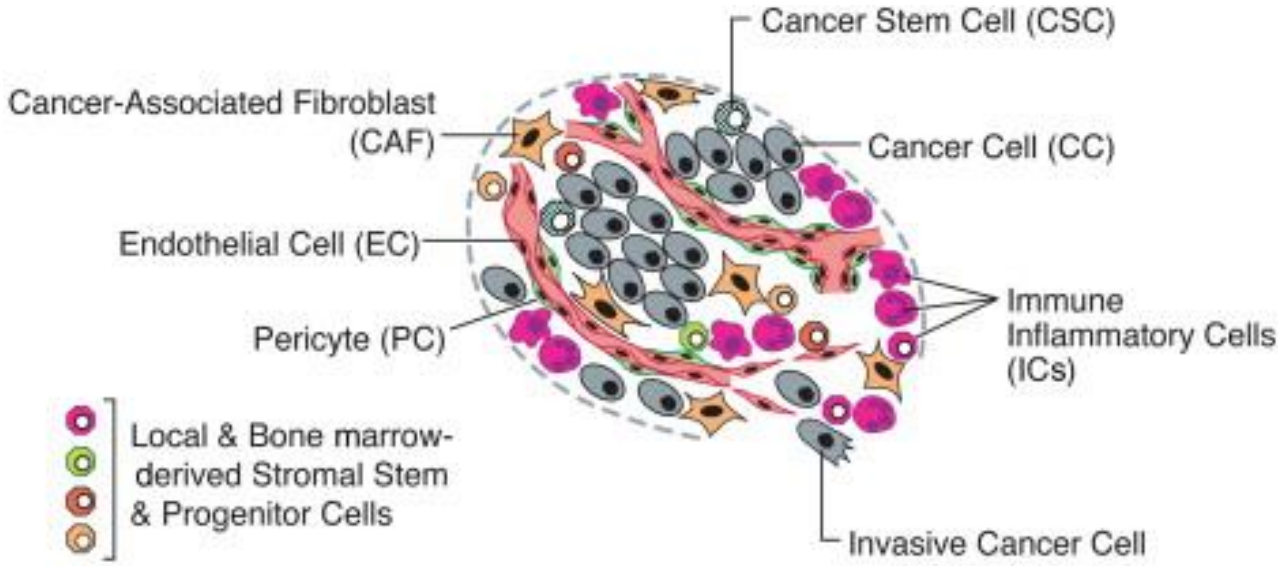
Within the tumor microenvironment, exosomes play a critical role in facilitating cross-talk between cancer cells and stromal cells.

Exosomes have been shown to promote inflammation, tumor progression, angiogenesis, and metastasis within the tumor microenvironment.



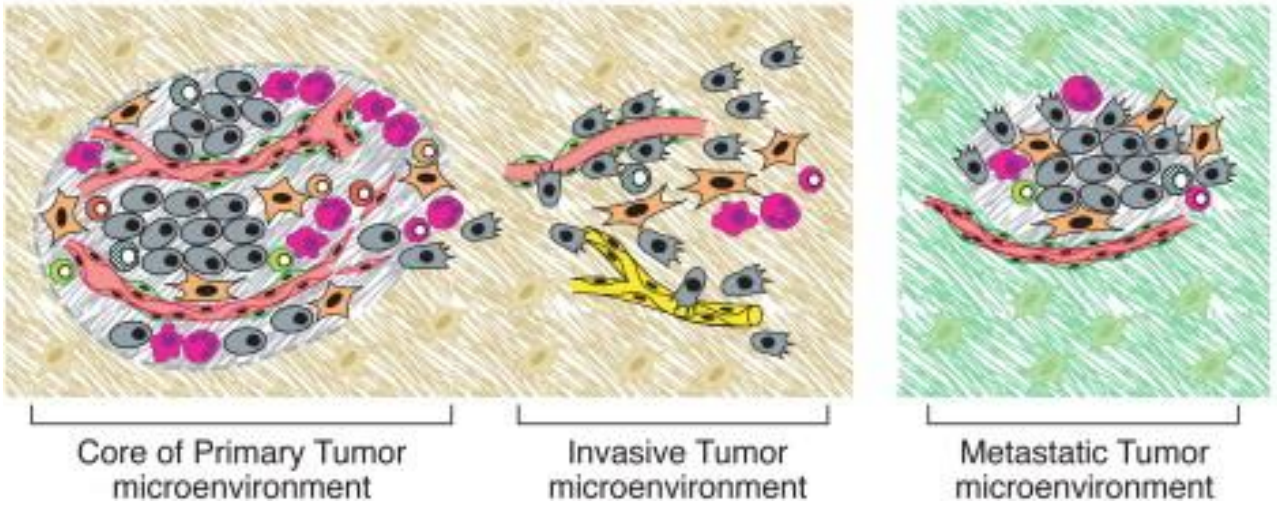

Anderson & Simon,
Current Biology 30, R921–R925 (2020)
Picture: https://bmcbiol.biomedcentral.com/articles/10.1186/s12915-016-0268-z

# Tumor microenvironment




(TOP) Assemblage of different cell types make up most solid tumors.

(BOTTOM) Different stages of the tumor face changing micro-environments.




Hanahan & Weinberg, *Cell* **144**, 646–674 (2011)

# Summary

Cancer arises from mutations accruing within cancer cells, but both disease progression and responses to therapy are strongly modulated by non-mutant cells within the tumor microenvironment.

Cancer cells can hijack surrounding immune cells and epithelial cells for their own benefit, e.g. in securing oxygen supply and waste removal.

Remodelling of the ECM is important for EMT and metastasis.

CAFs are perhaps the most effective cell within the tumor microenvironment at depositing and remodeling the ECM.

# Content of final exam

| Lecture | Slides relevant for exam |
|---|---|
| 1 | 17-38 |
| 2 | 11-13 |
| 3 | 8-17 |
| 4 | 1-3, 19-20 |
| 5 | 1-8 |
| 6 | 2-3, 9-18 |
| 7 | 1-18 |
| 8 | 1-17, 20-22 (V1-V8 as announced in V8) |
| 9 | all |
| 10 | none |
| 11 | all (1-26) |

| Paper | Figures relevant for exam |
|---|---|
| 1 | None |
| 2 | None |
| 3 | All figures |
| 4 | Figs 1, 2 |
| 5 | Figs 1, 2 |
| 6 | All figures |
| 7 | Figs 1, 2, 3 |
| 8 | None |
| 9 | Figs 1, 2, 3, 8, 9 |
| 10 | none |
| 11 | All figures |
| 12 | None |
| 13 | None |

# Typical exam questions

(1) About lecture 6 p.9:

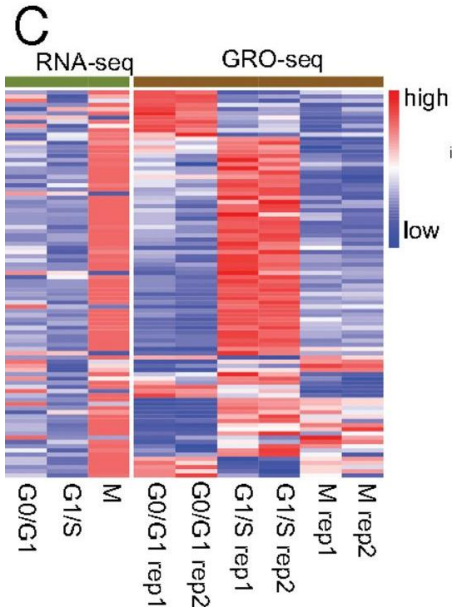
What is the phosphorylation status of the retinoblastoma protein during the cell cycle?

Answer: After cell division RB is unphosphorylated. During the next cell cycle, it is being phosphorylated at multiple sites. Generally, its phosphorylation level increases during the cell cycle.

(2) Fig. 1C of paper 4 shows RNA-seq and GRO-seq levels of known mitotic genes.

How do the results of these two techniques differ?

Why do they differ?




Answer: For RNA-seq, all known mitotic genes peak in M phase, for GRO-seq in G1/S phase.

RNA-seq measures aggregated expression levels, GRO-seq measures active transcription.

# Additional slides (not used)

# Cancer Genes: Gene Fusion (belongs to V10)

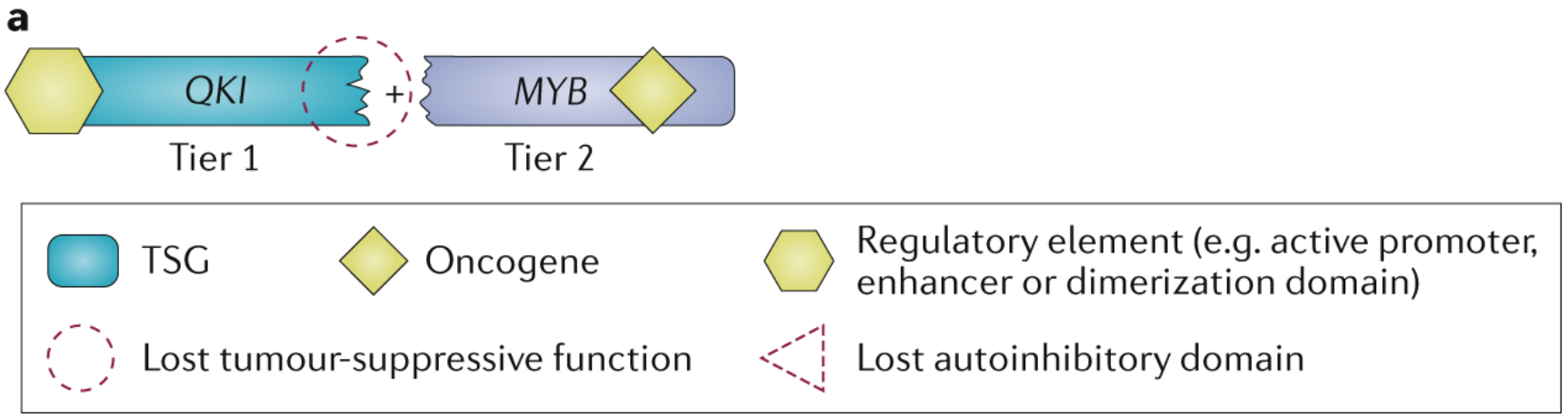
During oncogenic transformation, the intracellular regulatory network is disturbed, leading eventually to cell reprogramming that promotes unregulated proliferation and adaptation to the tissue environment.

Driver mutations will typically result in dysfunction, usually via protein structure change; dysregulation, altering regulatory signals that control gene expression; or complete abrogation, which occurs when the whole tumour-suppressor gene (TSG) is deleted.

Gene fusions form a specific class of genetic alteration associated with specific functional consequences. They usually arise as a consequence of genomic structural rearrangements and involve two distinct genes, forming a new chimeric gene with novel or dysregulated function.

Sondka et al, *Nature Rev Cancer* **18**, 696-705 (2018)

# Oncogenic gene fusions



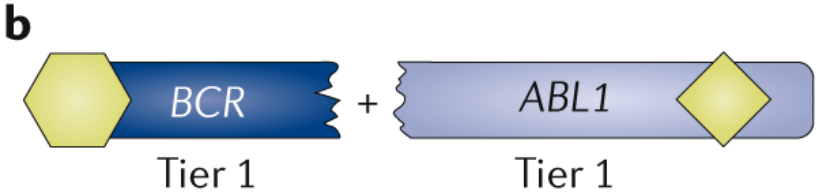

As a result of gene fusion, a tumor-suppressor gene (TSG) may loose its suppressive abilities and a proto-oncogene may be transformed into an oncogene.

An example of this type of mechanism is seen with *QKI–MYB*.

In angiocentric glioma, *MYB* is activated by truncation and the influence of the *QKI* enhancer, and thus, *QKI* loses its tumor-suppressive function

Sondka et al, *Nature Rev Cancer* **18**, 696-705 (2018)

# Oncogenic gene fusions



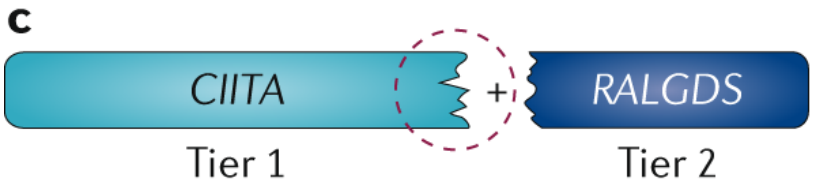

Genes that, after fusion, upregulate an oncogene through donation of a regulatory element (for example, an active promoter, enhancer or activating domain) are included in Tier 1.

An example of this type of mechanism is seen with *BCR–ABL1*.

In this fusion (also known as the Philadelphia chromosome), *BCR*, which is neither a TSG nor an oncogene, simply provides an oligomerization domain, which enables constitutive activation of *ABL1*

Sondka et al, *Nature Rev Cancer* **18**, 696-705 (2018)

# Oncogenic gene fusions

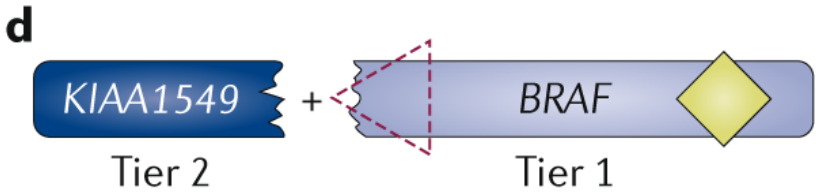



Fusion of genes *CIITA–RALGDS*.

In Hodgkin lymphoma, this fusion results in the amino-terminal part of CIITA, which loses its tumor-suppressive function, fused in an out-of-frame fashion to RALGDS, which is neither a TSG nor an oncogene in this case

Sondka et al, *Nature Rev Cancer* **18**, 696-705 (2018)

# Oncogenic gene fusions




A fusion may also result in hyperactivation of an oncogene owing to loss of an autoinhibitory domain, which is replaced by a fusion partner.

An example of this type of mechanism is seen with *KIAA1549–BRAF*.

In pilocytic astrocytoma, the amino-terminal BRAF autoregulatory domain is lost in the fusion protein, resulting in constitutively active BRAF expressed under the control of the *KIAA1549* promoter.

Sondka et al, *Nature Rev Cancer* **18**, 696-705 (2018)

# Adipocytes (II)

Breast cancer cells can stimulate adipocytes to undergo lipolysis, which breaks down lipid stores making free fatty acids available for uptake by the cancer cells. They then use these free fatty acids for energy production, cell membrane formation, lipid bioactive molecules and exosomes. Leptin is an important hormone produced by adipocytes that promotes tumor progression directly, by influencing breast cancer cell proliferation, and indirectly, by activation of macrophages. Adipocytes also play an important role in modifying extracellular matrix through secretion of metalloproteases, such as MMP-1, MMP-7, MMP-10, MMP-11 and MMP- 14. More than 40% of cancer patients are overweight, making obesity a major risk factor for many types of cancer, including breast, pancreatic and ovarian. White adipose tissue is an endocrine organ that can promote breast cancer cells to metastasize to the liver and lungs through paracrine signaling.

Anderson & Simon,
Current Biology 30, R905–R931, (2020)

# Stellate cells (I)

Stellate cells are quiescent stromal cells of mesenchymal origin located within the liver and pancreas. Upon tissue injury, stellate cells become activated, enter the cell cycle and are induced to transform into myofibroblasts. A characteristic feature of stellate cells is the deposition of vitamin A in lipid droplets. Hepatic stellate cells are normally located within perisinusoidal and portal areas of the liver and can constitute as much as 15% of liver mass. Hepatocellular carcinoma is the predominant form of liver cancer and hepatic stellate cells function to promote crosstalk within the tumor microenvironment.

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# Stellate cells (II)

A key signaling molecule, TGF-β, is produced by hepatocellular carcinomas and triggers hepatic stellate cells to become activated. Once activated, hepatic stellate cells modify the extracellular matrix and produce proangiogenic factors such as VEGF and MMP-2. Lipid droplets are critical structures in hepatic stellate cells that are used to produce new extracellular matrix and remodel it through the production of MMPs. Pancreatic ductal adenocarcinoma is the most common form of pancreatic cancer (95%), characterized by dense fibrotic tissue or desmoplasia. When pancreatic stellate cells are quiescent, they contribute to extracellular matrix modifi cation through the production of extracellular matrix proteins (such as desmin and vimentin) and degradation enzymes. Vitamin A depletion results in pancreatic stellate cell activation, leading to the secretion of cytokines and chemokines, enhanced migration and proliferation potential. Activated pancreatic stellate cells play a critical role in promoting the desmoplastic phenotype of pancreatic ductal adenocarcinoma tumors and their hypoxic microenvironments.

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# Therapeutic target of the tumor microenvironment

Over the last decade cancer treatment has undergone a revolution.

Traditionally, chemotherapy drugs targeted tumors more broadly; but now, new therapeutic strategies target specific cells within the tumor microenvironment. Immune checkpoint blockade therapy was the first generation of antibody-based therapies to target immune cells in the tumor microenvironment (for example, CTLA4 and PD1). These therapies work by blocking receptor–ligand interactions, dulling T-cell activation and function.

Patients who respond to immune check-point blockade therapy have significant clinical benefit, but at this point in time, most patients are unresponsive. The identification of relevant biomarkers is required to recognize patients who are expected to benefit from immune check-point blockade therapy. Therapeutically

targeting dendritic cell activation through the use of dendritic-cell vaccination has been successfully used in the treatment of prostate cancer.

The ‘Provenge’ protocol involves harvesting monocytes from prostate cancer patients, differentiating them into dendritic cells, activation with prostatic acid phosphate antigen, and then re-introducing them back into patients. Provenge therapy can result in significant reduction in tumor burden in prostate cancer patients.

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# Therapeutic target of the tumor microenvironment (II)

Growing tumors require the formation of new blood vessels to relieve oxygen deprivation and accumulating metabolic waste; therefore targeting angiogenesis was an attractive strategy.

Antiangiogenic therapy has focused on targeting the VEGF–VEGF receptor signaling axis and has included: a neutralizing antibody to VEGF (Bevacizumab); decoy receptor for VEGF (Aflibercept); tyrosine kinase inhibitor (Sorafenib); and antibody that blocks VEGF binding its receptor (Ramucirumab). As a single agent, most patients either do not respond to antiangiogenic therapy or develop resistance. Successful integration of antiangiogenic therapy into the clinic will likely require combination with other agents or approaches. For example, Bevacizumab in combination with PDL-1 has shown some success for the treatment of hepatocellular carcinoma and renal cancer. While therapeutically targeting the tumor microenvironment is an attractive strategy for the treatment of cancer, existing FDA-approved treatments have limited efficacy. As we continue to understand how the tumor microenvironment contributes to tumorigenesis, new therapeutic targets and strategies will be identified.

Promising preclinical studies have shown potential for the use of chimeric antigen receptor natural killer cells, liver stellate cells and fibroblasts.

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