2 Biological background[1]

With P. Macklin

In this chapter, we present some of the key biological concepts necessary to motivate, develop, and understand the tumor models introduced in this book. We introduce the molecular and cellular biology of noncancerous tissue (Section 2.1) and then discuss how this biology is altered during cancer progression (Section 2.2). The discussion may in some areas be more detailed than is necessary for the models that we present; the intent is to offer a sampling of the rich world of molecular and cellular biology, helping the reader to consider how these and details may need to be incorporated in the work of cancer modeling. For greater depth on any of the topics, please refer to such excellent texts as [12] for molecular and cellular biology, as well as [386] for cancer cell biology.

2.1 Key molecular and cellular biology

We focus upon the molecular and cellular biology of epithelial cells, the stroma, and the mesenchymal cells that create and maintain the stroma (Section 2.1.1). Specific and often anisotropic adhesive forces help to maintain tissue architecture (Section 2.1.2). Epithelial and stromal cells have the same basic subcellular structure (Section 2.1.3) and share much in common. They progress through a cell cycle when preparing to divide, can control their entry into and exit from the cycle, and can self-terminate (apoptose) when they detect irreparable DNA errors or other damage (Section 2.1.4). Their behavior is governed by a signaling network that integrates genetic and proteomic information with extracellular signals received through membrane-bound receptors (Section 2.1.5). Sometimes, cells respond to signaling events by moving within the stroma or along the basement membrane (Section 2.1.6). In pathologic conditions leading to hypoxia, cells can respond through a variety of mechanisms, or can succumb to necrosis; in some cases, necrotic cellular debris is calcified (Section 2.1.7).

[1] This introduction to cancer biology updates and expands the original exposition in [433].

2.1.1 Tissue microarchitecture and maintenance

Epithelium is composed of sheets of tightly-adhered epithelial cells that cover organ surfaces and often perform specialized functions. The epithelium is supported by the *stroma*, a loose connective tissue. The main component of the stroma is the *extracellular matrix* (ECM), a scaffolding of fibers (collagen, elastin, fibronectin, etc.) embedded in a mixture of water and glycoproteins. The ECM is secreted and maintained by *stromal cells*, specialized mesenchymal cells that can freely move within the stroma as they maintain the tissue; fibroblasts are the primary stromal cells in loose connective tissue (epithelial stroma). The stroma is interlaced by blood vessels, nerves, and lymphatic vessels, and it may rest on an additional layer of muscle or bone, depending upon the location. A thin, semi-permeable *basement membrane* (BM: a specialized type of ECM) separates the epithelium from the stroma. See Figure 2.1.

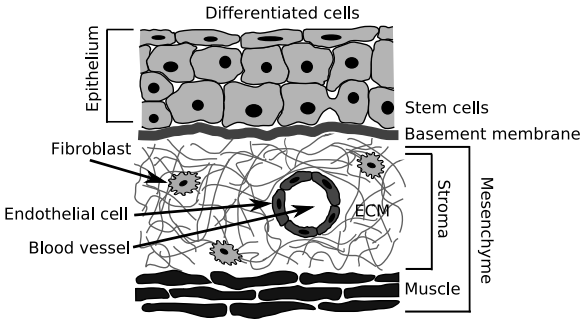

Figure 2.1 Typical tissue structure showing epithelium separated from the stroma by a basement membrane.

This complex tissue structure is maintained by careful regulation of the cell population and a specific balance of adhesive forces. These processes are often tied together through cell signaling. For further information on tissue and organ structure, please see [220], [12], and the references therein.

Population dynamics:
Each cell type population must be regulated by balancing proliferation and apoptosis. When a differentiated cell dies, a *somatic stem cell* may divide either symmetrically into two new stem cells or asymmetrically into a stem cell and a *progenitor cell*. The progenitor cell either further divides or terminally differentiates into the desired cell type, migrates or is pushed to the correct position, and assumes its function. This process is tightly regulated by intercellular communication via biochemical signals (growth factors) and mechanics; stromal cells help maintain this signaling environment [425, 496, 728]. Each cell's response to the microenvironment is governed by surface receptors that interact with an internal signaling network. We note that stem cell dynamics are not fully understood; please see the excellent overviews in [73, 728].

Epithelial cell polarity and adhesion:
Epithelium can be broadly classified as *simple* or *stratified* based upon its cell arrangement. In simple epithelium, cells are arranged in a single layer along the basement membrane. The cells are *polarized*, with a well-defined base adhering to the BM and an apex exposed to the *lumen* (e.g., a cavity in an organ); the apical side of the cell is often used to release secretory products. The epithelial cells adhere tightly to one another along their non-apical, non-basal sides. See Figure 2.2: left. In stratified epithelium, a single cell layer adheres to the BM (similarly to simple epithelium), with additional layers above. The cells in the upper layers adhere to the layers above and below them and tend to be flattened. See Figure 2.2: right. Overall, the careful orchestration of cell-BM and cell-cell adhesion helps determine the tissue geometry [352, 303, 688]. In fact, heterogeneities in the balance of cell-cell and cell-BM adhesion can lead to epithelium invagination [402], folding [675], and other nontrivial geometries [636]. The molecular mechanisms of adhesion are further explored in Section 2.1.2. More information on epithelial cell polarization can be found in standard biology texts, such as [12].

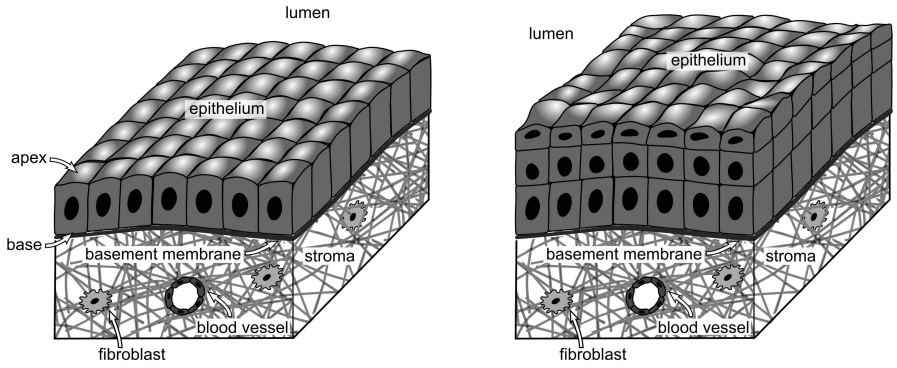

Figure 2.2 Simple (**left**) and stratified (**right**) cuboidal epithelium.

Interaction between cell adhesion and population dynamics:
Cell adhesion and population dynamics are, in fact, linked to one another. Epithelial cell cycle progression and proliferation are controlled in part by cell-cell adhesion: when an epithelial cell is in (adhesive) contact with many neighbors, its cell cycle and proliferation are suppressed. This helps to maintain the epithelial cell population by reducing proliferation when the epithelium is fully populated, and by increasing proliferation near gaps in the epithelium (e.g., due to apoptosis) [144, 303, 688]. Hence, cell-cell contact-dependent proliferation helps prevent overproliferation. This theme is further discussed in Section 2.1.5.

Cell populations are also controlled by contact with the extracellular matrix and basement membrane. Polarized epithelial cells often become apoptotic after losing adhesive contact with the BM [246, 332, 278, 643, 680]; this specialized

type of apoptosis, termed *anoikis*, helps prevent overproliferation of unattached cells into the lumen [164]. The ECM also plays a major role in regulating stromal cells [278]. For example, ECM-bound proteoglycans control the proliferation, differentiation, and apoptosis of bone marrow stromal cells [70], and integrin ligands in the ECM regulate endometrial stromal cells [601].

2.1.2 Cellular adhesion and cell sorting

Adhesion is essential to multicellular arrangement and motility: cell-cell, cell-ECM, and cell-BM adhesion are responsible for maintaining the tissue arrangement, while cell-BM and cell-ECM are essential for traction during motility.

Adhesion

Cells can exhibit both homophilic and heterophilic adhesion. In *homophilic* adhesion, adhesion receptor molecules on the cell surface bond to identical ligands (a receptor's "target" molecules) on neighboring cells (in cell-cell adhesion) or in the microenvironment (in cell-ECM or cell-BM adhesion). This is the mode of E-cadherin-mediated cell-cell adhesion in epithelial cells, including carcinoma [524]. In *heterophilic* adhesion, surface adhesion molecules of one type bond to unlike ligand molecules in the extracellular matrix, on the basement membrane, or on neighboring cells. Cell-ECM and cell-BM adhesion are heterophilic between integrin molecules on the cell surface and ligands such as laminin and fibronectin in the microenvironment [92]. Heterophilic cell-cell adhesion is also observed, such as in T-cell lymphocytes via immunoglobulin-integrin bonds [633, 657, 429].

Cell adhesion and cell sorting

While epithelial cell-cell adhesion is generally homophilic and mediated by E-cadherin, other cadherins complicate the picture. For example, E-cadherin binds with greatest strength and specificity to E-cadherin, but can also bind to N-cadherin [524] and certain integrins [363]. Hence, the mixture of adhesion molecules on two cells' surfaces (and the specificity and kinetics of the bonds between the molecules) will determine the stength of their adhesion. Adhesive differences between cell types can lead to self-sorting behavior based upon adhesion gradients, which contributes to epithelial cell organization in tissues [554]. Such cell sorting has been observed experimentally [43].

2.1.3 Subcellular structure

A cell is composed of a well-defined nucleus containing its DNA, surrounded by cytosol (the liquid in the cell) and enveloped in a bilipid cell membrane. The cytoplasm contains organelles that carry out the cell's functions, such as the mitochondria (which synthesize adenosine triphosphate (ATP) from glucose and oxygen to provide energy to the cell) and endoplasmic reticulum (which provides ideal conditions for protein synthesis, folding, and transport), all sup-

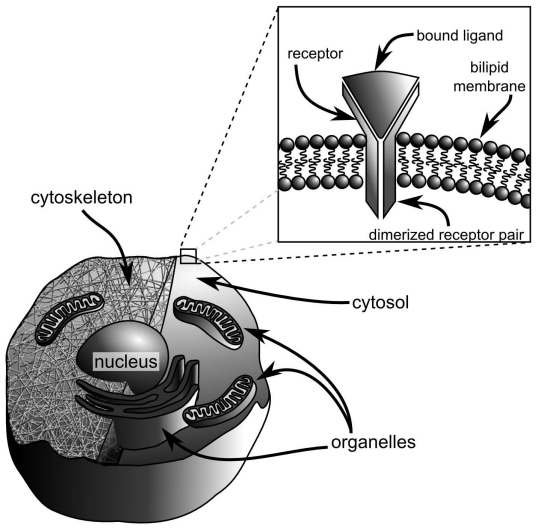

Figure 2.3 Diagram of a eukaryotic cell: A bilipid cell membrane contains the cytosol, nucleus, and organelles, all supported by a cytoskeleton. ***inset:*** Membrane-embedded receptors transmit microenvironmental information to the cell interior.

ported by a *cytoskeleton* of microtubules and actin polymer fibers. See Figure 2.3. The bilipid membrane separates the cell from the microenvironment. It is permeable to passive diffusion of small molecular species such as oxygen and glucose, actively pumps other molecular species (e.g., potassium and sodium) to maintain the cell's internal pH and chemical composition, and is impermeable to other, larger molecules such as growth factors. Embedded in the membrane are a variety of macromolecules that pump smaller molecules (e.g., potassium) against gradients; exchange mechanical forces with the extracellular matrix, basement membrane, and other cells; and transmit microenvironmental information to the cell interior.

2.1.4 Cell cycle, proliferation, and apoptosis

Cell division is regulated by a highly regimented series of stages known as the *cell cycle*. In the first stage in the cell cycle, G1 (gap 1), the cell physically grows, proteins are synthesized, new organelles are constructed, and the cell prepares for DNA replication. In the following S (synthesis) phase, the DNA is copied, and in the G2 (gap 2) phase, final preparations are made within the cell nucleus for the division of the cell. In the final M (mitosis) phase, the two copies of the DNA are separated and incorporated into two nuclei (*mitosis*), and the cytoplasm and the organelles are divided into two daughter cells (*cytokinesis*). See Figure 2.4.

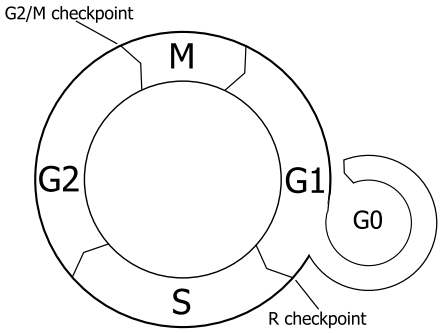

Figure 2.4 The cell cycle.

The cell cycle contains numerous checkpoints that allow the cell to check for and repair DNA damage, as well as to control or halt cycle progression. At the R (restriction) checkpoint late in the G1 phase, the cell either commits to division (and progresses to the S phase) or exits the cell cycle (and enters the G0 *quiescent state*) [720, 72]. Most noncancerous somatic cells stay in this "resting" state due to microenvironmental signals received prior to the R checkpoint, maintaining homeostasis; after the R checkpoint, cells are committed to division and are less responsive to environmental signals to halt the cycle [609].

There are numerous checkpoints in the S and G2 phases to detect and repair DNA damage (e.g., between G2 and M). See Figure 2.4. Cells that fail to repair DNA damage at such checkpoints induce apoptosis [140]. In the process, "executioner" proteins (Caspases) in the cytoplasm break down the organelles, degrade the cytoskeleton, and fragment the DNA. The cell shrinks, and the degraded cell contents are released as harmless (i.e., chemically inert) vesicles known as *apoptotic bodies*, which are ingested (phagocytosed) by specialized immune cells as well as neighboring epithelial cells [371, 391].

A cell's speed cell cycle progression is regulated by the production and balance of internal chemical signals, principally *cyclins* and *cyclin-dependent kinases* (CDKs). Surface receptors help control gene expression levels through complex signaling pathways. The gene expression pattern, in turn, determines the production and balance of proteins (including cyclins and CDKs). Hence, cell cycle progression is regulated by a complex interaction between the cell's internal biomachinery and its surrounding environment [140].

2.1.5 Genetics, gene expression, and cell signaling

Oncogenes and tumor suppressor genes

The correct interpretation of growth and inhibitory signals is key to maintaining healthy tissues. If the cell receives both growth-promoting and -inhibiting signals, its behavior is determined by the balance of the signals and the resulting gene expression pattern. Two types of genes are particularly relevant to regulating cell

proliferation. *Oncogenes* respond to or create growth signals and promote cell cycle progression. *Tumor suppressor genes* (TSGs) respond to inhibitory signals, retard or halt the cell cycle, ensure proper DNA repair, and may trigger apoptosis under certain circumstances. Cancer initiation, or *carcinogenesis*, starts with the malfunction of one or more of these types of genes [302].

Genetic mutations can cause overactivity in oncogenes and impair the function of tumor suppressor genes. Sometimes, a single uncorrected point mutation is sufficient to affect the function of an oncogene [451] or functionally neutralize a tumor suppressor gene [325]. In other cases, cell division errors (e.g., during M phase) can create a mutant fusion oncogene, where the protein coding portion of an oncogene is mistakenly fused with the triggering portion of another, frequently expressed gene. As a result, signals are "misrouted" to the oncogene, thus boosting its activity. See [396], which describes the activation of the *MYC* oncogene by translocation with an immunoglobulin gene.

Other errors during cell division may cause a daughter cell to mistakenly receive extra copies of an oncogene (e.g., [111, 119, 217]) or too few copies of a TSG. Because normal cells possess two copies of each tumor suppressor gene, both copies must be damaged for a total loss of function of the gene. (See the Knudson two-hit model [388, 389], which led to the first discovered TSG [245].) While the probability of independent mutations in both copies of the TSG is ordinarily small, *loss of heterozygosity* (two damaged copies of the TSG are passed to a daughter cell) can significantly accelerate the process [503]. Furthermore, the loss of just one TSG copy can significantly impair its activity and increase the probability of completing a multi-step carcinogenesis pathway [558].

Changes in gene expression

Gene expression is essential to maintaining proper cell function. Recent research has examined the over- and underexpression of genes, rather than outright genetic damage, as a potential contributor to unchecked cell proliferation. Viral infections (e.g., human papillomavirus can induce cervical cancer [695]) and microenvironmental signals (e.g., hypoxia; see Section 2.1.5 and references therein) can also induce changes in gene expression. Because gene expression patterns can be heritable, such changes can potentially affect a cell's malignant transformation (e.g., by disabling a tumor suppressor gene) in the same way as a genetic mutation [356]. Lastly, we note that the biochemistry of gene expression is very complicated and is beyond the scope of this introduction; see [357, 356, 425, 191] for more on this topic.

Cell signaling networks

Gene expression is controlled by cell surface receptors after activation by various signaling factors. Internal chemical species (e.g., oxygen) can also affect gene expression. The cell integrates such information with its genetic and proteomic state using a complex signaling network to determine its phenotype. Aberrant

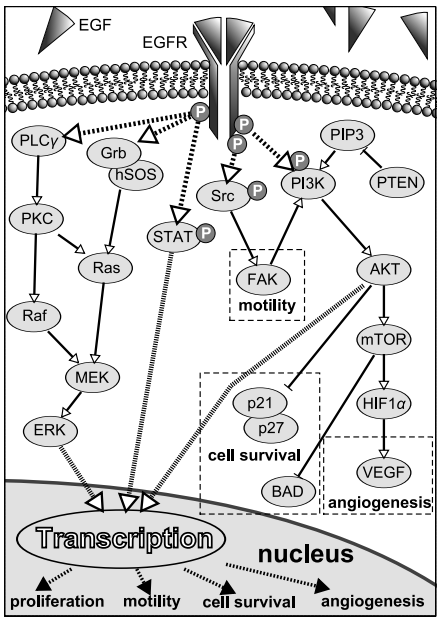

Figure 2.5 Simplified EGFR Signaling: Dimerized EGFR can transmit signals through a variety of molecular pathways that trigger proliferation, motility, and increased resistance to apoptosis

cell signaling is often implicated in cancer, making it a key topic to molecular and cellular cancer biology. We illustrate with a few examples:

Example: HIF-1α signaling:
A cell's response to hypoxia (low oxygen levels) is a key example of how internal protein levels can affect gene expression without need for additional receptor signaling. All cells create HIF-1α (a hypoxia-inducible factor) that is ordinarily degraded in the presence of oxygen [87, 602, 247, 289]. When a cell experiences hypoxia, HIF-1α accumulates and activates downstream "target" genes. Among targets of importance to cancer biology, HIF-1α upregulates motility, secretion of angiogenic-promoting factors, and anaerobic glycolysis (an inefficient metabolism attained by reacting glucose with glucose, rather than oxygen); downregulates cell-cell and cell-ECM adhesion; and reduces sensitivity to apoptotic signals [305, 716, 13, 543]. We discuss the significance of this signaling pathway in cancer biology in Sections 2.1.7 and 2.2.2.

Example: EGF signaling:
Epidermal growth factor (EGF) can bind to and subsequently activate EGF receptors (EGFR). When two activated EGFRs bind to one another (dimerize), they can transmit signals leading to increased HIF-1α secretion, increased cell proliferation, increased cell motility, and reduced sensitivity to apoptosis. See

Figure 2.5 and the excellent reviews in [314, 505, 134]. Malfunctions in this signaling process have been implicated in several cancers. For example, a mutant form of EGFR (HER2) commonly found in breast cancer is constitutively (i.e., permanently) active and does not require EGF binding for signaling activity; moreover, HER2 can bind to activated EGFR to provide a "shortcut" in the EGFR signaling cascade and thus increase EGFR signaling activity [192, 134]. In non-small cell lung carcinoma (NSCLC), downstream targets of EGFR are often mutated, most notably a constitutively-active form of K-ras that can function independently of upstream EGFR signals. Indeed, NSCLC with K-ras mutations are generally resistant to therapies that target EGFR [193, 525]. Both these mutations effectively activate downstream targets of EGFR independent of receptor activity; i.e., the EGFR pathway switch is "stuck in the ON position," leading to excessive proliferation and other cancer-promoting activity.

Example: E-Cadherin/β-Catenin signaling:
Some receptors have multiple, simultaneous roles. E-cadherin mediates homophilic epithelial cell-cell adhesion (Section 2.1.2). The intracellular domain of E-cadherin binds to α-catenin (using β-catenin as an adapter protein) to mechanically couple an adhered cell to its actin cytoskeleton [387, 189]. Ligated E-cadherin also binds to β-catenin, which sequesters it at the cell membrane and prevents its downstream signaling. Unsequestered β-catenin would otherwise promote cell cycle progression by triggering transcription of Cyclin D1, c-myc, and Axin2. Hence, E-cadherin not only plays a mechanical role in cell-cell interactions, but also a signaling role by inhibiting cell cycle progression when physically adhered to epithelial cells [71, 600, 430, 315]. This signaling pathway plays a key role in maintaining normal epithelial tissue microarchitecture [144, 303, 688]; see Section 2.1.1. In many cancers (e.g., breast cancer [419]), the E-cadherin/β-catenin signaling pathway can be disrupted, leading to increased downstream oncogenic activity (e.g., increased cell cycle progression due to Cyclin D1 overexpression [464]).

2.1.6 Cell motility

Motile cells demonstrate directed motion by a complex interaction between cell signaling, their cytoskeleton, and adhesion with the ECM or BM. We describe here the key aspects of this process; more detail can be found in [145, 280, 405].

Gradients in microenvironmental signaling molecules (e.g., EGF) can be amplified by the multiple steps in signaling networks, leading to pronounced interal signaling gradients [379]. A key downstream effect of motility signaling is actin polymerization (the formation of linked chains of actin monomer that extend the actin cytoskeleton) and depolymerization (the spontaneous degradation of actin polymers). This process takes place within a thin region just below the cell membrane [359, 405]. Wherever polymerization exceeds depolymerization, there is net outward growth of the cell's cytoskeleton, which, in turn, deforms and

extends the cell membrane. If net actin polymerization continues in a consistent direction, the cell forms a pseudopod (i.e., a "false foot") that extends from its leading edge into the microenvironment. Net actin depolymerization at the cell's trailing edge, along with internal microtubule activity, leads to cell contraction [145, 280, 405]. The signaling network creates and maintains this bias in actin polymerization. For example, dimerized EGFR can activate Src, which, in turn, can mediate the formation of Arp2/3-N-WASP complexes that nucleate actin polymerization; microenvironmental EGF gradients thus create internal polymerization gradients towards the cell's leading edge [596, 145, 481, 692, 691].

Cell motility requires mechanical interaction between cell membrane protrusions and the microenvironment. Individual cells may move through the stroma (in 3D) in an amoeboid motion by squeezing between ECM fibers (e.g., T-lymphocyte migration [703]) or by extending a slender, finger-like pseudopod (a *filopodium*) that forms focal adhesions with the ECM to exert traction [405]. The latter, which occurs during cancer cell invasion of the stroma [235, 702], requires directed, coordinated degradation of the ECM to create space for motion, and is accomplished by forming tiny invadopodia on the filopodium surface that secrete proteases to degrade the ECM [367, 174, 687]. In other cases, cells may move along a surface by extending a sheet-like pseudopod (a *lamellipodium*) that focally adheres to the surface for traction [405]. This has been observed in Paget's disease of the breast (cancerous epithelial cells chemotax along the breast duct basement membrane towards the nipple [78]), wound healing (keratinocytes crawl along the top of granular tissue [403]), and fibrosarcoma metastasis (cancer cells crawl along lymph vessel walls [712]). Following membrane protrusion, non-amoeboid motility requires the release of integrin bonds along the cell's trailing edge and subsequent cell contraction, allowing net forward motion [405]. Directed cell motility also requires active intracellular transport of actin monomer [689], integrins [280], and other cytoskeletal components between the cell's trailing and leading edges [405].

2.1.7 Hypoxia, necrosis, and calcification

In Section 2.1.5, we discussed some of the cellular adaptations to hypoxia. Sustained hypoxia (as well as sustained hypoglycemia), such as that encountered in ischemic tissue [385, 252, 583] and in larger tumors [114, 214], can lead to ATP depletion and consequently cell death. This unplanned cell death is referred to as *necrosis*.

When a cell becomes necrotic, its surface ion pumps cease to function, resulting in osmosis of water into the cell, cell swelling, and subsequent bursting [51]. This differs from apoptosis, where the volume loss is orderly and the intracellular contents are contained in apoptotic bodies [51]. In necrotic cells, the remaining solid cell fraction is generally not phagocytosed by surrounding cells, as they themselves are typically also necrotic. In some cancers (e.g., breast cancer [641], liver cancer [310], ovarian cancer [631], and lymphoma [336, 137]) and other

pathologic conditions (e.g., tuberculosis [54] and abscesses [398, 701]), necrotic tissue can undergo calcification: the solid cell components are replaced by calcium phosphate and/or calcium oxalate molecules that bond together to form calcite crystals that grow into hard *microcalcifications* [446].

2.2 The biology of cancer

Most simply stated, cancer occurs when defective genes cause cells to malfunction and interact with the body in an aberrant, hyperproliferative manner (either by increased cell proliferation or reduced cell apoptosis). We now examine how the molecular and cellular biology previously introduced in Section 2.1 can break down, leading to cancer. Our discussion primarily focuses upon *carcinoma* (cancers arising from epithelial cells) rather than *sarcoma* (cancers arising from mesenchymal cells).

2.2.1 Carcinogenesis

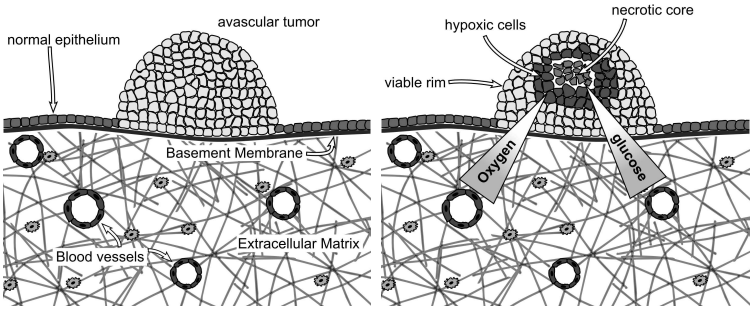

Figure 2.6 **Left:** Initial avascular tumor. **Right:** Substrate gradients lead to hypoxia and central necrosis

Carcinogenesis is a multistage process thought to begin with a genetic mutation or epigenetic alteration that overexpresses an oncogene or underexpresses a tumor supressor gene in one or a small number of cells. If the cell survives and the mutation escapes its DNA repair mechanisms, the cell (or its descendants) may over time acquire further mutations to ignore growth-inhibiting signals from its neighbors, bypass its internal controls and checkpoints, and form a colony of hyperproliferative, aberrant cells. This accumulation of mutations may require years to progress, but can be accelerated by exposure to carcinogens and other harsh, DNA-damaging environmental effects.

Differentiated cells can only divide a limited number of times before reaching *senescence*: the point at which they permanently arrest in G0 or apoptose. Thus,

differentiated cells alone cannot drive unlimited tumor growth without additional mutations to overcome senescence. Recent studies suggest that cancer may arise from mutated somatic stem cells rather than differentiated cells [58, 425, 608]. In this scenario, the tumor is a mixed cell population whose overgrowth is driven by a small sub-population of cancer stem cells, rather than by differentiated cells that have overcome senesence. With or without cancer stem cells, the result is the same at the multicell and tissue scales: a mass of hyperproliferative cells that fail to respond to ordinary physiologic limits to their growth (Figure 2.6: left).

2.2.2 Avascular solid tumor growth

Once a tumor has established a foothold in its host tissue, it begins an early period of growth as it becomes an *in situ* cancer. Epithelial cells are generally constrained by the basement membrane.

The limiting role of oxygen and nutrient diffusion, hypoxia, and necrosis

In this early stage of cancer, the tumor has no vascular system of its own, and so it must rely upon the host vasculature in the nearby stroma for crucial oxygen, nutrients, and growth factors; we refer to these generically as "substrates." Substrates diffuse from the surrounding vascularized tissue, enter the tumor, and are uptaken by proliferating tumor cells. This motion of substrates from external sources (the host vasculature) to internal sinks (the metabolically active tumor cells) causes substrate gradients to form within the tumor. Of particular importance is oxygen, which generally diffuses on the order of 100-200 μm into tissue before dropping to levels insufficient for cellular metabolism [114, 151, 214, 437, 439]. Interior tumor cells experience hypoxia and respond to their harsher microenvironment in a variety of ways (Section 2.1.5). Deeper within the tumor, oxygen and glucose levels drop to critcally low levels that cause the tumor cells to necrose. These dynamics are manifested as an outer tumor viable rim of proliferating cells, an interior band of hypoxic cells, and a central necrotic core. See Figure 2.6: right.

This affects the tumor mechanically. Prior to the formation of a necrotic core, proliferation throughout the tumor causes a net outward cell flux that expands the tumor (Figure 2.7: left). Simultaneously, the proliferating tumor cells absorb fluid from the interstitium to fuel their growth and eventual division, resulting in a net fluid flux into the tumor. Once a necrotic core has formed, cell lysis reduces the tumor cell volume and releases fluid that leaves the necrotic core and enters the proliferative rim interstitium. The subsequent reduction in mechanical pressure in the necrotic core redirects some of the viable rim cell flux towards the tumor interior (Figure 2.7: middle). As the tumor grows, the volume of its necrotic core increases, thus accentuating its cell volume sink effect. Once the tumor grows large enough, the cell flux resulting from proliferation balances with the fluid flux stemming from necrosis, leading to zero outward cell flux. This gives rise to a steady-state tumor spheroid (Figure 2.7: right).

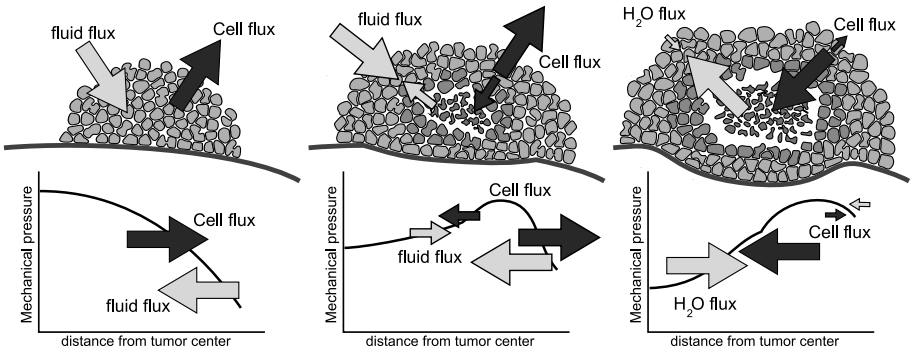

Figure 2.7 Cell and fluid flux in early (**left**), later (**middle**), and long-time (**right**) tumor growth.

2.2.3 Interaction with the microenvironment

As the nascent tumor grows in its host tissue, it interacts with the surrounding microenvironment in a variety of ways. It mechanically displaces and compresses the surrounding tissue, including the basement membrane (Figure 2.7: middle and right). The tumor degrades and remodels the extracellular matrix (ECM), both biomechanically and biochemically by the secretion of matrix degrading enzymes such as matrix metalloproteinases (MMPs) that degrade the ECM. The degraded ECM, in turn, can release ECM-associated growth factors that fuel further tumor growth [647]. The degradation of the ECM by the MMPs increases the ability of the tumor to push into the surrounding tissue, both by reducing the mechanical rigidity of the surrounding tissue and by creating extra space for the growing tumor [327]. The combination of proliferation-induced pressure and proteolytic degradation of the surrounding tissue results in *tissue invasion*: the invasion of sheets or "fingers" of tumor cells into the surrounding tissue along paths of least mechanical resistance. *Acidosis* (a decreased microenvironmental pH resulting from anaerobic glycolysis in hypoxic tumor cells) has also been hypothesized to play a role in tumor invasion, by inducing apoptosis in the surrounding normal epithelium, by giving invasive tumor cells a selective advantage over tumor cells that have not adapted to acidity, and by contributing to ECM degradation (due to proteases released by apoptotic cells) [283, 529, 264, 266, 629, 265, 630, 627, 282, 281, 268, 628, 209, 284, 267].

There is recent evidence that tumors induce changes in gene expression in the nearby stroma that help sustain tumor growth [328, 728]. For instance, carcinomas may release signaling molecules (e.g., IL-1β) that stimulate fibroblasts to secrete hepatocyte growth factor (HGF). The HGF, in turn, promotes tumor cell growth, decreases cell-cell adhesion, and increases MMP secretion [459]. Tumors may also alter gene expression in nearby, non-cancerous epithelial cells [335].

2.2.4 Vascular growth and metastasis

The next stage in cancer development can be viewed as a response to hypoxia. The ultimate result is *angiogenesis*, where the tumor induces endothelial cells to form a new vasculature that directly supplies the tumor with the nutrients, enabling further expansion. Some of the same mechanisms responsible for angiogenesis play a role in *metastasis*, the spread of tumor cells to distant locations.

Angiogenesis

As discussed in Section 2.1.5, hypoxia-inducible factors (e.g., HIF-1α) accumulate in hypoxic cells, which can trigger numerous downstream genetic targets. In particular, the hypoxic cells secrete tumor angiogenic growth factors (TAFs) such as vascular endothelial growth factor (VEGF) [716, 364, 13, 543]. These TAFs diffuse outward from the hypoxic regions of the tumor and eventually reach nearby blood vessels. See Figure 2.8: left.

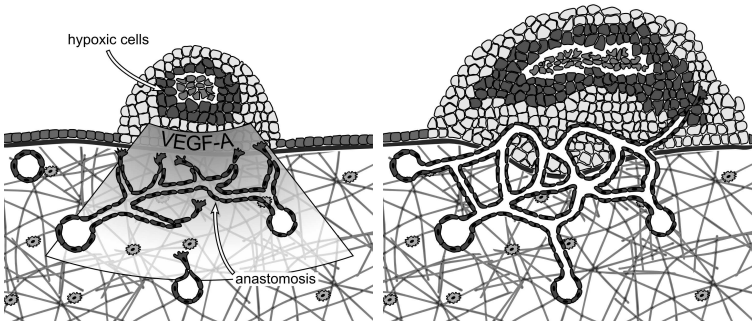

Figure 2.8 Left: Angiogenic growth factors such as VEGF-A are secreted by hypoxic tumor cells, leading to angiogenesis. **Right:** The fresh nutrient supply allows for renewed tumor expansion.

Blood vessels are composed of tightly connected squamous (flat and scale-like) endothelial cells that are surrounded by a basement membrane and other supporting cells, including smooth muscle cells and pericytes [426]. When the endothelial cells detect the TAF gradient emanating from the tumor, they secrete MMPs that degrade the basement membrane and extracellular matrix [48] (Figure 2.8: left). This allows the endothelial cells to migrate away from the blood vessel and toward the TAF source in the tumor. The leading endothelial cells are referred to as *sprout tips*; immediately behind the sprout tips, other endothelial cells divide, migrate, align, and form tubes of polarized endothelial cells surrounding a vascular lumen [494]. The vessels then link with one another to form a network of loops in a process called *anastomosis* (Figure 2.8: left). It can take on the order of 10 to 21 days for new vessels to form and connect to the parent vessels [285, 48, 489].

The end result is a *neovasculature* that provides the tumor with a direct supply of oxygen and nutrients. The configuration of the neovasculature is determined by the balance of pro- and anti-angiogenic growth factors, as well as by the mechanical pressures from the growing tumor and flow stresses within the nascent blood vessels [409, 653, 557, 287, 215]. The fresh nutrient supply allows a new stage of rapid tumor growth into the surrounding tissue (Figure 2.9).

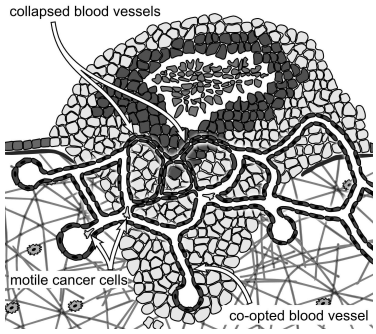

Figure 2.9 Invasive tumor growth into the stroma. The tumor grows to co-opt the neovasculature, leading to collapse of some vessels and renewed hypoxia.

Angiogenesis is not unique to tumor growth, but is also a key part of wound healing, the menstrual cycle, and embryonic development [114, 214]. However, we note that tumor angiogenesis is pathological in nature, and the resulting vasculature is inefficient in a number of ways: the vessels are often "leaky" due to large gaps between endothelial cells; the newly formed vessels are not as stiff and rigid as mature vessels and may collapse when subjected to tissue stress (such as that created by rapidly growing tumors); the basement membrane around the new vessels may not be fully formed; some of the newly formed vessel walls may be composed of a mosaic of tumor and endothelial cells; and the tumor neovascular network tends to be much more tortuous than regular vascular networks [218, 114]. See Figure 2.9. This inefficiency may hinder drug delivery within tumors [342, 623], as well as lead to the development of new hypoxic regions within the tumor and additional sessions of angiogenesis.

Tissue invasion and metastasis

A particularly damaging aspect of advanced cancer is *metastasis*, the spread of tumor cells to form secondary tumors in distant locations. Metastasis occurs most commonly in breast, prostate, and lung cancers [66], and it is estimated that over 90% of all deaths from solid tumors result from metastasis [300]. In spite of the great clinical importance of metastasis, it is poorly understood [362].

Metastasis is a complex phenomenon involving several mechanisms that are closely related to tissue invasion. Genetic instability, intrinsic limits (e.g., senescence), and extrinsic selective pressures (e.g., limited nutrients,

immune system attacks) lead to competition within heterogeneous tumor cell populations and the eventual selection for pro-metastatic genes [300]. Hypoxia creates a strong selective pressure, leading to increasing internal HIF-1α levels in the tumor cells and the expression of genes responsible for increased motility, glycolysis, reduced response to apoptotic pathways, and increased production of MMPs [305]. The selective pressures also lead to increased expression of genes responsible for locomotion [544]. As a result, tumor cells degrade the BM and ECM and invade the stroma, either individually, as small clumps of cells (emboli), or in cohort motion of sheets of cells linked by cell-cell adhesion [490, 300]. Eventually, invasive tumor cells can enter the vasculature or lymphatic system. See Figure 2.9.

For sarcomas (which already reside in the stroma), this is accomplished by the proteolytic degradation of the ECM and BM surrounding the stromal vessels, followed by direct entry into the vessels. For carcinomas (which are separated from the stroma by the BM), entry into the vasculature could also indirect via the lymphatic system [200]. The mesenchymally-derived sarcoma cells move with built-in cellular machinery in a contractile manner: by first degrading the ECM on their leading edge, adhering to the ECM, and contracting, followed by rebuilding the ECM on the trailing edge [672]; see Section 2.1.6. Epithelial-derived carcinoma cells initially lack this locomotive ability, but mutations and altered gene expression can restore these locomotive mechanisms; the process is often referred to as the *epithelial-mesenchymal transition* (EMT) [544, 672].

Once the metastatic tumor cells have reached the vasculature, they circulate in the blood. Initially, survival of the circulating tumor cells is inhibited by the immune system, which kills most of the individual cells; emboli consisting of 5 to 10 cells are more likely to escape attack by the immune system [200]. Note that the complex role of the immune system is poorly understood and may both promote and inhibit metastasis. Circulating tumor cells that do survive can eventually lodge in the capillary bed of distant organs; the most frequent destinations include the liver, lungs, and bones [66].

However, without further tumor-host interaction, the destination microenvironment will not support the newly arrived metastatic tumor cells. Different types of tumor cells tend to metastasize to specific tissues. This "seed and soil" idea, that only specific tissues are suitable to each tumor cell line, was first formulated by Stephen Paget in 1889 when studying breast cancer metastases [519, 172, 487]. The reasons for this are only now being elucidated in an emerging area of cancer research. The theory is that tumors release cytokines, VEGF, and other chemical signals into the circulatory system that recruit progenitor and endothelial cells from the bone marrow and vasculature to assist in creating a *pre-metastatic niche*: a modified microenvironment in a distant host tissue that is suitable for tumor metastasis [300]. In the process, the chemical signals alter the gene expression in the endothelial cells in capillary walls at the destination tissue, which then express additional adhesion molecules and secrete MMPs to

degrade the basement membrane surrounding the capillaries [316, 200, 362]. The newly-expressed adhesion molecules on the inner surface of the capillary bed improve the ability of the metastatic tumor cells to arrest at the destination, and the degraded BM assists in the extravasation of the tumor cells from capillaries into the destination tissue.

Once the metastatic tumor cells successfully invade the destination tissue, they secrete growth factors that induce additional changes in the new location. Growth is similar to the mechanisms of tissue invasion that were introduced earlier, but with additional elements. Tumor-induced changes in the stromal cells cause them to degrade and remodel the matrix, even as the tumor cells also secrete MMPs to degrade the matrix. Growth-promoting molecules that were previously sequestered in the ECM fuel further tumor growth [200]. With ample room to grow and a favorable microenvironment, these tumor cells can develop into secondary tumors. Because the metastatic tumor cells have been selected for their invasive phenotype, they are capable of expressing pro-angiogenic growth factors to initiate angiogenesis and enter vascularized growth. The tissue specificity of this process is likely due to the combination and balance of cytokines and chemicals secreted by the tumors, which, in turn, depends upon the genetic makeup of the tumors [626]. It is thought that only a small fraction of the cells in the primary tumor have the ability to recruit the proper progenitor and endothelial cells to build the pre-metastatic niche [300].

The scientific understanding of metastasis is advancing rapidly, and the reader is encouraged to read the reviews by [200, 300, 362, 521]. The reviews on bone metastases by [421, 66] provide well-written, concrete examples of the process, and they give an excellent overview of the latest in metastasis research.

2.3 Concluding remarks

In this chapter, we presented a simplified overview of the major topics in biology that relate to cancer. Cancer modelers may wish to keep these topics in mind as they study and extend the models presented in this book, and to explore the excellent references cited in this chapter and elsewhere to learn more about these biological themes in greater depth. In the following chapters of Part I, we present state-of-the-art continuum, discrete, and hybrid models that incorporate a broad spectrum of the tumor progression and behavior presented in this chapter.

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