Chapter 9
Periodic table of diseases

(Please comment if anything is unclear or if there are typos.)

Congratulations! We arrived at our last chapter. To celebrate, let's take a nice deep sigh of relief. Here, we tie together the themes and principles of this book in a periodic table of diseases.

Periodic table of diseases

As a metaphor, consider Mendeleev's periodic table of elements. In 1869, while preparing a chemistry textbook, Dmitry Mendeleev noticed patterns in the chemical properties of the elements known at the time as a function of their molecular weight (Fig 9.1).

Figure 9.1: One of the original versions of Mendeleev's periodic table.

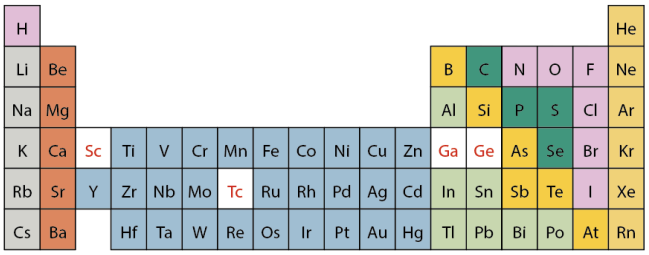

Figure 9.2: A modern periodic table with Mendeleev's four predicted elements in white squares.

These patterns allowed Mendeleev to predict several new elements (Fig 9.2 white squares). For example, there was an empty space below aluminum that suggested an element similar to aluminum but heavier, with a low melting point and a density of about $6\ g/cm^3$. The predicted element, Gallium, was discovered six years later with the correct density and melting point. The other 3 predicted elements were also discovered in due course.

The periodicity of the table remained a mystery for several decades, until quantum mechanics offered the explanation in terms of orbitals.

Metaphors are crucial in science. They let us make inferences about something that is unknown, based on something we know. When we say light is a wave or light is a particle, we entail certain features of waves or particles on light. If that seems interesting, I recommend the book "Metaphors we live by" by Lakoff and Johnson.

So, let's use the periodic table metaphor to organize cell types and diseases. Of course, physiology is much more complex than atoms. The metaphor is imperfect. For example, it won't be a *periodic* table (no repeating period). But there will be patterns and predicted diseases.

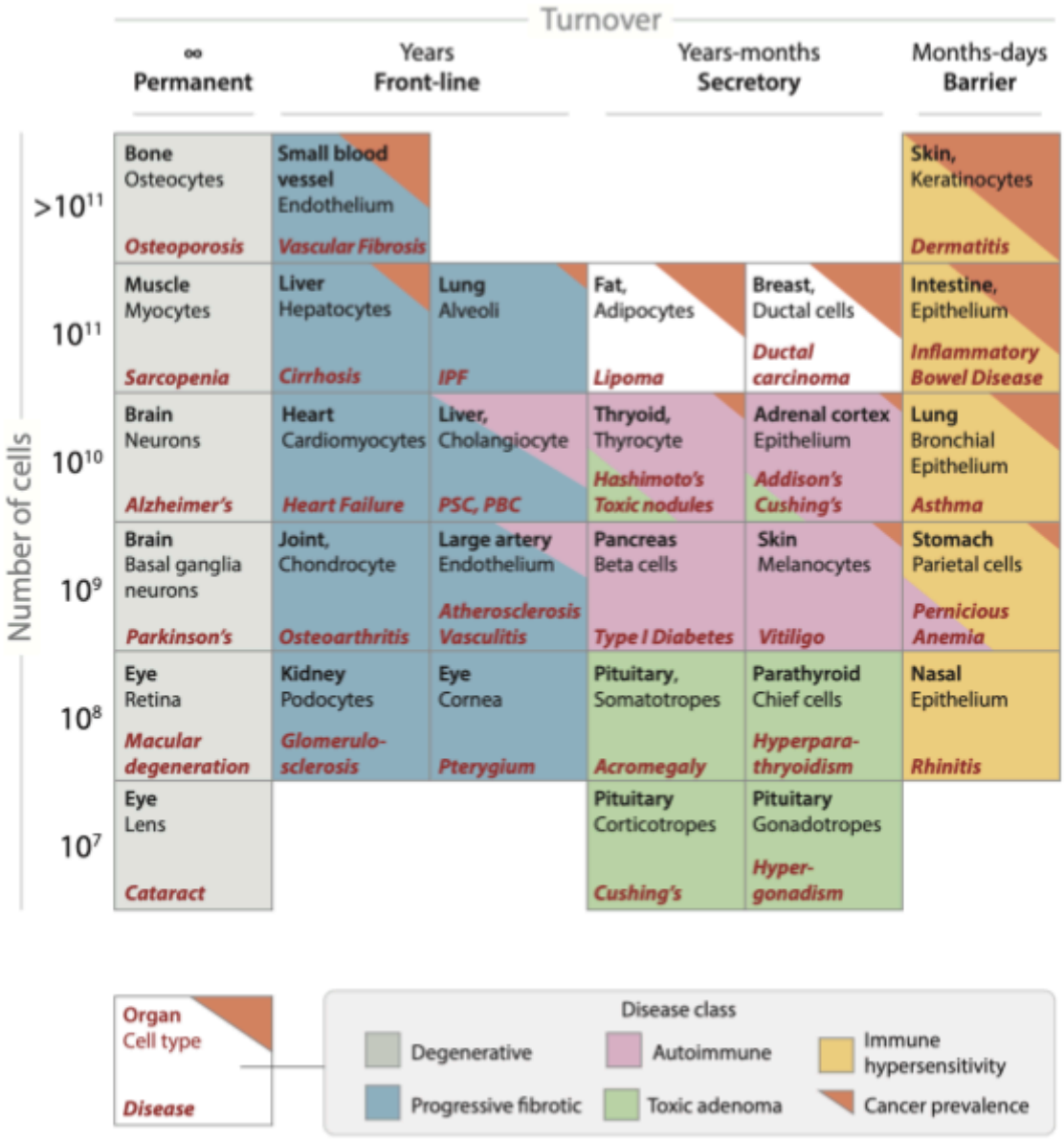

Figure 9.3 Periodic table of cell types and diseases. Selected cell types with major acquired diseases are arranged according to cell number and cell turnover/tissue function. Disease class is indicated in color. Cell numbers for basal ganglia are shifted for clarity.

Cell types can be classified by abundance and turnover

Diseases are traditionally classified in four ways: (1) Anatomically, by organ or tissue, such as heart diseases and liver diseases, (2) Physiologically, by function, such as respiratory diseases and metabolic diseases, (3) Pathologically, by the nature of the disease process such as neoplastic diseases (tumors) and inflammatory diseases, and (4) etiologically, by their cause, such as fungal or streptococcal infections.

These classifications are embedded in the international disease code system used to

catalog diseases. More recently, diseases have been arranged as networks, where diseases with shared genetic risk factors or symptoms are connected by links [ref].

Here, we make a new classification inspired by the physiological circuit motifs we have studied. The circuits describe the dynamics of cell numbers and cell turnover. We therefore arrange cell types in a table by their number (abundance) and their turnover rate. We will then see how this table reveals patterns of diseases that correspond to each cell type.

Every "element" in the table is thus a cell type (Fig 9.3). The rows go by the number of cells of that type in the body. This ranges from rare cell types, like the parathyroid gland whose size is like a grain of rice with 10^8 cells, to very numerous cell types like the 10^{12} skin cells called keratinocytes that make up the several kilos of skin tissue.

To be more tangible, a billion cells weigh about a gram. Exceptions are large cells like neurons, fat cells and muscle cells which are each 100 times bigger than most cells, so that the 1kg brain has about 10^{10} neurons.

The columns go by the turnover time of the cell types. Some cell types, like neurons, have no turnover in adulthood. They are called **permanent** cell types. Other cell types, like fat cells, have turnover times of many years. Still others, like liver hepatocytes, turn over with a timescale of a year. Most organs have turnover times of months, with an average cell turnover of about 100 days in the body (Sender and Milo, 2021). **Barrier tissues** which stand between the outside and inside typically have the fastest turnover, such as 50d for skin keratinocytes and a few days for the gut epithelium.

The position of a cell type in the table, namely its abundance and turnover, is determined by its physiological function. For example, the size of an endocrine gland is roughly proportional to the size of the target organs. Glands that supply a hormone to the entire body weigh about 10 grams, like the thyroid and adrenal. Their 10^{10} cells can make the required amounts of hormones. In contrast, glands that need to supply only a relatively small target organ have fewer cells. Pituitary gland cell types, like those that make ACTH for the adrenal, weigh about 0.01g, or about 10^7 cells. This is perfect for supplying enough hormone for their 10g target organ.

The same goes for larger secretory organs. At 100g are the breast ductal cells that need to secrete large amounts of milk. At 1kg are the liver hepatocytes that produce massive amounts of proteins and metabolites. In the 10kg range are the skin and fat, all according to their purposes. Skin covers a large area, fat stores fuel.

Turnover is likewise determined by function. Neuron circuits which encode information are permanent and do not replace their neurons. In contrast, barrier cells like skin cells face damage and need to be replaced often.

The table shows broad patterns of diseases

We now consider the main diseases of each cell type, listed in red in each element box (Fig 9.3). The point is that **the diseases show patterns in the table**. Each column has its own class or classes of diseases. These classes are shown in color, corresponding to degenerative diseases, progressive fibrotic diseases, autoimmune diseases, toxic adenomas and immune hypersensitivity diseases. The orange triangles represent the prevalence of cancers (Fig 9.3).

The first hint of this way of arranging diseases arrived when Yael Korem and I asked which endocrine organs get autoimmune diseases and which do not. We saw a pattern in which organs with less than 10^9 cells get toxic adenomas while organs with more than 10^9 cells get autoimmune diseases, as discussed in chapter 4. I began experimenting with the relation between diseases and cell number and turnover around 2019, and the table slowly took. Its current graphical form arose in discussion with several scientists, especially Michael Elowitz.

Is it a table of diseases or cell types? Because we consider cell-type-specific diseases, it is both, where each disease has a cell type, and each cell type can have several diseases.

In this chapter, we will analyze the patterns in the table and their origins in the circuit motifs.

First, however, there are some caveats. The table in Fig 9.3 includes only a small fraction of the cell types in the human body, and only the most prevalent diseases. It is a working draft for us to see patterns. Some classes of diseases do not fit easily into the table. This includes systemic diseases such as lupus and psychiatric diseases such as bipolar disorder, schizophrenia and depression.

Cancer risk rises along the diagonal of the table

To explore the patterns in the table, let's start with cancer prevalence. The lifetime risk of cancer in a given cell type rises along the diagonal of the table: the more cells and the more exposure, the more mutations in a lifetime and the higher the cancer risk (Fig. 9.4).

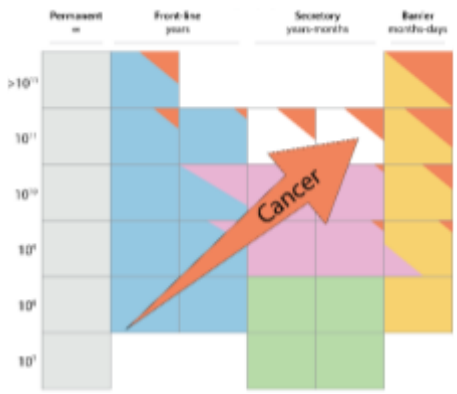

Figure 9.4: Risk of cancer, represented by the orange triangles, rises with cell number, cell turnover and exposure to environmental toxins and mutagens.

The main effect is the number of cells. Cells accumulate about 50 mutations per year, regardless of their division rate (Cagan *et al.*, 2022) (Miller 2022). Each cell division adds several additional random mutations. The dependence on total cell number is evident in the increasing risk of cancer with height. Each 10cm of height raises the risk of cancer by a factor of about 1.1. Males have overall 20% more risk of cancer than females, due in part to height difference.

This picture modifies previous notions that the main determinant of cancer risk is the number of lifetime stem-cell divisions (Tomasetti and Vogelstein, 2015; Tomasetti, Li and Vogelstein, 2017), a theory that could not explain prevalent tumors in slowly dividing tissues. Abundant but slowly dividing cell-types get common tumors; these tumors, thankfully, are benign -- they don't spread to make metastases, and are not lethal. This includes fat cells that have a turnover of years but show lipomas in at least 2% of people. Small blood vessels (capillary endothelial cells) are also very abundant, amounting to 2Kg in a 70Kg person, and get benign angiomas in most people with age.

Exposure to toxins and mutagens further enhances risk, which is why the risk is highest in barrier tissues- the rightmost column in the table. Barrier tissues are exposed to factors that cause mutations and inflammation, such as UV in the skin, smoking in the bronchi of the lung and toxins in the gut. They hide their stem cells in a protected niche, as far from the damaging factors as possible. These tissues get prevalent cancers: skin basal cells result in benign tumors in 30% of people; colon and bronchi give rise to colon cancer and lung cancer, each in about 3% of the population; these two currently account for most of the deaths from cancer.

In contrast, permanent tissues cease to divide in adulthood and almost never get cancer in adults; Their rare cancers occur in childhood, such as neuroblastomas (neurons) and osteosarcomas (bone).

Secretory cells show three zones: toxic adenomas, autoimmune diseases and cancer

Each column in the table has its own pattern of diseases. Let's start with the column of secretory cells (Fig. 9.5), because we have seen it before in Chapter 4.

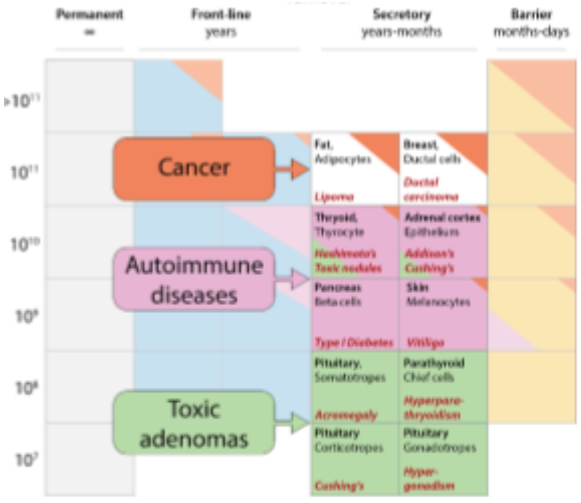

Figure 9.5: Secretory cells show three zones: toxic adenomas at the smallest cell numbers, autoimmune diseases between a billion and ten billion cells, and cancer at high numbers of cells.

The secretory cells have a turnover time on the order of weeks to months, except for some cell types like beta cells which have slower turnover. Listing the most common diseases of these cell types indicates a striking pattern with three zones of diseases according to cell number.

The cell-types with the smallest numbers of cells, below 1g or about 10^9 cells, get toxic adenomas, benign tumors that hyper-secrete the hormone. Examples are parathyroid adenomas that hyper-secrete parathyroid hormone causing too much calcium, and adenomas of the pituitary that secrete TSH causing hyperthyroidism.

Then, at more abundant cell types, the disease class changes. Cell types between about 1g and 10g get cell-type-specific autoimmune diseases in which T-cells systematically destroy the organ. Examples are type-1 diabetes that destroys beta cells and Hashimoto's thyroiditis that destroys thyroid cells. Instead of too much hormone as in toxic adenomas, these diseases eliminate the endocrine organ and cause too little hormone.

Above 10^{10} cells or 10g, the most prevalent disease switches again, to cancer. Cancer cells grow, become de-differentiated and stem-like so they stop their normal function (e.g. stop secreting hormones), and sometimes form metastases that can be lethal.

At the boundaries between the zones we see an overlap of diseases: the 10g thyroid gets common autoimmune disease (Hashimoto's thyroiditis), but also cancer (thyroid cancer) and toxic adenoma (hot thyroid nodules). The prostate (30g, not shown in the table) gets cancer and more rarely an autoimmune disease.

The three zone pattern can be explained by circuit motifs

An explanation for this three-zone pattern arises from a shared circuit motif, and from law 3—cells mutate, as we saw in chapter 4. Secretory cells share the 'secrete-and-grow' circuit in which a signal controls both secretion and cell growth (Fig 9.6). This circuit is fragile to mutant cells that hyper-sense the signal. Such mutant cells can grow into an adenoma that hyper-secretes the hormone.

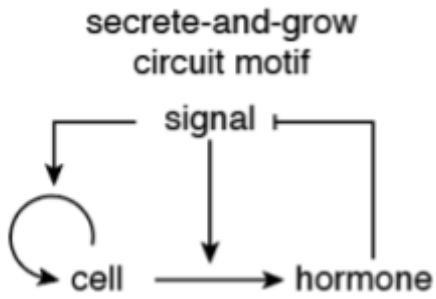

Figure 9.6: The secrete-and-grow circuit motif.

The cell types below 1g have so few cells that there is a low chance for hyper-sensing mutants during reproductive years, and even less for the multiple mutations needed for cancer. The strategy is therefore 'let it be', with a risk of hyper-secreting adenomas at old age.

The mid-range cell types at 1-10g have more cells. At birth there are already numerous cells bearing the hypersecreting mutations. To avoid hypersecreting adenomas, we saw that the body may use autoimmune surveillance—the self-attacking T cells we discussed in chapter 4—to selectively kill the hypersecreting cells. The cost is autoimmune disease with a young age of onset in a fraction of the population.

The third zone in this column occurs at more abundant cell types, above 10g or 10^{10} cells. These cell types do not show autoimmune diseases or toxic adenomas as their main malady. Instead, they show cancer.

One reason for the high cancer prevalence is that at such high cell numbers, one cannot continue to use autoimmune surveillance T cells because you need so many of these self-attacking T cells that autoimmune disease becomes very likely. There is therefore a switch of strategy. Instead of the differentiated cells making more of themselves as in the thyroid and adrenal (Fig 9.7), these heavier

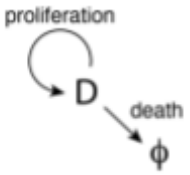

Figure 9.7: A cell type which renews itself.

tissues increasingly rely on stem cells (Fig 9.8).

Recall that stem cells are professional dividing cells. They can reduce the number of divisions and hence the number of mutations. The trick is to first differentiate into **transit amplifying cells**: cells which can divide a limited number of times and give rise to the final differentiated non-dividing cell type (Fig. 9.8).

For example, if each transit amplifying cell divides 10 times, you get $2^{10} = 1024$ differentiated cells D per stem cell division. This amplification reduces the number of divisions and hence mutations in stem cells, the cells that stay in the body for a lifetime. The mutations that arise in the divisions of the transit amplifying cells are not very dangerous, because these cells are soon removed with the natural tissue turnover.

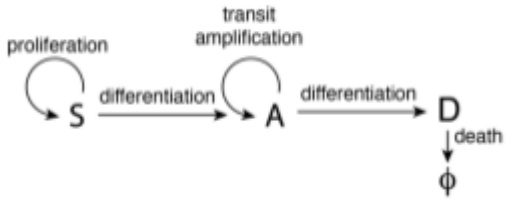

Figure 9.8: A cell type which depends on stem cells that differentiate into transit amplifying cells.

For our purposes, it is important that the stem cell circuit decouples cell division from secretion, and thus does not have the same fragility to hypersecreting mutant clones as the cells with the secrete-and-grow circuit motif.

Why don't all tissues use stem cells? Stem cells have a cost – risk of cancer. Their stemness provides several hallmarks of cancer even without mutations, such as the ability to divide indefinitely. Stem cells remain in the body and can accumulate the mutations needed for cancer. Thus, one idea is that there exists a tradeoff between hyper-secreting mutants and cancer for cell types in this column; at a certain number of cells, the balance is tipped towards stem cells and cancer.

The periodic table explains autoimmune diseases of non-endocrine cells in the 1-10g range

We can begin to use the generalizing power of the table to understand other autoimmune diseases that affect non-endocrine cells, that is cells that do not secrete hormones. We discuss two examples - the diseases multiple sclerosis and ITP. The idea is that cell types in the 10^9 -10^{10} 'autoimmune zone' with an analogous circuit motif are also fragile to autoimmune disease.

Consider cell types that do not secrete molecules but have a function that needs to be kept under control, and this control is achieved by a circuit analogous to the 'secrete-and-grow' circuit. For example, the autoimmune disease multiple sclerosis (MS) affects brain cells called oligodendrocytes whose role is to coat – to myelinate - neurons in the brain with an insulative wrapping that includes the protein myelin. There are about 10^9 oligodendrocytes in the brain, placing them in the autoimmune zone. Our familiar circuit is at play, in which a "myelinate me" signal from unmyelinated neurons causes the oligodendrocyte precursors to both myelinate and

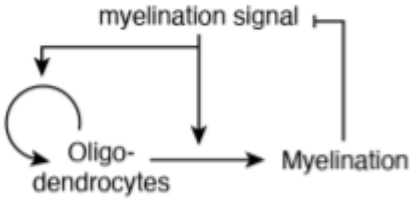

Figure 9.9: Oligodendrocytes that myelinate neurons show a circuit in which

grow (Fig. 9.9).

In multiple sclerosis, T-cells kill oligodendrocytes, causing severe neurological problems. The main autoantigen is myelin. Multiple sclerosis may thus be a side effect of T cells that weed out mutant oligodendrocytes that sense too much “myelinate me” signal; such mutant cells would otherwise grow to hyper-myelinate the neurons around them.

A second example is an autoimmune disease that affects blood clotting. In this disease, called immune thrombocytopenic purpura (ITP), T-cells kill bone marrow cells called megakaryocytes, also in the 10^9 zone. These are large cells that produce platelets. Platelets are crucial for blood clotting, and purpura eliminates them. This system shows the same circuit motif, with a signal (the hormone thrombopoietin that is degraded by platelets) that makes megakaryocytes both produce platelets and grow (Fig. 9.10). Again, the autoimmune disease may be a side effect of autoimmune surveillance T-cell pruning of hypersecreting mutant megakaryocytes.

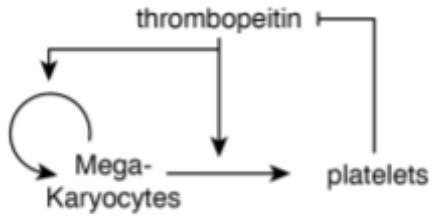

Figure 9.10: Megakaryocyte cells produce platelets required for blood clotting. They show a circuit in which a signal controls both growth and function, similar to the secrete-and-grow motif.

The autoimmune zone of 1-10g or 10^9 -10^{10}cells also extends right and left to some of the other columns, as we will see.

Permanent tissues have degenerative diseases of failed maintenance

Let’s go to the column of permanent tissues (Fig. 9.11). It includes cell types like neurons, skeletal muscle, bone and the lens of the eye.

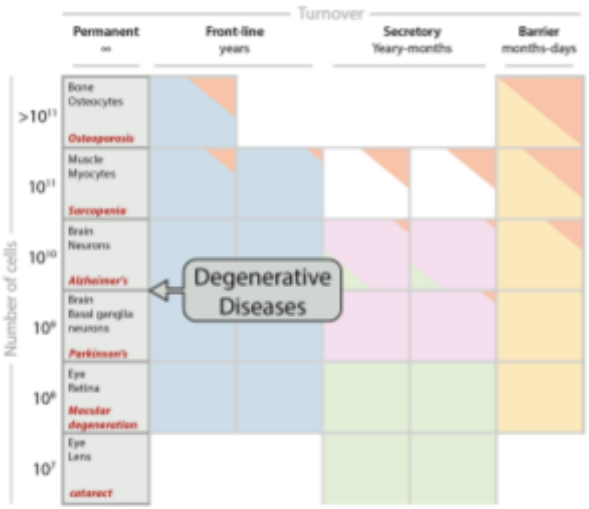

Figure 9.11: Permanent tissues show degenerative diseases which are age dependent. Many of these diseases are very prevalent.

These cells do not divide in adults, but they do have mutations, damage and continuous maintenance processes. Bone is remodeled at about a teaspoon a day. Neurons are trimmed and repaired by the immune cells of the brain, the glia.

With age, damage production rate rises, due in part to DNA alterations that accumulate linearly with chronological age. Maintenance capacity is, however, limited. Eventually the trucks of chapter 7 become overloaded - maintenance processes saturate according to law 2. In parallel, inflammation rises, further delaying maintenance programs.

These effects lead to diseases of maintenance at old age. Bones show osteoporosis,

neurons show neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Skeletal muscles show an age-related degenerative disease called sarcopenia in which lean muscle mass is lost at old age at 3-5% per year if an individual is not active.

Similarly, the lens of the eye shows cataracts. It becomes cloudy, impairing vision, in about 90% of people by age 90. Cataracts are caused by denatured proteins due to slowdown in their removal processes. It is accelerated by diabetes and hypertension, as well as cumulative UV exposure.

The circuit at play summarizes how damage X is produced at a rate that rises with age and saturates its own removal processes, Fig 9.12.

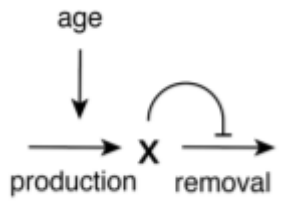

Figure 9.12: The circuit for the saturating removal theory of aging. Damage X is produced at a rate that rises with age and saturates its own removal processes.

Because of the properties of this circuit that we studied in chapters 7 and 8, the incidence of degenerative diseases depends strongly on age. Incidence does not, however, depend on organ size: the tiny lens and heavy skeletal muscles both have high prevalence of degeneration. In fact, many of these diseases are nearly universal and are part of the shared aging phenotype.

Barrier tissues get immune hypersensitivity diseases

At the other extreme, the barrier tissue column, are the cell types with the fastest turnover (Fig. 9.13). These tissues stand between the outside world and the inside. This includes the lining of the gut, skin and lungs.

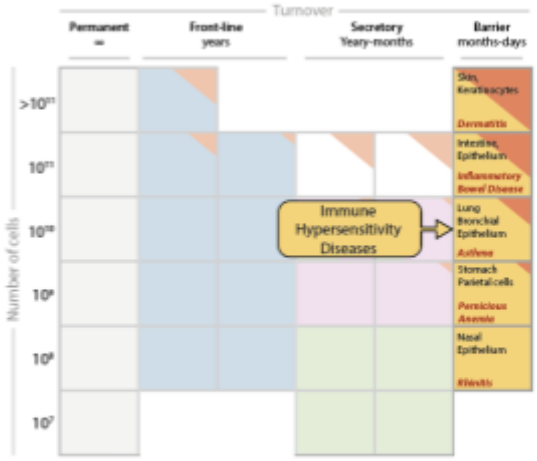

Figure 9.13: Barrier tissues show immune hypersensitivity diseases. Most of these diseases have a very young age of onset and can have high prevalence.

These organs carry out barrier functions, which are modulated by the immune system by means of signal molecules called cytokines. For example, skin thickness is increased at points that are repeatedly bruised. Thickness is increased also upon recurring signals of pathogens or toxins.

When this regulation is dysregulated, immune hypersensitivity diseases occur. These diseases typically have a young age of onset. An example is psoriasis in which skin cells multiply to cause scaling and inflammation. The inflammation creates positive feedback, with the immune system trying to thicken the barrier even more.

There are three immune hypersensitivity diseases that are often classed together, called the **atopic triad** - asthma in the bronchi, dermatitis in the skin and atopic rhinitis in the nose. Susceptibility to these diseases often occurs in the same individual, a phenomenon known as **comorbidity**.

This column also includes inflammatory bowel disease (IBD), sometimes called the psoriasis of the gut. The two common inflammatory bowel diseases are Crohn's disease that can occur anywhere in the intestinal tract, and ulcerative colitis (UC), restricted to the colon. These diseases are common, on the order of 1% of the population, with a young mean age of onset.

The prevalence of these diseases has increased over the last century in high income countries. One hypothesis, called the 'old friends' hypothesis, is that improved hygiene has reduced contact with parasites and microbes that used to be common; in the old days, they provided a high 'background signal' for the development of the immune system in childhood. Today's low background, due to the lack of these old friends, causes the immune system to develop a more hypersensitive state (Medzhitov and Stearns, 2015).

Infectious diseases occur mainly in barrier tissues

The diseases in the periodic table of Fig 9.3 are non-communicable diseases like cancer and Alzheimer's disease. These account for 9 of the top 10 causes of death in high-income countries, when we include heart disease and stroke caused by the vascular

pathology of atherosclerosis discussed below. In contrast, in low income countries these diseases account for only 3 of the top 10 causes of death. Infectious diseases are major causes of death, along with neonatal conditions (Fig 9.14).

One can add infectious diseases to the periodic table. There are a vast number of infectious diseases, and again we add only the most prevalent ones that are cell-type

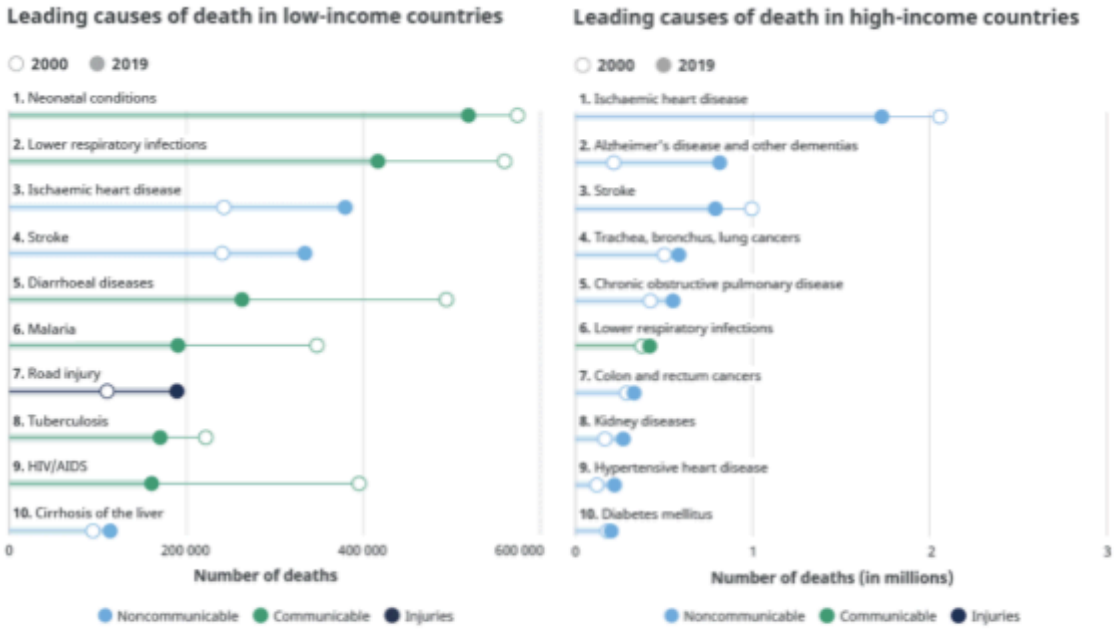

Figure 9.14: Leading causes of death in high and low income countries. Source: World health organization.

specific, or at least have a well-defined cell type as the first site of infection (Fig. 9.15). We thus exclude infections that can affect many organs such as staphylococcus and streptococcus infections.

Most infections occur in barrier tissues. The larger the tissue the more infections, with the skin afflicted with bacteria, virus, fungi and parasites, and the gut hosting numerous diarrheal diseases and parasites. Other barrier tissues include the urogenital tract with sexually transmitted diseases. We show the urogenital tract and other cell types not in the original table as boxes below the table.

The liver, which is considered part of the digestive system and receives blood directly from the gut, is also a hot spot for parasites and viruses like hepatitis. Many blood-borne diseases like yellow fever and dengue fever target cells of the immune system as their first cell-type hosts. Neurons have specific pathogens like herpes and rabies. Strikingly, most of the internal cell types, including all secretary cell types in the table, lack prominent cell-type-specific infections.

Front-line tissues get progressive fibrotic diseases of old age

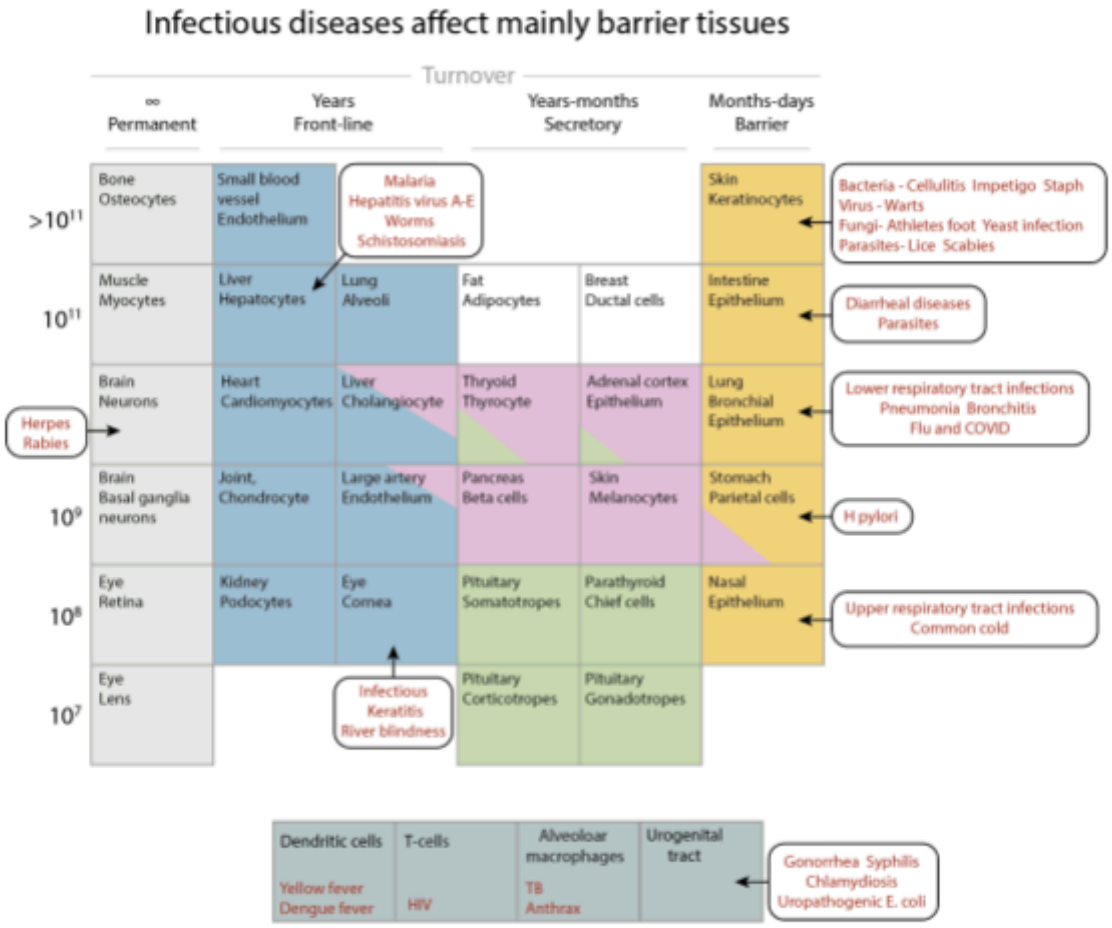

Figure 9.15: Infectious diseases affect mainly barrier tissue cell types. Cell types not included in the periodic table of Fig 9.3 are shown as squares below the table.

Based on our work in chapter 8, we devote a column in the table for **front-line tissues** (Fig. 9.16)**.** Recall that these tissues have structures that do not allow them to protect their stem cells. The stem cells are at the front line and are removed and damaged about as often as the differentiated cells. We saw the example of the lung alveoli that must be thin for oxygen diffusion and so they can't hide their stem cells.

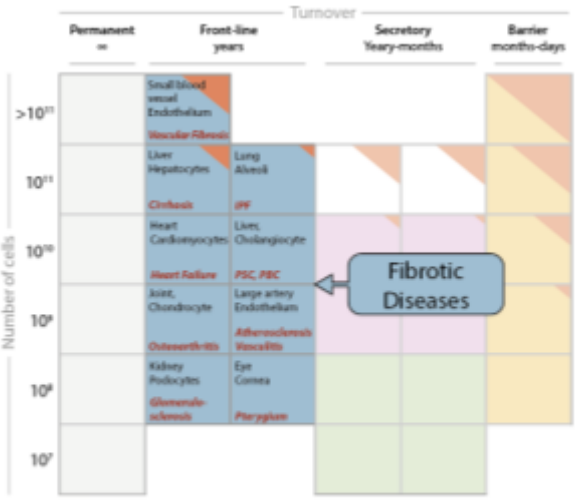

Figure 9.16: Front line cell types, in which stem cells are exposed to damage, show progressive fibrotic diseases. These diseases are age-dependent.

Front-line tissues display age-related progressive fibrotic diseases (Fig 9.16) exemplified by IPF and osteoarthritis discussed in chapter 8. Progressive diseases develop over time and are generally incurable; End-stage disease is

treatable only by organ replacement.

These progressive diseases differ from fibrosis after acute injury, which can occur in many organs, especially organs with poor regenerative capacity. An example of acute fibrosis is heart fibrosis after a heart attack. Heart attack is caused by blocked arteries, cutting off the oxygen supply for heart cells and killing them. Another common example of acute fibrosis occurs in the brain after a stroke.

In contrast to acute injury, progressive fibrotic diseases often don't have a clear source of extrinsic damage. As we saw in chapter 8, the circuit motif at play suggests a common cause for different diseases in this class. They can result from a drop in progenitor proliferation rate below the rate of removal, causing a local collapse of the tissue.

Heart attacks and stroke are often caused by a progressive fibrotic disease of blood vessels, the common age-related pathology of **atherosclerosis**. The arteries are blocked by fatty clots called plaques. The plaques occur in regions of shear stress such as bifurcations of blood vessels, where cell removal rate due to damage is highest. The damage incites inflammation which causes macrophages to accumulate in the lining of blood vessels . Risk of atherosclerosis is increased by factors that damage blood vessels, such as diabetes, smoking and hypertension. The circuit at play is discussed in exercise 9.5. Senescence enhances the risk of plaque formation, and the incidence of plaques rises exponentially with age according to the principles discussed in chapter 8.

There is a hierarchy of blood vessels from the largest arteries and veins with diameters of centimeters to the smallest capillaries with diameters of microns. The smaller the diameter, the more endothelial cells in total in that class of vessels - the small vessels are numerous because they need to fill space. The large arteries show an additional fibrotic pathology- a fibrotic stiffening with age, especially when blood pressure is high. These large arteries are in the 10g range- the autoimmune disease range- and indeed also get organ-specific autoimmune diseases (vasculitis).

We further include in this column cardiac muscle cells called cardiomyocytes. The heart gets a progressive fibrotic disease leading to **congestive heart failure** when it needs to do excess work over decades, as occurs in chronic high blood pressure. The cardiomyocyte progenitor cells, called satellite cells, are exposed to damage due to the continuous beating of the heart, and are thus at the front line.

Other front-line tissues include kidney cells called podocytes. These cells wrap around capillaries and help to filter out waste from the blood and move it into the urine. To function as a filter they are arranged in a single layer of cells. These cells participate in fibrotic diseases that cause kidney failure. They number about 10^9 cells, placing them in the zone of autoimmunity, and indeed they also show a class of antibody-based autoimmune diseases.

Front-line tissues also occur in the lining of liver bile ducts in secretory cells called

cholangiocytes. These cells secrete water and bicarbonate. Cholangiocytes are vulnerable to a progressive fibrotic disease called PSC. They total about 1g and hence lie also in the zone of autoimmune disease. Cholangiocytes indeed show an autoimmune disease in which T-cells specifically kill them, called PBC. Thus, this cell type has both an autoimmune disease and a fibrotic disease.

Liver hepatocytes likewise are exposed to toxins since they are the first station for the blood that flows directly from the gut. They are arranged in monolayers sandwiched between blood vessels, a front line structure. The liver is prone to fibrotic diseases called cirrhosis. Cirrhosis is caused by damaging agents including viral infection, alcohol, certain drugs and obesity (fatty liver disease).

Fibrotic diseases often raise the risk of cancer, as in the liver and pancreas, because they supply half of the AND gate: chronic inflammation.

Circuit motifs underlie the disease patterns in the table

This is a good point to make a partial summary. Cell-type specific diseases show broad patterns when arranged in a table by their number and turnover. The disease class in each column is fundamentally due to the kind of circuit motif at play. These circuit motifs act to control organ function and size (law 1, all cells come from cells) and have fragilities to saturation (law 2) and mutation (law 3) that lead to specific types of diseases. It's striking to plot the motifs on the periodic table, as in Fig 9.17.

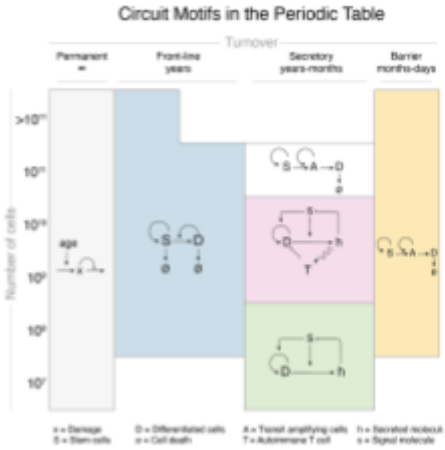

Figure 9.17: Each class of diseases in the periodic table corresponds to a specific cell circuit motif.

Age of onset and lifetime risk show patterns in the table

The table can help to identify additional broad patterns. For example, plotting the mean

age of onset of each disease shows a trend in which onset age drops from left to right (Fig 9.18). Onset thus roughly goes with cell turnover time. Degenerative disease like cataract and Alzheimer's disease peak above age 80, many fibrotic diseases have peak onset at ages 60-70, toxic adenomas at ages 50-60, autoimmune diseases like thyroiditis peak at age 20-40, with type-1 diabetes peaking earlier around age 10. The youngest mean age of onset is for barrier tissues diseases like asthma and dermatitis which often arise in early childhood.

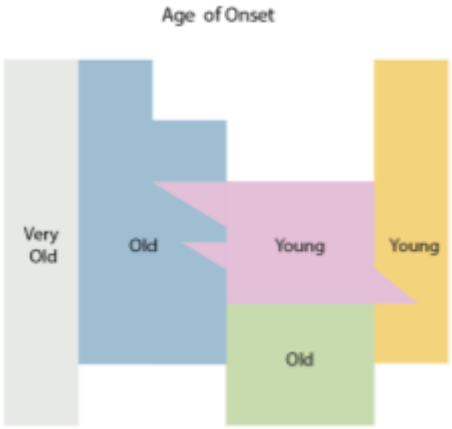

Figure 9.18: Age of onset shows patterns in the periodic table of diseases. Disease age of onset from youngest to oldest ranks as immune hypersensitivity, autoimmune, toxic adenoma, progressive fibrotic and degenerative diseases.

Likewise the lifetime risk (susceptibility) shows broad patterns (Fig.9.19). Many degenerative diseases have almost universal susceptibility, 50% to over 90%. Next are barrier diseases with susceptibility on the order of 1-10%, autoimmune diseases with 0.1%-5%, fibrotic diseases with about 0.1%-1% (except for very common arterial fibrosis and osteoarthritis) and toxic adenomas at 0.01%-1%.

Figure 9.19: Disease prevalence shows patterns in the periodic table of diseases. Shown are typical values, some diseases are exceptions.

We can also use the table to summarize the major classes of treatment (Fig 9.20). Degenerative diseases like Alzheimer's currently have no effective treatment. Progressive fibrotic diseases at their end stage require organ replacement, such as joint replacement or transplants of heart, kidney, liver or lung. Autoimmune diseases are treated by hormone replacement such as insulin pumps and thyroid hormone supplement. Toxic adenomas are treated by surgical removal. Hypersensitivity is treated by cytokine inhibitors such as TNF antibodies for psoriasis and IBD, glucocorticoids and other anti-inflammatory agents.

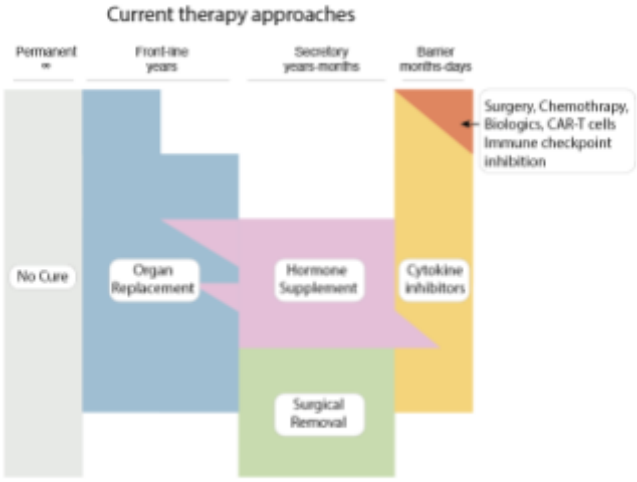

Figure 9.20: Current treatments for each class of diseases.

In this book we described several potential treatment strategies for the future (Fig 9.21). Age-related diseases can be treated by senolytics or other approaches that slow the core drivers of aging (Zhang *et al.*, 2022). This is the Geroscience hypothesis, that many

age-related diseases can be treated at once by targeting their main risk factor, aging. Progressive fibrotic diseases may be treatable by disrupting the fibrosis circuit, such as inhibition of the myofibroblast autocrine loop of chapter 5. This is an example of therapy that aims to tune ecosystems of interacting cell populations by taking advantage of their most sensitive interactions. An adaptation of this strategy may target the cell populations that make up the cancer microenvironment.

Figure 9.21: Future treatments for each class of diseases discussed in this book.

The mutant surveillance theory for autoimmune diseases suggests that the autoimmune surveillance T cells may have special 'license to kill' properties that could make them potential targets for therapy. These cells should thus be unlike standard T cells that require license signals to be active, called secondary signals, such as signals that signify inflammation; autoimmune surveillance T cells should kill even without inflammatory signals. This special ability may require a differential molecular composition that can be used to target them.

It seems likely that therapeutic approaches for a given disease could be adapted for diseases that are adjacent on the table.

Predicted diseases in the table:

We can continue with the periodic table metaphor and look for unknown diseases which it predicts.

If we see a secretory cell type in the 1-10g range, we can predict a T-cell-based autoimmune disease. One place to look is in classes of immune cells that secrete alarm signals (Fig. 9.22).

For example, plasmacytoid dendritic cells - pDC cells for short- are the main source of the alarm signal interferon-1, which causes cells to raise their defenses against pathogens. The pDC cells sense pathogens using an innate immune receptor (TLR7), which controls their growth and interferon secretion, in a 'secrete and grow' circuit (Fig 9.22).

The pDC cell type is in the 1g range, predicting an autoimmune disease analogous to type-1 diabetes. The T_{007} cells should target interferon-1 peptides, and in the predicted disease should activate B cells to make antibodies against interferon-1 (Fig 9.22, bottom panel).

Indeed, about 1% of humanity has anti-interferon-1 antibodies. These individuals have defects in their response to infection, with an increased risk for severe COVID19 (Manry *et al.*, 2022).

There may thus be a yet unnamed T-cell based autoimmune disease against pDC, as a fragility of surveillance against hypersecreting pDC clones that would put the body in perpetual alarm (Fig. 9.23).

There are predicted analogous autoimmune diseases for other types of immune cells. These diseases may explain the prevalence of anti-cytokine antibodies which are currently a mystery.

Another class of predicted diseases concerns toxic adenomas. If we see a secretory cell type with about 10^8 cells (0.1g) or fewer, we can guess it might show a hyper-secreting adenoma, a mutant-expansion disease.

As an example, pancreatic alpha cells are in

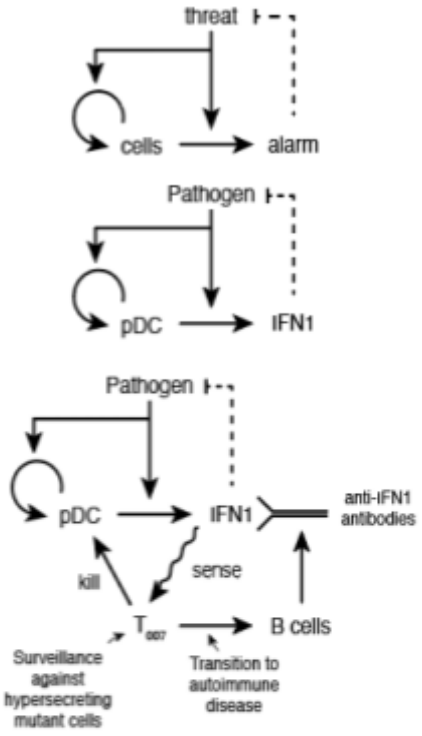

Figure 9.22: A predicted autoimmune disease may explain anti-interferon autoantibodies. A circuit in which a signal affects both growth and function of an immune cell is fragile to mutants that hyper-sense the signal. These mutant cells can expand and raise a perpetual alarm. An example is pDC cells that secrete the alarm signal interferon. The immune surveillance theory suggests that T cells can remove hyper-secreting mutant pDC cells by sensing an interferon antigen, with the potential to set off a disease in which B cells produce anti-interferon autoantibodies.

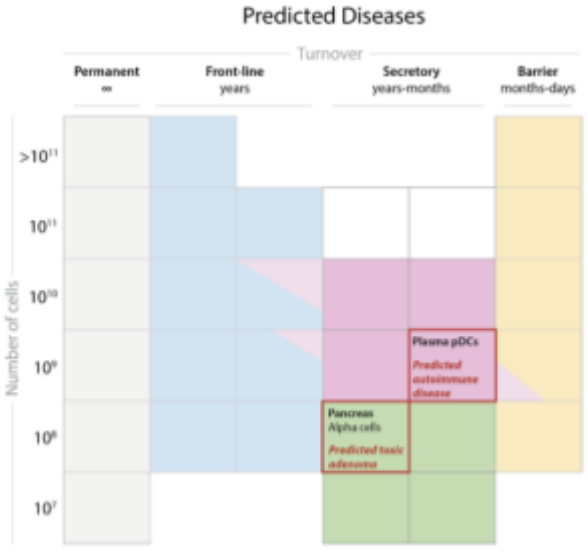

Figure 9.23: Examples of predicted diseases in the periodic table of diseases.

this range. Alpha cells are in the islets together with beta cells. They secrete glucagon, the counter-hormone to insulin, which causes the liver to make glucose out of amino acids, raising blood glucose levels.

The periodic table predicts a mutant-expansion disease of alpha cells at old age, causing excess glucagon, perhaps with a prevalence of around 0.1%. The symptoms should be similar to type-2 diabetes: excess glucose. Such expansions might contribute to diabetes in a small fraction of cases.

A brief technical note: the predicted toxic adenomas are distinct from ultra-rare cancers called neuroendocrine tumors (in this case, glucagonomas). Neuroendocrine cancer is caused by oncogenic mutations that make the cells grow uncontrollably, whereas toxic adenomas remain under control of their size-control circuit. The toxic adenoma cells behave like normal endocrine cells responding to high signal, due to the 'delusion' caused by their hyper-sensing mutation.

Another example is a cell-type in the kidneys that secretes renin, a hormone that raises blood pressure. There are about 10^8 such renin-secreting cells in the kidneys, called juxtaglomerular cells. The predicted toxic adenomas should cause hypertension -- chronically high blood pressure. They might explain a small part of this prevalent condition. Thus, one might expect toxic adenomas in tissues with a small number of cells which have the secrete-and-grow circuit.

This discussion raises the possibility of cell-type-specific diseases that are under the radar. These diseases go undetected because their symptoms are subclinical in most conditions. Or perhaps they go undetected because their symptoms are too similar to a common condition like diabetes, hypertension or obesity. The latter possibility suggests ways to find new causes for common pathologies, operative in a small number of cases. Such cases may be unresponsive to the standard treatments for these conditions.

The book is almost at its end! To celebrate, let's take a nice deep sigh of relief. I hope that you enjoyed our journey. We began with basic physiological laws and used them to define circuit motifs. These circuits carry out essential functions like organ size control. They also provide robustness to variations in physiological parameters. However, they have fragilities which are the basis for diseases. The circuits define disease classes that can be organized in a periodic table. I wonder what additional patterns and unifying principles await to be discovered.

Exercises

9.1 Comorbidity: suppose that an individual is susceptible to two age-related diseases. In the model of chapter 8, the diseases have thresholds X_{c1} and X_{c2}.

(a) Is there a predicted order in which the diseases occur in the same individual?
(b) Design a computational experiment to discern such ordering in a medical dataset which shows the age of onset of diseases in a large number of individuals.
(c) What might be confounding factors in such an attempt to discern ordering?

9.2 Disease networks: Diseases can be arranged in networks, where two diseases are linked if they share genetic risk factors or phenotypic features (Barabási, Gulbahce and Loscalzo, 2010). Compare this approach to the periodic table. What are its main merits?

9.3 Female-Male prevalence: Most autoimmune diseases in the secretory cell column are more common in females than males (McCombe and Greer, 2020). Most toxic adenomas in the same column are also more prevalent in females. Form a hypothesis for how the autoimmune surveillance mechanism of chapter 4 may contribute to the origin of a higher female prevalence. Note the fact that many of the endocrine glands involved undergo enhanced cell division during female reproductive cycles.

9.4 Biphasic mechanism: We discussed how plasma dendritic cells (pDCs) may harbor a predicted autoimmune disease. These cells show an exhaustion mechanism in which they down-regulate themselves if their receptor is activated for long times (Macal *et al.*, 2018). Discuss this in analogy to biphasic mechanisms like glucotoxicity of chapter 2.

9.5 Rare genetic disorders: read about cell-type-specific diseases caused by mutations in the fertilized egg, such as cystic fibrosis and Duchenne muscular dystrophy. How would you add them to the table? Do they tend to conform to the disease class of their cell type, or to different classes?

9.6 Atherosclerosis master exercise: Read about the mechanisms of atherosclerosis. In atherosclerosis, macrophages and other white blood cells accumulate at a point of inflammation in the artery wall. They recruit smooth muscle cells to proliferate and secrete fibers in a way analogous to myofibroblasts. The macrophages ingest cholesterol-carrying particles (LDL) which get oxidized by the inflammatory environment, and these oxidized LDL particles further stimulate inflammation, macrophage recruitment and macrophage senescence. The upshot is a fibrous and fatty plaque that can grow and eventually block the artery.

(a) Write a cell circuit analogous to the fibrosis circuit of chapter 5.
(b) Explain why LDL levels in the blood are a risk factor for atherosclerosis, and derive a mathematical expression for this effect.
(c) Explain how senescent cells with their inflammatory factors could push blood vessels across a threshold for atherosclerosis.
(d) Explain the exponential incidence of vascular disease with age along the lines of the disease-threshold model of chapter 8.

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