Systems Medicine 2021 BE333 Lecture Notes
Uri Alon
Lecture 9
Periodic table of diseases

Finally! We present a grand organization of tissues in a 'Mendeleev table of diseases'. We discuss the underlying principles that unify the course. A list of songs we did is provided in the appendix.

Mendeleev table of diseases

As a metaphor, let's consider Mendeleev's table of elements, the periodic table. In 1869, while preparing lecture notes for a chemistry course, Dmitry Mendeleev noticed patterns in the chemical properties of the 56 elements known at the time, as a function of their molecular weight (Fig 9.1).

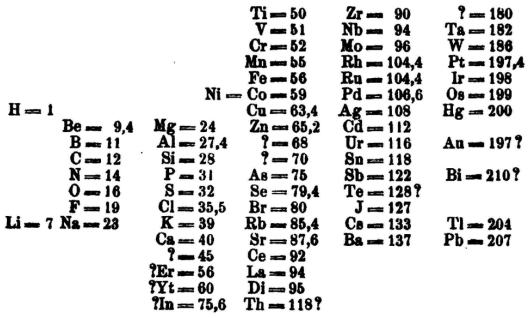

H = 1
Li = 7 Na = 23
Be = 9,4 B = 11 C = 12 N = 14 O = 16 F = 19
Mg = 24 Al = 27,4 Si = 28 P = 31 S = 32 Cl = 35,5 K = 39 Ca = 40 ? = 45 ?Er = 56 ?Yt = 60 ?In = 75,6
Ni = Co = 59 Cu = 63,4 Zn = 65,2 ? = 68 ? = 70 As = 75 Se = 79,4 Br = 80 Rb = 85,4 Sr = 87,6 Ce = 92 La = 94 Di = 95 Th = 118?
Ti = 50 V = 51 Cr = 52 Mn = 55 Fe = 56 Co = 59 Cu = 63,4 Zn = 65,2 ? = 68 ? = 70 As = 75 Se = 79,4 Br = 80 Rb = 85,4 Sr = 87,6 Ce = 92 La = 94 Di = 95 Th = 118?
Zr = 90 Nb = 94 Mo = 96 Rh = 104,4 Ru = 104,4 Pd = 106,6 Ag = 108 Cd = 112 Ur = 116 Sn = 118 Sb = 122 Te = 128? J = 127 Cs = 133 Ba = 137
? = 180 Ta = 182 W = 186 Pt = 197,4 Ir = 198 Os = 199 Hg = 200 Au = 197? Bi = 210? Tl = 204 Pb = 207

Figure 9.1

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

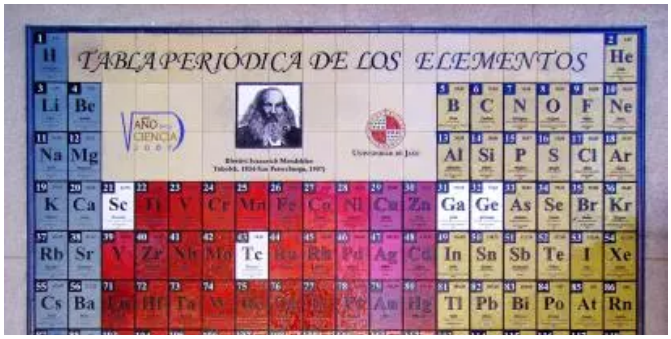


Figure 9.2

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

Metaphors ae crucial. They let scientists make inferences about something that is unknown, based on something we know. I recommend reading the slim book "Metaphors we live by".

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, but it's a good start. For example, it won't be a *periodic* table (no repeating period). But there will be patterns and missing diseases.

Periodic table of cell types and their diseases arranged by turnover and cell number

We will use the principles in this course to make a table of tissues and diseases and discern patterns. The table organizes diseases into classes (Fig. 9.3).

Each "element" in the table is a cell-type. In analogy to the atomic number, melting point and so on, we record several facts for each cell type: the number of cells of its type in the body, the turnover of the cells, and the diseases specific to that cell type with their prevalence in, men and women. For now, we won't include infectious diseases or congenital diseases.

We next arrange the cell types in a table with two coordinates. The rows go by the number of cells of that type in the body. A gram of cells typically has about 10^9 cells, so the 1 Kg liver has about 10^{12} hepatocytes. Exceptions are cells like neurons, fat cells and muscle cells which are 100 times larger, so that the 1Kg brain has about 10^{10} neurons. There are also cell types with only about 10^8 cells in the body, or 0.1g, such as the parathyroid gland.

The columns go by the turnover time of the cell type. There are permanent tissues with no turnover like most neurons. Other tissues have turnover time of many years like fat cells, others of about year like hepatocytes. Most organs have turnover times of months. Barrier tissues which stand between the outside and inside typically have the fastest turnover, such as 50d for the skin keratinocytes and a few days for the gut epithelium.

Both the turnover time and the number of cells are determined by the function of the tissue. Neuronal circuits cannot tolerate neurons being replaced, except during development and in some special brain areas. They are permanent, and so is the lens of the eye, the heart muscles which need to continually beat and cannot be replaced easily. In contrast, barrier tissues face a lot of damage and need to be replaced often.

Turnover

Number of cells

permanent	10-1 years	Front-line	100-30d	3-30d
Bone	Fat			Skin
Muscle			Breast	
	Liver	Endothelium	Pancreas	Bronchi
		Alveloi	Thyroid	Colon
		Joints	Beta cells	
lens			Parathyroid	

Figure 9.3

The number of cells is also determined by organ function. For example, endocrine glands which need to supply the entire body weigh 10 grams, like the thyroid and adrenal. Their 10^{10} cells can to 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 0.1g, or about 10^8 cells. Gland size is proportional to the number of target cells for the gland.

Continuing to more abundant cell types, we find at 100g the pancreas ductal cells and the breast ductal cells that need to secrete large amounts of fluid. At 1Kg the liver hepatocytes and the lung bronchi, and at 10Kg the skin and fat, all according to their purposes. Skin covers a large area, fat stores fuel, etc.

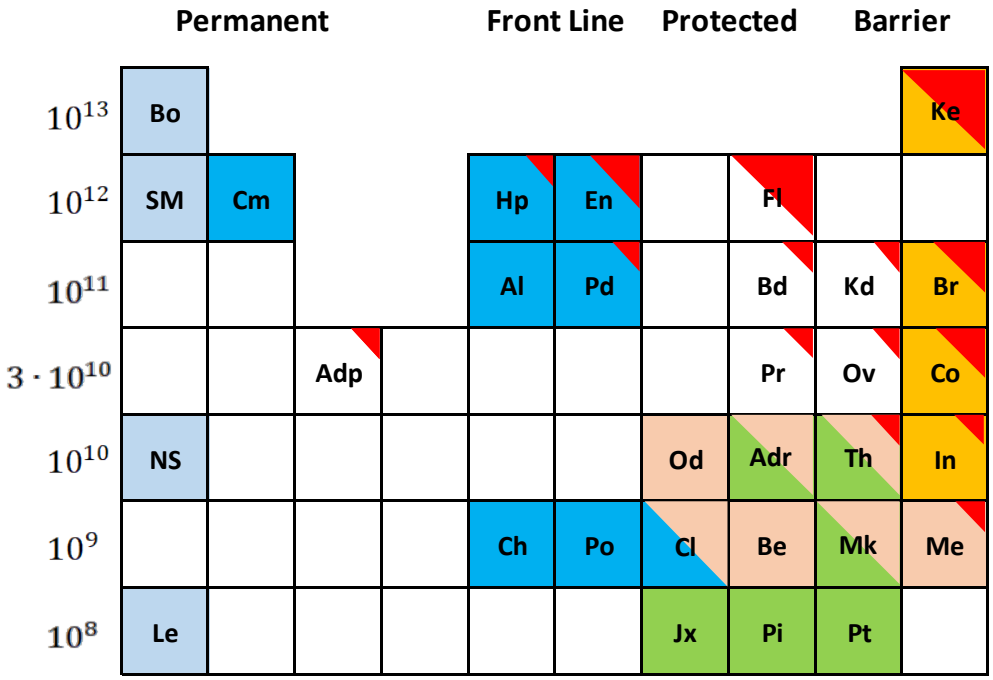


Figure 9.4

Permanent tissues have degenerative diseases of failed maintenance

We begin our survey of the table from the column of permanent tissues (Fig. 9.5). Classic examples are neurons, skeletal muscle, bone, the lens of the eye and heart cardiomyocytes. Neuron stem cell divisions occur only in specific brain areas such as the hippocampus.

These tissues do not have cell division, but they do have mutations, damage and continuous maintenance processes. Bone is remodeled at about a teaspoon a day. Neurons are trimmed, snipped and re-myelinated by the immune cells of the brain, the glia. These maintenance processes saturate according to our law 2. The saturation leads 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 in which

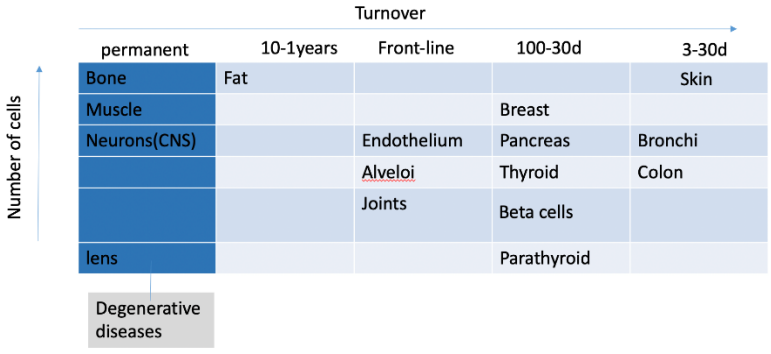


Figure 9.5

lean muscle mass is lost at old ages called sarcopenia. There is 3-5% loss of muscle per year if not active. Heart tissue shows chronic heart failure with attendant fibrosis.
Lens shows cataract in which the lens becomes cloudy, impairing vision, in about 90% of people by age 90. It is caused by denatured proteins, and apparently due to slowdown in their removal processes. Cataract is accelerated by diabetes and hypertension, as well as cumulative UV exposure.
The prevalence of degenerative diseases depends strongly on age. It does not depend on organ size: the tiny lens and heavy skeletal muscle have high prevalence of degeneration.

Barrier tissues get immune hypersensitivity diseases

Let's go now to the column at the other extreme, the organs with the highest turnover (Fig. 9.6). These are the barrier tissues, which stand between the outside world and the inside. This includes the gut, the skin and lungs. The immune system modulates their barrier function using cytokines. For example, skin thickness is increased when there are signals of pathogens or toxins.

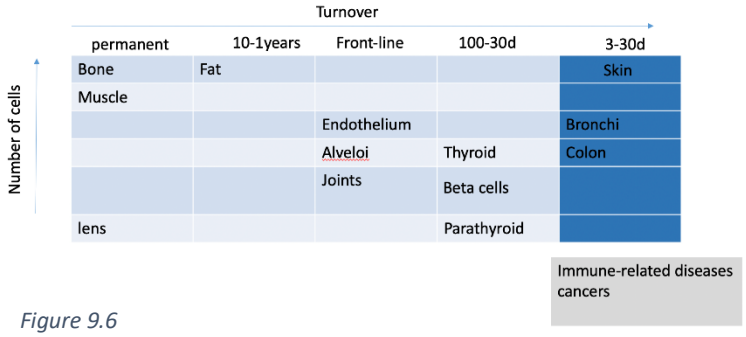


Figure 9.6

When this regulation gets out of balance, immune-related diseases occur. These diseases have a young age of onset typically. An example is psoriasis in which skin cells multiply causing scaling and inflammation. The inflammation creates a positive feedback with the immune system trying to thicken the barrier even more.
There are three analogous diseases, called the **atopic triad**, are asthma in the bronchi, exema in the skin and atopic rhinitis in the nose. Susceptibility to these diseases often occurs in the same individual, a phenomenon known as **comorbidity**.
Other examples may include 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 in the last century in industrialized countries. One hypothesis, called the 'old friends' hypothesis, is that improved hygiene has reduced the contact of the immune system with parasites and microbes that used to be common, and which provided a high 'background signal' for the development of the immune system in childhood. Todays 'low background' due to lack of these old friends, causes the immune system to develop to a more hypersensitive state.

Barrier cells divide often and are removed often. As mentioned above, their turnover is

as quick as a few days in the gut, and 50d in the skin. According to the number of stem cell divisions and exposure to toxins, these barrier tissues also get prevalent cancer, which we describe next.

Cancer risk rises along the diagonal of the table

Cancer also shows a pattern in the table (Fig. 9.7). The lifetime risk of cancer in a given cell type rises with the number of stem-cell divisions in that cell type. This risk thus rises along the diagonal of the table: the more cells and the faster the turnover, the more mutations in a lifetime (Fig 9.7). The connection between lifetime stem cell divisions and risk of cancer per tissue was noted by Tomasetti and Vogelstein (2015,2017) (Fig 9.8). There have been several criticisms of the methods in these studies, but their essential premise seems to hold true.

Turnover

Number of cells

permanent	10-1years	Front-line	100-30d	3-30d
Bone	Fat			Skin
Muscle			Breast	
		Endothelium	Pancreas	Bronchi
		Alveoli	Thyroid	Colon
		Joints	Beta cells	
lens			Pituitary	

Cancer

Figure 9.7

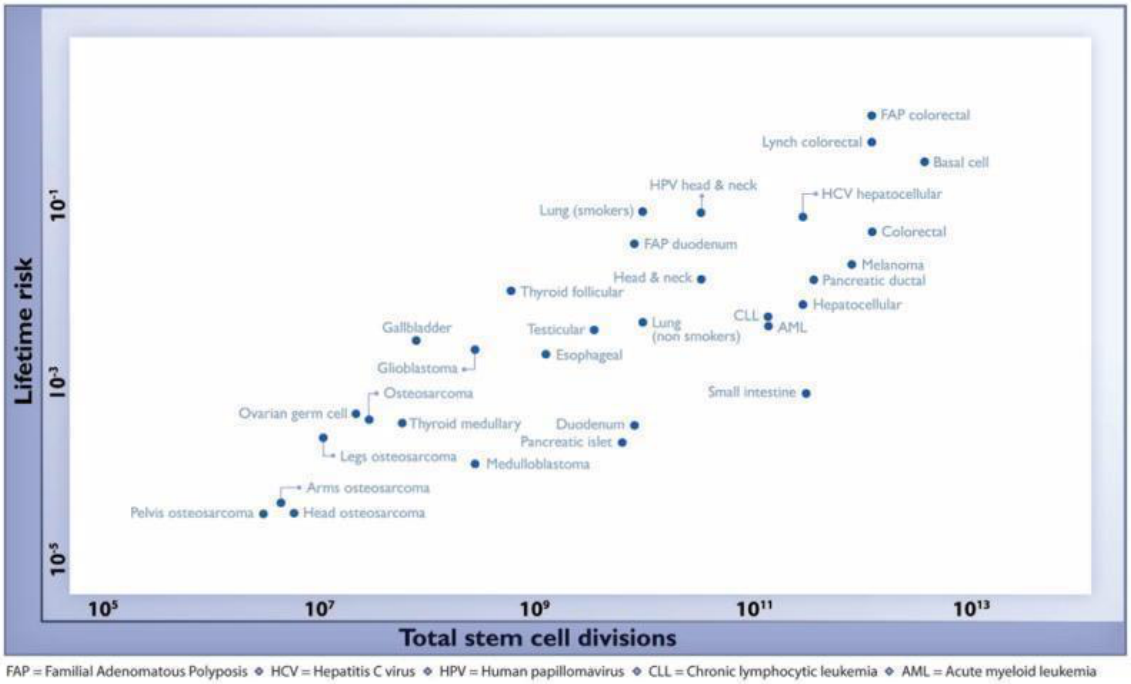


Figure 9.8

Thus, cancer risk is due to a first approximation, to bad luck: several random mutations in the same cell, in a region with chronic inflammation that makes the cells open to changing their state. It's like an AND gate: mutations and inflammation. Other risk factors are important but more secondary in most cancers. Roughly two thirds of the variation in cancer risk is due to bad luck (random mutations), and one third to genetics (inherited

oncogenic mutations) and environment (smoking, UV, toxins).

Indeed, barrier tissues exposed to environmental factors that cause mutations and inflammation tend to hide their stem cells in a protected niche, as far from the damaging factors as possible. Examples include the lung bronchi and skin in which stem cells are at the bottom layer of the tissue away from the exposed epithelium, and the intestinal epithelium in which the stem cells are at the bottom of the crypts. Another protected niche is bone marrow, which houses the stem cells that make the blood cells, hidden safely inside the bones.

These tissues get age-related cancer: skin basal cells result in benign tumors in 30% of people; colon, bronchi and bone marrow give rise to colon cancer, lung cancer and leukemias.

The dependence of cancer prevalence on total cell number is evident also in the increasing risk of cancer with height. Each 10cm of height raises the risk of each cancer by a factor of about 1.1 (thus a 2% risk turns into a 2.2% risk). Men have overall 20% more risk of cancer than women, due in part to height difference (15cm mean height difference). Women have more cancer in organs related to reproduction, more on that soon.

Tissues with front-line stem cells get progressive fibrotic diseases of old age:

Based on our work in the last lecture, we can make a column in the table for **front-line tissues** (Fig. 9.9)**.** These tissues have a special structure that does not allow them to protect their stem cells or progenitor cells. The stem cells are at the front line, and get removed and damaged about as often as the differentiated cells.

Turnover

Number of cells	permanent	10-1years	Front-line	100-30d	3-30d
	Bone	Fat			Skin
	Muscle			Breast	
			endothelium	Pancreas	Bronchi
			Alveloi	Thyroid	Colon
			Joints	Beta cells	
	lens			Parathyroid	

Progressive fibrotic diseases

Figure 9.9

We saw the example of lung alveoli that must be thin for oxygen diffusion and so they can't hide the stem cells. Similarly, joint chondrocytes can't move due to the cartilage matrix so that stem cells need to be near the working end of the joint that gets the friction and the damage.

Front-line tissues display age-related progressive fibrosis diseases (Fig 9.9): IPF and osteoarthritis. They don't often get cancer, due to their relatively slow turnover and, in the case of joints, low cell numbers.

Front-line tissues also include kidney glomerular 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 they are arranged in a single layer of cells. These cells participate in a fibrotic disease that causes kidney failure called glomerulosclerosis.

Similarly, endothelial cells that line the blood vessels have a front-line structure. Damaged endothelial cells are replaced by divisions of their neighboring endothelial cells. This cell-type shows the common age-related pathology of atherosclerosis, in which fatty clots called plaques can block arteries. The blocked arteries cause heart-attacks and strokes. The plaques occur in regions of shear stress such as bifurcations of blood vessels, where cell removal rate due to damage is highest. Senescence cells play a role in plaque formation, along the principles discussed in lecture 8.

Other front-line tissues include the lining of bile ducts: pancreatic duct cells and liver cholangiocytes. These are secretory cells that secrete water and bicarbonate. Cholangiocytes are vulnerable to a fibrotic disease called PSC, and pancreatic ducts show fibrosis. Liver hepatocytes likewise are exposed to toxins since they get blood straight form the gut. They are arranged in monolayers sandwiched between blood vessels. The liver is prone to fibrotic diseases called cirrhosis. Cirrhosis is caused by damaging agents including virus 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.

Protected tissues show three zones: hypersecreting tumors, autoimmune disease and cancer

We arrive at an intriguing column with three zones of diseases (Fig. 9.10). This is the column of cell types in internal organs with a turnover time on the order of weeks to months. Listing the most common diseases of these cell types indicates a striking pattern that we mentioned back in the first part of the course. There are three zones according to cell-number.

Bone	Fat			
Muscle			Breast	
	Liver	Endothelium	Pancreas	Bronchi
		Alveloi	Thyroid	Colon
		Joints	Beta cells	
lens			Parathyroid	

Figure 9.10

The cell-types with the fewest numbers of cells, below 1g or about 10^9 cells, get adenomas, benign tumors that hyper-secrete the hormone. 'Benign' means that the tumor doesn't spread to make metastases. The mid-range cell types, between about 1g and 10g, get organ-specific autoimmune diseases like type-1 diabetes (T1D) and Hashimoto's thyroiditis. The heaviest cell-types, above 10-30g, get cancer.

Thus, the three zones are hyper-secreting tumors, autoimmune disease, cancer. At the boundaries between the zones you see an overlap of the diseases: the 10g thyroid gets common autoimmune disease, but also rare cancer. Prostate (30g) gets cancer and more rarely an autoimmune disease.

The explanation of this three-zone pattern arises from law 3, cells mutate. The lightest cell types below 1g have so few mutations that there is a low chance for mis-sensing mutants during the 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 tumors at old age. Toxic adenomas such as hyperparathyroidism cause too much calcium, and pituitary adenomas cause too much cortisol (Cushing's syndrome), too much growth hormone (acromegaly and gigantism, like the actor Andre the giant) and so on.

The mid-range cell types at 1-10g have more cells and total divisions. In fact, at birth there have already been so many divisions just to make the organs that many cells bearing these mutations are already present. To avoid hypersecreting tumors, the body has autoimmune surveillance- the T_{007} we discussed- that selectively kill the hypersecreting cells. The cost is autoimmune disease with a young age of onset.

The autoimmune zone of 1-10g extends left and right to the other columns. Front-line tissues like liver cholangiocytes, are in this zone. They show an autoimmune diseases in which T-cells specifically kill them, called PBC, together with their vulnerability to fibrotic disease like PSC. Similarly, melanocytes which are a barrier cell type totaling about 10^9 cells, placing them in the autoimmune zone. They show vitiligo in which T cells kill them specifically. Melanocyte cancer, melanoma, is rare but deadly because this cell type easily migrates and forms metastases. It is interesting to think how melanoma evolves to avoid the T-cell killing of melanocytes. Similarly, the 1g of podocytes in the kidney get autoimmune nephritis.

The third zone in this column occurs at heavier cell types, above 10-30g. These cell type 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 T_{007} cells because you need so many of these self-attacking T cells that autoimmune disease becomes very likely. There is a therefore a switch of strategy. Instead of differentiated cells arise from differentiated cells of the same type,

$$D \rightarrow D$$

As in the thyroid and adrenal, the heavier tissues increasingly rely on stem cells.

Stem cells are professional dividing cells. They can reduce the number of divisions and hence reduce the number of mutations. The trick is to first differentiate to **transient amplifying cells**: cells which can divide a limited number of times and give rise to the final differentiated non-dividing cell type.

$$S \rightarrow D' \rightarrow D$$

For example, if each transient amplifying cell D' 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. Mutations that arise in the divisions of the transient amplifying cells are not very dangerous, because these cells are soon removed with the natural tissue turnover.

Why don't all tissues use stem cells? Stem cells also have a cost–the risk of cancer. Their stemness features makes them show 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 is a tradeoff between hyper-secreting mutants and cancer for cell types in this column, and that at a certain number of cells, the balance is tipped towards stem cells.

Stable massive tissues get very common benign tumors

Some heavy (numerous) cell-types do not make use of a stem cell strategy as the main source of cells. Instead the cells originate from divisions of cells of the same type. These include blood vessels (endothelial cells) that amount to about 100g, and tissue-resident fibroblasts that amount to 100-300g.

These tissues get common tumors, but the tumors are benign. Blood vessels get angioma which occurs in most people with age. Large blood vessels are in the 10g range- the autoimmune disease range- and indeed also get organ-specific autoimmune disease (vasculitis). Smaller vessels have many more endothelial cells in total, but their most common autoimmune disease is actually caused by an autoimmune killing of neutrophils: the neutrophils explode when killed, causing collateral damage to the capillaries.

Fibroblasts get fibromas, which also occur in most people with age. Rarely, fibroblasts give rise to aggressive cancers called sarcomas. Fat cells show lipomas in at least 2% of people (they total 10s of Kg, but cells are ~100 times larger than regular cells, and divide much slower once every ~10years, accounting for relatively low cancer incidence).

Missing diseases in the table:

We can continue with the periodic table metaphor and look for missing diseases.

If we see an endocrine or secretory cell type in the 1-10g range, we can predict a T-cell based autoimmune disease.

One place to look for predicted autoimmune diseases is in classes of immune cells that secrete important signals called cytokines (Fig. 9.11). For example, pDC cells are the main source of the inflammation alarm signal interefron1, and are in the 1g range. An autoimmune disease is predicted to target interefron1 peptides. Indeed, about 1% of

humanity has anti-inetferone1 antibodies, and some of these individuals have defects in response to infection, most famously with an increased risk for severe COVID19. There may thus be a yet unnamed autoimmune disease against pDC, as a side effect of surveillance against hypersecreting pDC clones that would put the body in perpetual alarm.[1]

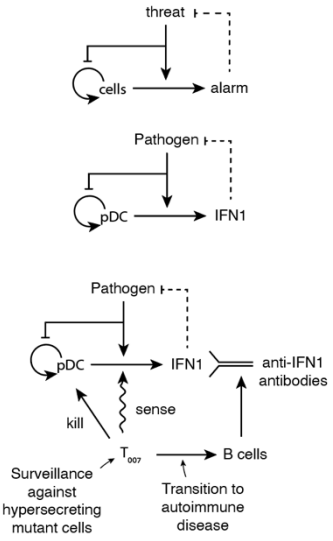


Figure 9.11

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

If we see an endocrine or secretory cell type with fewer cells, say about 10^8 cells (0.1g), we can guess it might show a hyper-secreting mutant-expansion pathology.

As an example, pancreatic alpha cells are in this range. Alpha cells are in the islets together with beta cells. They secrete glucagon, which raises blood glucose levels (the opposite hormone to insulin).

The table predicts a mutant-expansion disease of alpha cells at old age, causing excess glucagon, perhaps with a prevalence of around 1%. The symptoms should be similar to type-2 diabetes: excess glucose. Perhaps such expansions contribute to the prevalence of diabetes in a small fraction of cases.

Another example is a cell-type in the kidneys that secretes renin, a hormone that raises blood pressure. There are about 10^8 renin-secreting cells in the kidney, called juxtaglomerular cells. The predicted toxic adenomas, have been documented and called reninomas. They cause hypertension. This might explain a small part of this very prevalent condition. One might expect toxic adenomas in tissues with a small number of cells which have a size-control circuit.

Other missing diseases might affect hormone-secreting cells in the intestine. These include the 1g of L-cells in the colon, which show a regulated growth secretion circuit based on nutrient inputs, like the circuit motif of chapter 3. They secrete several hormones: glp2 that causes growth of intestinal tissue, glp1 that enhances insulin secretion, and peptides that affect hunger. They are in the table '1g-10g' range of autoimmune disease, whose symptoms should mimic the lack of these hormones, including the possibility of obesity.

Other hormone-secreting cell types are present at smaller abundance, are therefore predicted to have hormone-secreting tumors (neuroendocrine tumors, NET). Such NETs indeed occur with prevalence of about $10^{-5} - 10^{-4}$ in the intestine and lung.

Another possible 'missing' spot is cancers/tumors of tissue-resident macrophages, which total about 300g. An example is liver-resident macrophages, called Kupfer cells, that

[1] pDC proliferation is controlled by the same receptor that senses pathogen signals, TLR7. There also an exhaustion mechanism in which pDC downregulate themselves if excited for long times. This is analogous to the biphasic mechanism against mutants like glucotoxicity. Macal et al Immunity 2020.

divide every 20 days. Such macrophages exist in almost every tissue.
Possible examples of the missing cancer is Kupfer-cell hyperplasia. A well-known example is the macrophage-like cancer of glial cells in the brain (~1% prevalence). Unlike neurons, glia are not permanent but instead have a normal turnover of about 5 years.

This raises the question of whether there are cell-type specific diseases that are 'under the radar'. These diseases might go undetected because their symptoms are subclinical-perhaps another system compensates for the disease. Or perhaps they go undetected because their symptoms are too similar to a common condition like diabetes, hypertension or obesity. The latter possibility opens the way to find new causes for common conditions, operative in a small number of cases. Such cases may be unresponsive for some of the usual treatments for these conditions.

Caveats:
Some diseases do not fit easily into the table. These diseases have symptoms that are across organs. One example is a class of antibody-based autoimmune diseases like lupus. In this disease an antibody-DNA complex accumulates in different tissues.
There are thousands of cell types in the body. The present table contains only a few tens.

Female:male disease frequency in cell-types with reproduction roles
The table can help to form hypotheses about female:male biases in the prevalence of diseases. The idea is sexual dimorphism - the fact that males are larger on average, and that females have more cell divisions in reproductive organs.
To see this, we can add another piece of information to the table, listing whether the cell type has enhanced rate of divisions in the female reproductive process, including menstrual cycle and pregnancy.
A well-known example of the effect of divisions is breast cancer: breast cancer is much more common in women than in men, and breast epithelium indeed proliferates in menses under control of estrogen/progesterone. Breast cancer risk in women is reduced the fewer the number of menstrual cycles, as in late start of menstruation or more pregnancies.
Reproductive cell divisions may explain also why autoimmune diseases are usually more prevalent in women. Classic explanations focus on the immune system (e.g. women have a different immune system so as not to attack the fetus). However, an explanation based on ASHM is that organs such as the thyroid and adrenal expand during pregnancy. More divisions in women means more mutations. This requires more T_{007} cells and hence more risk of autoimmune disease in the 1-10g organs.
A prediction from this theory is that in small glands, under 1g, hypersecreting tumors should occur more often in women if the gland plays a role in female reproduction.

Indeed, women get more hypersecreting pituitary adenomas that produce ACTH, TSH, prolactin and sex hormones, as well as a hypersecreting adenoma disease of the parathyroid gland. These hormones are important during pregnancy and breastfeeding. For example, parathyroid control the calcium needed to make the fetal bones and mother's milk. Prolactin controls lactation.

There are exceptions in which the female:male ratio is 1:1, or even a male bias for such hypersecreting clones. These exceptions are revealing. The only pituitary hormone with more hypersecreting tumors in males is growth hormone, causing acromegaly (gigantism in children). The growth axis is more active in men than in women, and one would expect more cell division in men in the growth hormone pathway.

On the autoimmune side, type-1 diabetes has a 1:1 ratio. Although beta-cells are very active and may expand in pregnancy (at least in rodents), there may be more divisions in males overall. Finally, vitiligo of melanocytes is an autoimmune disease more prevalent in men, perhaps due to larger skin area.

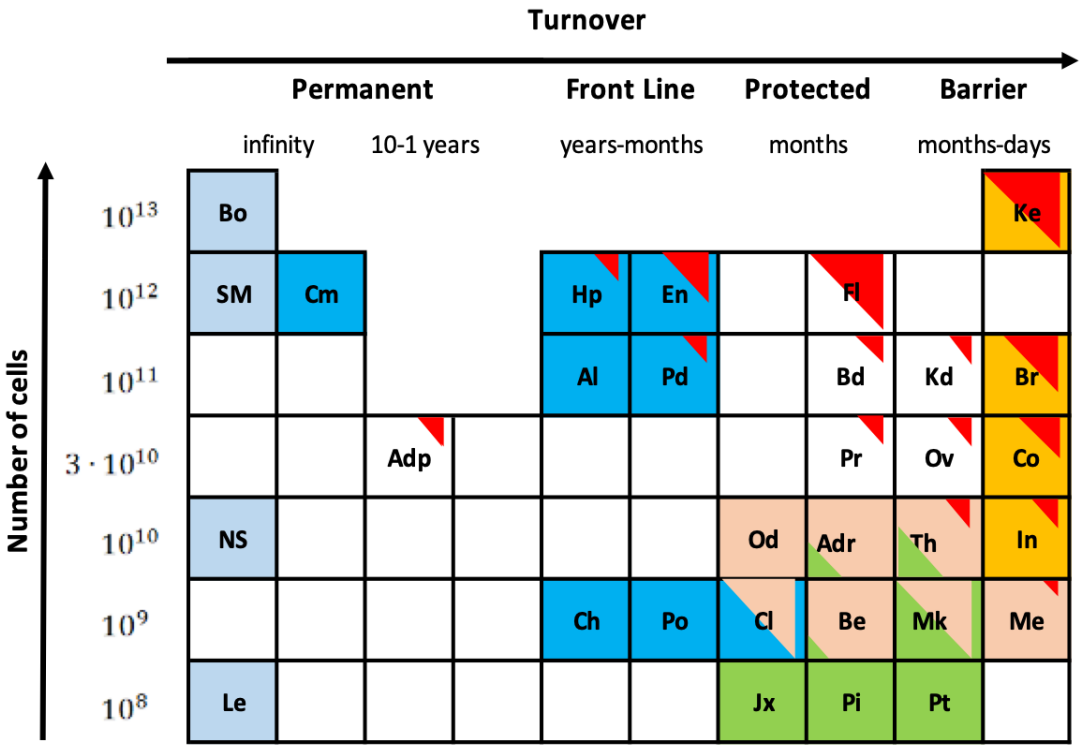


Figure 9.12

I hope that you enjoyed the periodic table of diseases and cell types. I wonder what additional patterns and unifying explanations remain to be discovered.

Appendix 1: This course is based on three basic principles

The work we did in this course provides a basis for understanding these patterns of diseases. It can all be boiled down to three basic principles, or biological ground truths. These principles are:

1) **All cells come from cells.** $\frac{dX}{dt} = (\boldsymbol{p} - \boldsymbol{r})\boldsymbol{X}$

2) **Cells mutate** $\frac{dX^*}{dt} = \boldsymbol{m}\,\boldsymbol{X}$

3) **Biological processes saturate.** $\frac{X}{k+X}$

Together with a dynamic process:

4) **Natural selection maximizes reproduction given the limited resources of the organism.**

$$\boldsymbol{X} = \boldsymbol{argmax}(\boldsymbol{F})$$

Thus, physiology is not designed to maximize health or well-being, but rather to maximize the chances of passing genes to the next generation, including copies of the genes in family members, called **inclusive fitness**.

Here are examples of how these principles can be used to derive important aspects of physiological circuits and diseases.

1. ALL CELLS COME FROM CELLS: exponential dynamics require feedback circuits for size-control, providing compensation to physiological parameters

In a simple tissue, cells X arise from proliferation at rate p and removal at rate r, so that $dX/dt = pX - rX$. In order to avoid degeneration (p<r) or exponential expansion (p>r) requires $p = r$. Thus, feedback control is required to make proliferation match removal. To provide the right tissue size, the feedback needs to rely on a signal that is directly related to the organ function.

An example from the lectures is the beta-cell-glucose-insulin model (BIG). Here feedback on p and r by glucose keeps beta-cell population size under control. This feedback has additional remarkable features: beta-cell numbers can grow and shrink over weeks to buffer variations in insulin resistance and blood volume, to keep glucose at 5mM. This allows the flexibility to allocate glucose to different tissues by means of changes in insulin resistance on the fast timescale. The compensation of changes in blood volume allows beta-cell numbers to remain proportional to the changing body size during children's growth and during pregnancy.

A second example occurs when two glands form a feedback loop to maintain each others

size. This happens in the HPA axis where A (adrenal) and P (pituitary corticotrophs) secrete hormones that affect each other's growth rate. Again, this feedback loop has advantages beyond maintaining gland size. The glands grow and shrink on a timescale of months, providing a seasonal oscillator that can change the hormonal setpoint according to the seasons. The two-gland feedback circuit also creates a search mechanism that can guide behavior to optimal stimulation levels, analogous to bacterial chemotaxis.
In a major theme in this course, essential circuits like this have fragilities that give rise to diseases. In the case of the HPA axis, the fragilities include addiction and mood disorders with timescales determined by tissue turnover times of months.

2. DIVISIONS BRING MUTATIONS requires mutant resistance mechanisms, with fragility to metabolic and autoimmune diseases

Principle 1 'all cells come from cells' makes it necessary to have feedback loops on cell growth. Due to the inevitable mutations that come with cell division, there will be mutants in the sensing component of these feedback loops. These mutants have a growth advantage and threaten to take over the tissue. They must be eliminated. We saw two principles for resisting such mis-sensing mutants.
The first principle is biphasic control in which both low and high signal levels cause cell death. This gives mutants that mis-sense the signal a selective disadvantage. The down-side of this strategy is a fragility to a dynamical disease, in which fluctuating physiological signal levels can cross an unstable fixed point and lead to a vicious cycle of cell death. Such a mechanism can explain late-stage type-2 diabetes in which glucotoxicity causes loss of beta cells.
The second mechanism is immune surveillance where T cells recognize and kill the mutants. The mutants are detected by their increased secretion, and thus increased presentation of antigens in the secretion pathways. The immune surveillance uses self-reactive T cells we called 'T007' cells. T007 kill the cells with the highest secretion. The downside of this strategy is that it provides the hardware for auto-immune diseases like type-1 diabetes.
A recurring theme in the course is the tradeoff between the beneficial function of a mechanism and its disease costs. Natural selection maximizes reproduction by choosing the lesser of two evils. It eradicates beta-cell mutants that would kill almost everyone due to hypoglycemia, at the cost of type-1 diabetes that kills 1% of children.

3. **REPAIR PROCESSES SATURATE causes damage like senescent cells to accumulate with age, causing exponentially rising incidence of age-related diseases**

In the young, senescent cells are important for wound healing. However, we are not designed to be old. Senescent cell production rate rises with age because of mutations in stem cells (principle 2). Their removal the immune system is a finite resource whose amount is set by evolution to maximize reproduction in the reproductive years. Thus, rising production eventually saturates the removal of senescent cells. Their amount rises

sharply and the damage they do exceeds their benefit in the old: They cause inflammaging and slow regeneration. These effects can push tissues over a threshold in which stem cells collapse (division rate <removal rate) causing fibrotic diseases. It also pushes wound-healing into the fibrotic basin of attraction. Saturation of immune surveillance by senescent cells reduces the other functions of surveillance, and therefore provides vulnerability to cancer and infection.

Many diseases of old age are thus threshold-phenomena, in which a catastrophe happens when parameters cross a threshold. The stochastic process of senescent cells converts this threshold crossing process into a first-passage-time problem, yielding the universal incidence curve of age related diseases: an exponential rise with age, with a drop at very old ages.

Thus, a theme for age-related diseases is that they originate in crossing of a threshold. This threshold varies between people with genetics and environment, so that only a fraction of the population is susceptible to a given disease.

A better coordinate is total lifetime mutations in dividing cells, but mass is a good proxy. Total lifetime mutations M is given by the total number of dividing cells N (total mass divided by mass-per-cell) times the number of lifetime divisions per cell (lifetime divided by turnover) times the mutation rate.

Thus

$$M = \left(\frac{W}{m}\right) \cdot \left(\frac{L}{\tau}\right) \cdot \mu$$

where W is total weight, m is mass per cell, L is lifetime, τ is turnover time, and μ is mutation rate.

Mass W is a good proxy for M for most non-permanent cell types. This is because turnover is $\tau \sim 100$ days for most cell types, except fast cell types (colon 5d) and slow cell types (fat 10y). Cell mass is also about the same for most cell types: cell mass is about m=1ng making 10^9 cells per gram, except large cells (fat cells are 100 times bigger). Mutation rate is about the same in different tissues, $\mu = 10^{-9}$/bp/division. Tissues with exposure to damaging agents, such as lung in smokers, may have higher mutation rate mu in smokers. Thus, total cell mass W makes sense as a proxy for M.

Exceptions: fat (divides 10 times slower, mass is 100 times bigger, so 10Kg are effectively like 100g. indeed lipoma prevalence is 2%, like smaller tissues)

Colon epithelium: W=30g but turnover is 20 times faster, so like a 600g tissue. indeed, cancer prevalence is like larger tissues.

Review on epithelial barrier hypothesis for allergy and autoimmunity increase

Akdis, C.A. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions?. *Nat Rev Immunol* (2021). https://doi.org/10.1038/s41577-021-00538-7

Appendix 2: songs in the course

Songs

1 Insulin-glucose: Hormones everywhere. Tangled up in glucose

2 Diabetes-biphasic: I'm a hyper-sensing mutant baby, watch me grow

3 HPA seasonality: Psychokiller HPA.

4 Autoimmunity: I am just a T-cell and my stories seldom told

5 Fibrosis: When I find myself in times of swelling (let it be)

6 Ageing basics: Ageing here and there. Tonight, we are young. When I'm 64

7 Dynamics of ageing: Mamamia, here we go again. And may you be forever young (Dylan)

8 Age-related diseases, IPF: Alveoli (hallelujah).

9 Periodic table of diseases

Previous course:

1 COVID: We shall overcome

5 Addiction: Cocaine/rehab/river was whisky

6 Immune FCD:

Appendix 3: overview of principles:

1 Minimal model helps us ask questions: robustness to insulin resistance
2 Cells come from cells: need size control
→ Dynamic compensation -->adapt to blood volume, insulin resistance
Cell division generates mutations-->need to resist mutants
Biphasic mutant resistance
→ creates fragility to stability, type 2 diabetes
[lesser of two evils] Diseases have essential physiological counterparts
-->mild missing mutants need mechanism
3 mis-sensing mutants an unavoidable problem-->immune surveillance-->creates fragility to autoimmune diseases
organs without AID (small glands) show hypersecreting benign tumors
[lesser of two evils]

4 separation of timescales in two-gland feedback (HPA): tissue turnover of weeks adds seasonal clock (driven damped oscillator) and fragility to dysregulation (dex withdrawal, mood disorders-bipolar]
11 separation of timescales: toggle switch can generate depression state, long timescale of treatment
12 separation of timescales: addiction - long timescale of tolerance (exact adaptation, FCD), withdrawal (undershoot- new phase).
HPA as navigation in behavior space- mathematical analogy to bacterial chemotaxis.
[addiction as fragility of stimulotaxis]
10 Sizostat- exact adaptation offers guidance to growth percentile- catchup growth, noise driven oscillations [mini growth spurts, maybe bipolar]

8 Bistability and nullclines: inflammation-fibrosis, depression (lecture 11)

6-7 All biological processes saturate- we are not designed to be old-->SR model of aging first passage time problem, potential and Kramer's approx.-->Gompertz law
8: age-related diseases as threshold processes, prevalence and incidence
Stem-Diff cell equations, need for stability, bifurcation-->IPF,OA mathematically analogous diseases

9 Multi objective evolution in medicine- ParTI division of labor in tissues and in cancer, universal cancer tasks

Appendix 4 - joint chondrocyte fun facts:

The 1g total weight of joint chondrocytes put that tissue also in the range of autoimmune disease. This disease may be rheumatoid arthritis, whose origin is not well understood (prev 0.5-1%, 2.5:1 F, onset midage).(total chondrocyte mass: $100cm^2 * 3mm = 30cm^3$ per joint (correct for knee, 20ml), $5 * \frac{10^6 cells}{gram\ 10} joints = 10^9\ cells = 1g$) [evidence: Autoantigens fall into two major groups: first, those that are associated with the joint, such as collagen type II, human chondrocyte glycoprotein 39, and proteoglycans, for which a pathogenic role is easily understood; and second, those proteins not associated with the joint. note RA starts in synovial lining]

Appendix 3 MS facts:

Oligodendrocytes- make up 20% of brain cells (mouse), turnover at 10-40d and remyelinate (mice) (but only 0.3% annual turnover in human bomb data), thus may be the rationale for MS(!) a simple AID against myelin. weight: there are 300g of oligodendrocytes, but if they are 100 times bigger than typical cells, it puts them in effective weight of 3g!

Appendix 5: Hormone concentrations and gland weight

Hormone concentration versus gland mass:

10g

cort: 500nmol/L

T4: 100nmol/L

(17g probably 3g) Testosterone 10nmol/L

1g

insulin 10-100 pmol/L

0.3g

GH 0-1000pmol/L

prolactin 100pmol/L

0.1 g

ACTH 10 pmol/L

PTH 10ng/L,~1-10pmol/L (3KDa)

0.01g[?]

renin:10 pg/ml =10ng/L ,(W=38kDa)=0.1 pmol/L

leptin 50 ng/ml=50 mu g/L= (16KDa) = nmol/L[?] secreted by 10Kg of cells.

Appendix 6: Notes on Alzheimers disease (AD)

- Memory loss due to neuron death in cortex and hippocampus.
- Diagnosed post mortem by amyloid plaques and neuronal tangles.
- Plaques deposition outside of neuron of Ab.
- Tangles: aggregate of misfolded tau.
- Amyloid normally removed by microglia, immune-like cells. They can expand after injury.
- Risk factors: 5% familial causative dominant mutations in amyloid or in the protease that cleaves it presnilin gamma. More wide variants: ApoE80% normal, 15% variant 20x risk, 5% variant: protective. ApoE in all cells, but may play role in microglial removal of amyloid, and is 5x expressed in microglia in AD patients.
- Microglia normally prune defective synapses from neurons.
- Theory: Neuron mutations rise linearly with age (Startton). Mutant neurons are $P{\sim}a\ t$. This causes defective synapases. Damage X, $dX/dt = b\ a\ t = \eta\ t$. Damaged synapses removed by microglia

$$\frac{dX}{dt} = \eta\ t - \beta \frac{X}{k+X} + noise.$$

Amyloid is produced at rate q and removed by microglia that are not working on synapses, namely $k/(X+k)$ of the microglia

$$\frac{dA}{dt} = q - w\ A\ \frac{k}{X+k}$$

$$\text{if } X_{st} = \eta \frac{t\ k}{\beta - \eta\ t} \text{ then } A_{st} = q \frac{X_{st}+k}{w\ k} \sim \left(\frac{q}{w}\right) \frac{\eta\ t}{\beta - \eta\ t}$$

Predictions:

Incidence has different slope from other age related diseases because of different η for neuron damage.

Standard incidence curve for the 5% families but shifted to lower threshold (higher q, lower w)

Prediction: should be mutations in neuronal repair systems that account for some of the variance (the η)- maybe wide spread. Radiation should increase prevalence.

	Permanent	**10y—1y**	**100d – Front line**	**30d -Protected**	**10d- Barrier**
10 K	Skeletal Muscle (15y turnover) Sarcopenia	Adipocyte (1kequiv) Lipoma (2%)			keratinocyte basal carcinoma(30%). Psoriasis/exema
	Bone Osteoporosis (55%)		Small endothelium angioma atherosclerosis	Fibroblast Fibroma (50%) SarcomA	
1K	CNS (10g equiv) AlzD,ParknsnD	Hepatocytes carcinoma cirrhosis		Glia	Bronchi Asthma Lung cancer
	Cardiomyocytes Heart failure		Alveoli IPF	Marrow (10^5 stem cells) Leukemia (1%)	
100g			Pancreatic duct cancer fibrosis	Kidney duct Clear cell carcinoma	colon UC IBD
				Breast duct	intestine IBD Celiac
30g			Large Endothelium Vasculitis atherosclerosis	Prostate prostitis	head/esophagous rhinitis

			s		
10g				Ovaries	Gastric cancer Pern. anem
			Joint chond Osteoarthritis A Rhumarth is	Thyroid Hashimoto/graves Nodule cancer	
			Cholangiocyte PBC PSC cancer	Adrenal Addison Cushing	
				Oligodendrocytes MS	
1g			Podocyte Nephritis Glomerulosclerosis	Beta-cell T1D FCH	Melanocyt Melanoma Vitiligo
				Megakaryocyte ITPurpura PNM	
0.1 g	Lens(.2g) cataract (~100%)			Parathyroid hyperPTH	
				Pituitary Cushing Prl/hypgond/thy/acromegaly	
				Jxtaglomerular reninoma	

toxic adenoma

immune-related disease (hypersensitivity)

Organ-specific autoimmune disease (CD8 T cells)

utoimmune disease (antibody mediated)

Progressive fibrotic disease

Cancer

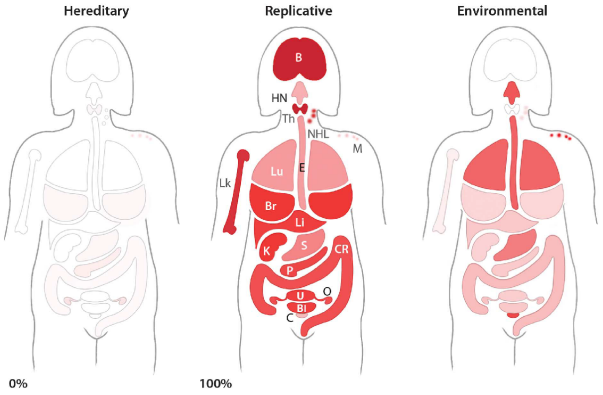
Degenerative disease

Mass	**Cell type**	**Stable/Labile M/F**	**Diseasep**
10Kg	Skin (50d,5g stem)	L	Basal carcinoma (30%)
10Kg	Adipocytes (3000d)	L	Cancer (lipoma, 2%)
3K	Endothelium(100d)	S	Cancer(Angioma,~100%), fibrosis(atherosclerosis)
1KG	Fibroblasts (connective tissue,50d-700d)	S	Cancer(Fibroma_~50%)
300-500g	Tissue resident macrophages	S	Predicted Cancer(kupfer cell hyperplasia)(?)
1 Kg	Bone marrow(30d, 0.1%stem)	L	Cancer (leukemia, 1%)
1Kg	Liver hepatocyte(300d)	L(EPCAM MUC6 stem cells), M=F	Cancer, fibrosis
500g	Breast ductal(1%stem,22-150d)	L, F	Cancer (F)
	Lung alveoli	L, front line	Fibrosis (IPF), rare Cancer
	Lung Bronchi	L	Cancer
100g	Pancreas ductal	L, M=F	Cancer
30g	Colon epithelium (5d,1%stem)	L	Cancer(5%), AID(Crohns,UC)
	Esophagus (11d,3%Stem)	L	Cancer
30g	Prostate (4mo,0.7%stem)	L,M	Cancer, AID (rarer)

20g	Small intestine epithelium (15d,1%stem)		Cancer(0.2%), AID(Crohns)
20g	Testes(3mo,.1%stem)	L,M	Cancer(.4%)
20g	Head-neck mucosa (20d,.1% stem)	L	Cancer(1%)
1g	Chondrocyte joint	L, front line	Fibrosis (OA), RA (AID F2.5:1)
10g	Thyroid follicular	S, F10:1 (pregnancy thyroid growth)	AID (Hashimoto 10:1,5%) F, Cancer (thyroid, non secreting)
3g	Melanocytes(150d)	S,	AID (vitiligo,.6%, M>F 1.5:1), Cancer (melanoma, 2%, M>F)
5g	Adrenal cortex(60d)	S,F	AID (Addison) F2:1 10^-4, hypersecreting (cushings) F
5g	Cholangiocyte	S, F (progesterone/estrogen prolif, pregnancy cholestasis)	AID (PBC) F4:1 10^-5, rare cancer
1g	Beta cell	S M=F	AID (T1D,1%) F1:1, rare cancer
0.3g	Lactotroph	S F (high during pregnancy)	
0.2g	Somatotroph	S M	Hypersecreting M=F (acromegaly)
0.1g	Gonadotroph	S F	Hypersecreting F
0.1g	Thyrotroph	S, F	Hypersecreting F>M (central hyperthyroidism)
0.1g	Corticotroph(60d)	S, F	Hypersecreting F (secondary Cushing F3:1)
0.2g	Parathyroid	S, F (high during lactation)	Hypersecreting F Primary hyperparathyroidism (F3:1, postmenopause 2%)

0.4g	Megakaryocytes-->platelets	L	AID (ITP, 10^-4);F1.5:1 'hypersecreting' tumor (MPN,10^-4)

Tomasetti Vogelstein 2017: most risk is due to random replication errors in stem cells. Note tissues on the eight that have environmental risk-melanoma, stomach, head/neck, esophagus, cervix

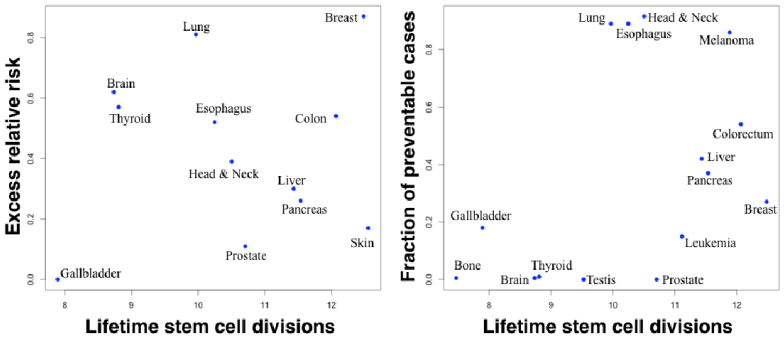


Tomasetti 2017 Supp Info: updated estimates for lifetime stem cell turnover

about 3 mutations per division in stem cells (Vogelsein 2017)

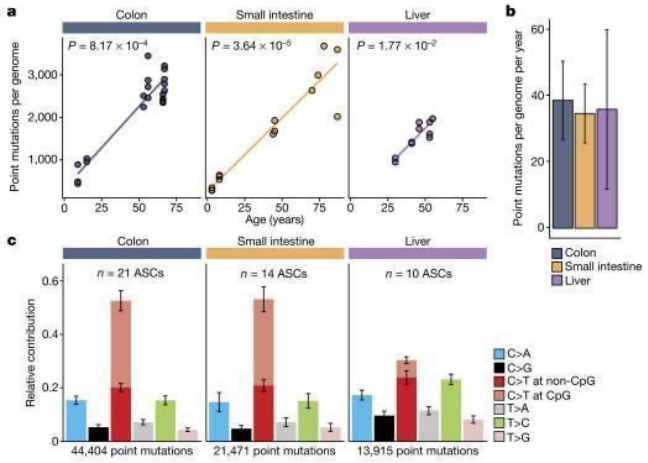
About 40 mutations per year in stem cells…

A **B**



Stem cells show about 40 mutations per year from age 3 to 90 in liver, intestine, colon using organoids to define stem cells.

Nature. 2016 Oct 13; 538(7624): 260–264.



Turnover

Number of cells

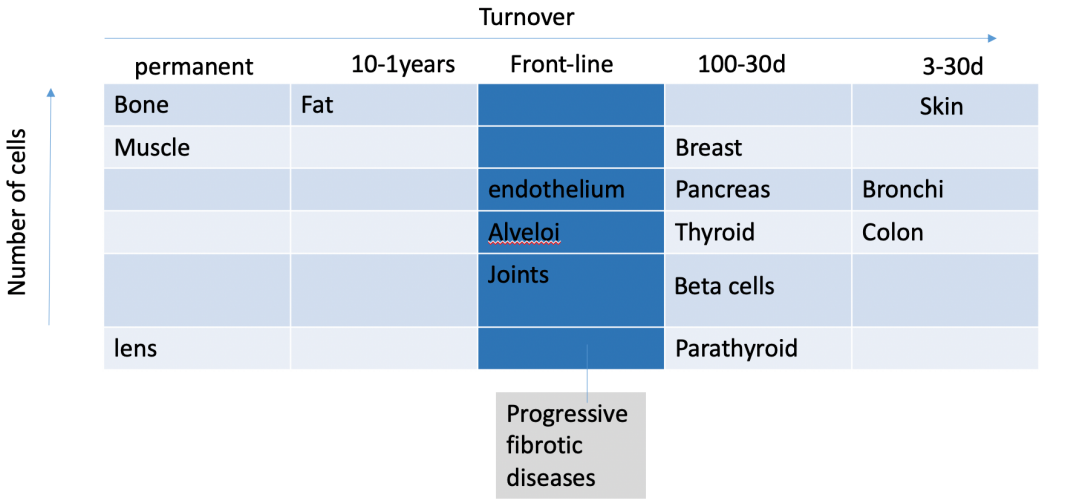
permanent	10-1 years	Front-line	100-30d	3-30d
Bone	Fat			Skin
Muscle			Breast	
	Liver	Endothelium	Pancreas	Bronchi
		Alveloi	Thyroid	Colon
		Joints	Beta cells	
lens			Parathyroid	

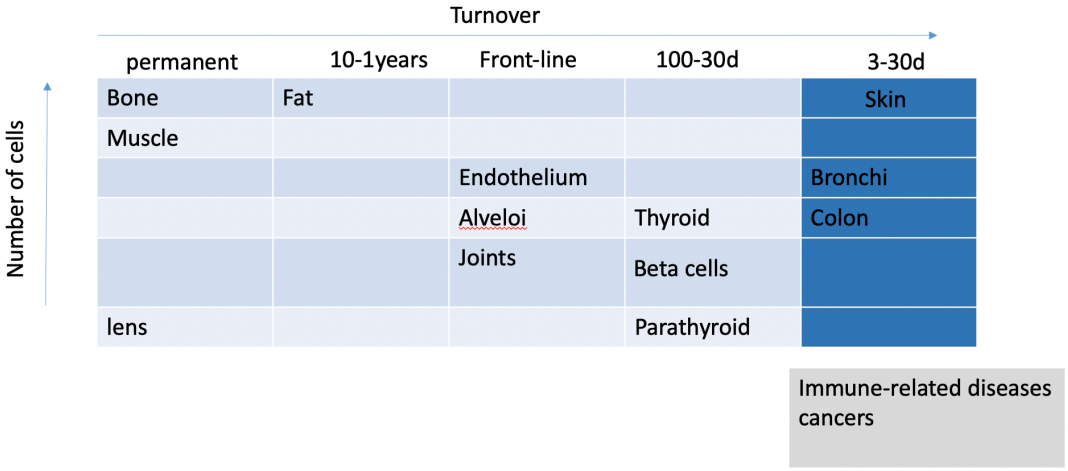
Turnover

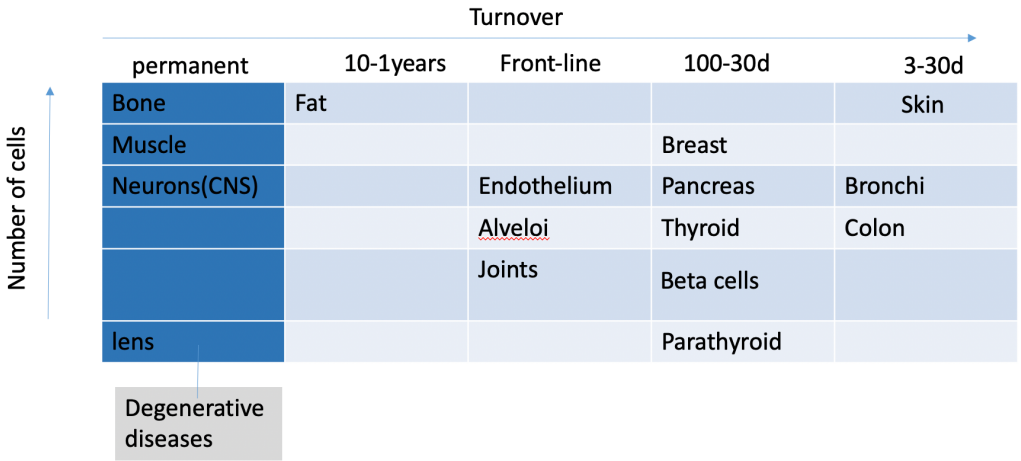
Number of cells

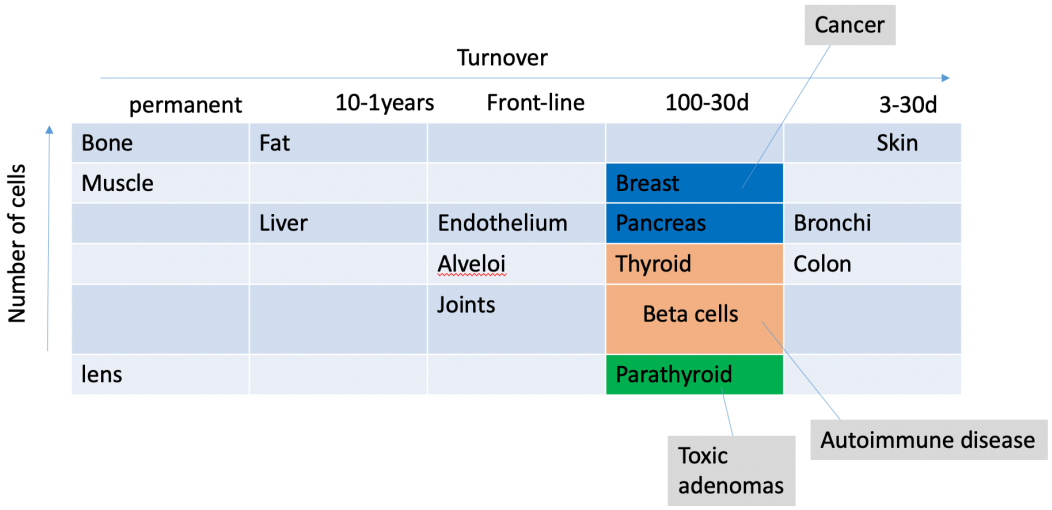
permanent	10-1years	Front-line	100-30d	3-30d
Bone	Fat			Skin
Muscle			Breast	
		Endothelium	Pancreas	Bronchi
		Alveloi	Thyroid	Colon
		Joints	Beta cells	
lens			Pituitary	

Cancer


Turnover
permanent
10-1years
Front-line
100-30d
3-30d
Number of cells
Bone
Fat
Skin
Muscle
Breast
endothelium
Pancreas
Bronchi
Alveloi
Thyroid
Colon
Joints
Beta cells
lens
Parathyroid
Progressive fibrotic diseases


Turnover
permanent
10-1years
Front-line
100-30d
3-30d
Number of cells
Bone
Fat
Skin
Muscle
Endothelium
Bronchi
Alveloi
Thyroid
Colon
Joints
Beta cells
lens
Parathyroid
Immune-related diseases cancers


Turnover
permanent
10-1years
Front-line
100-30d
3-30d
Number of cells
Bone
Fat
Skin
Muscle
Breast
Neurons(CNS)
Endothelium
Pancreas
Bronchi
Alveloi
Thyroid
Colon
Joints
Beta cells
lens
Parathyroid
Degenerative diseases


Cancer
Turnover
permanent
10-1years
Front-line
100-30d
3-30d
Number of cells
Bone
Fat
Skin
Muscle
Breast
Liver
Endothelium
Pancreas
Bronchi
Alveloi
Thyroid
Colon
Joints
Beta cells
lens
Parathyroid
Toxic adenomas
Autoimmune disease