Systems Medicine 2020 Lecture Notes

Uri Alon

Lecture 10

Aging-related diseases and their exponentially rising incidence with age

[Itay Katzir, Avi Mayo, Omer Karin, Uri Alon]

Many diseases occur at young ages, including autoimmune diseases we discussed in part 1, such as type-1 diabetes which has a maximum incidence around age 14. In addition, there is a large number of diseases whose incidence rises with age, called **age-related diseases**. Examples include cancer, failure of specific organs such as heart failure, kidney failure and lung failure, neuro-degenerative diseases such as Alzheimer's disease and Parkinson's disease, osteoarthritis and type-2 diabetes. With ageing also comes weakened muscle and bone strength, impaired hearing, susceptibility to infection, and slow healing from injury.

About 150 years ago the major causes of death were infectious diseases and childbirth. With the advent of clean water, disinfectants, vaccines and antibiotics, infectious diseases cause fewer deaths. Age-related diseases are now by far the major causes of death.

Age-related diseases are very diverse and affect different systems. It is thus striking that they share a common pattern in their incidence curves. **Incidence** is the probability to get the disease at a given age among all people who survive to that age. Incidence is often calculated by taking 100,000 people without the disease at age τ, and asking how many will be diagnosed in the year until age $\tau + 1$ year. **The incidence of age-related diseases rises exponentially with age, and drops at very old ages** (Fig 11.1). The slope of this exponential increase is similar for different disease, around 6-8% per year. Understanding this exponential rise is a major aim of this lecture. We need to understand what is different about the decade of age 20-30 and the decade of age 70-80 that makes these diseases so much more likely. That age-related disease are major killers can be seen by the risk of death plotted by different causes (Fig 11.2). The risk of dying from each of the diseases also rises exponentially with age.

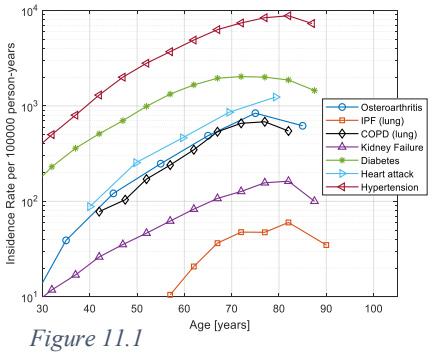

Figure 11.1

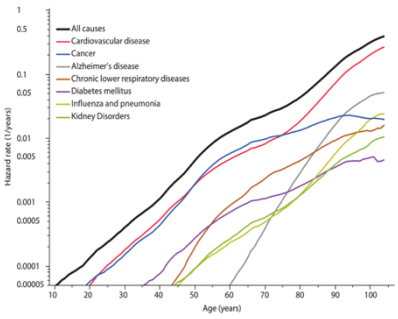

Figure 11.2

Diseases caused by threshold-crossing of a parameter affected by senescent cells have an exponential incidence curve

We build on the model for senescent-cell accumulation that we discussed in the last lecture.

We will show that a disease has an approximately exponential incidence curve with age, which declines at very old ages, in the following situation:

(i) Onset of the disease occurs when a physiological parameter ϕ exceeds a threshold, ϕ_c (Fig 11.3).

(ii) Senescent cells are a causal factor for the disease: the parameter ϕ increases due to the total body senescent cells level, X. Increasing levels of X can thus cause ϕ to exceed its threshold ϕc. The threshold is crossed when X reach a level X_c, called the **disease threshold** (Fig 11.4).

(iii) The disease threshold X_c varies between people due to genetic and environmental factors.

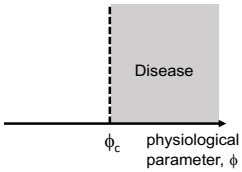

Figure 11.3

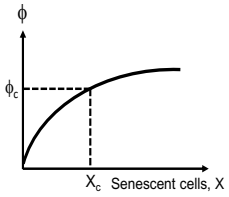

Figure 11.4

For each disease we need to find such a physiological parameter ϕ. In this lecture we will do so for several classes of disease. This parameter is affected by total body senescent cell load, because senescent cells secrete factors called SASP into the circulation that cause inflammation and slow stem-cell proliferation [55, 56]. Recall that these SASP factors are useful in young organisms for wound healing. However, with age senescent-cells accumulate to such as extent that the inflammation and reduced regeneration they cause triggers pathological processes. High senescent cell levels also saturate or exhaust the immune cells that remove them, including NK cells and macrophages, reducing total body immune capacity. Senescent cells can also have additional local effects in each organ.

When the above conditions are met, the disease arises in a given person when senescent cells level X crosses the disease-specific threshold X_c (Fig 11.5). Thus, incidence of the disease can be described as a first-passage-time problem, asking when the stochastic process of senescent cell accumulation first crosses the threshold X_c. It is likely that X must exceed the threshold for sufficient time for the disease to be expressed symptomatically. In practice, once X crosses the threshold, it tends to remain above the threshold for extended periods of time. Thus, a first-passage-time problem is a reasonable approximation for disease onset.

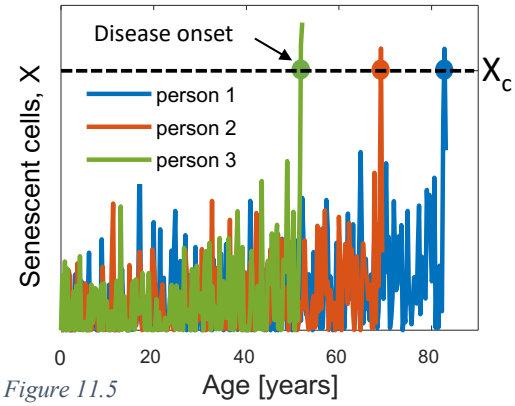

Figure 11.5

To describe the dynamics of senescent cell level X, let's use the SR-model of the previous lecture. Recall that senescent-cell concentration X is governed by a stochastic differential equation: $dX/dt = \eta t - \frac{\beta X}{\kappa + X} + \sqrt{2\epsilon}\xi$, with a production rate that rises with age ηt, a

saturating removal rate $\frac{\beta X}{\kappa+X}$, and noise modelled as a white-noise term $\sqrt{2\epsilon}\xi$. We use a reference set of parameters for humans. We assume for simplicity that the parameters are the same for different people. Simulations of this model show stochastically rising trajectory of X (Fig 11.5).

In the previous lecture we approximately solved the first-passage-time problem, asking about the distribution of times in which X first crosses a threshold. The solution to this first-passage-time problem is an exponential incidence curve that slows at very old ages (Fig 11.6, dashed line). The probability of crossing the threshold X_c rises exponentially with age, $e^{\alpha t}$, with a slope of approximately $\alpha \approx \frac{\eta X_c}{\epsilon}$, where η and ϵ are the senescent cell production and noise parameters. This explains the exponential rise of disease incidence. The threshold for death in Karin et al was estimated to be $X_c = X_{death} = 17$ (the units are such that in young individuals, $X = 1$ on average). Since diseases have different exponential slopes, each disease has its own threshold X_c, which does not exceed X_{death}. Each threshold X_c provides a different exponential slope.

Incidentally, a student asked why the slope is smaller if noise ϵ is larger. This is seen form the equation for the slope $\alpha \approx \frac{\eta X_c}{\epsilon}$. Alon Bar answered that this slope equation can be considered as a ratio between the strength of the production of senescent cells η and the noise ϵ. The larger the noise relative to production, the less strong the relentless pull towards high senescent cells by production, and the slower the rise of age-related phenotypes.

Decline of incidence at old ages is due to population heterogeneity

To explain the decline of incidence at old ages, we use the classic notion of population heterogeneity from epidemiology. The idea is that people differ in their risk for a given disease. To model this, we assume that a fraction *s* of the population has a low disease threshold Xc, due to genetic and environmental factors. We call this the *susceptible* fraction. The remaining population has high values of the disease threshold that are not reached during normal aging. We call these the *non-susceptible* fraction of the population. Thus, at very old ages, most of those that are susceptible have already succumbed to the disease. At these very old ages, the population is dominated by the non-susceptible fraction. This results in a decline in incidence rate (Fig 11.6, solid line).

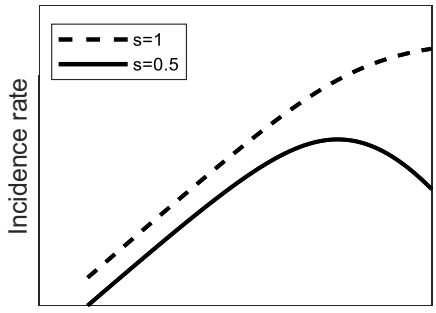

Figure 11.6

Another way of saying this is that when we calculate incidence at age 90, the 100,000 90-year-olds without the disease include very few susceptible people left- most susceptible people were already diagnosed at a younger age.

The model therefore has two free parameters for each disease: the susceptible fraction s and the disease threshold X_c. The susceptible fraction s varies between 10^{-4} for rare diseases like IPF and 0.3 for common diseases like osteoarthritis.

The model describes well the incidence curves of a wide range of age-related diseases

In order to obtain a global view of age-related diseases, we can compare to a large medical-record database from Clalit health services. This dataset includes about half of the Israeli population over a period of 14 years (2005-2018) totaling 50 million life-years, with broad socioeconomic and ethnic representation. This database includes about 900 disease category codes (ICD9 level 2 codes) found in the records of at least 10^4 people. Of these, about 200 rise at least 6% per year between ages 30 and 80, and can be defined as age-related diseases.

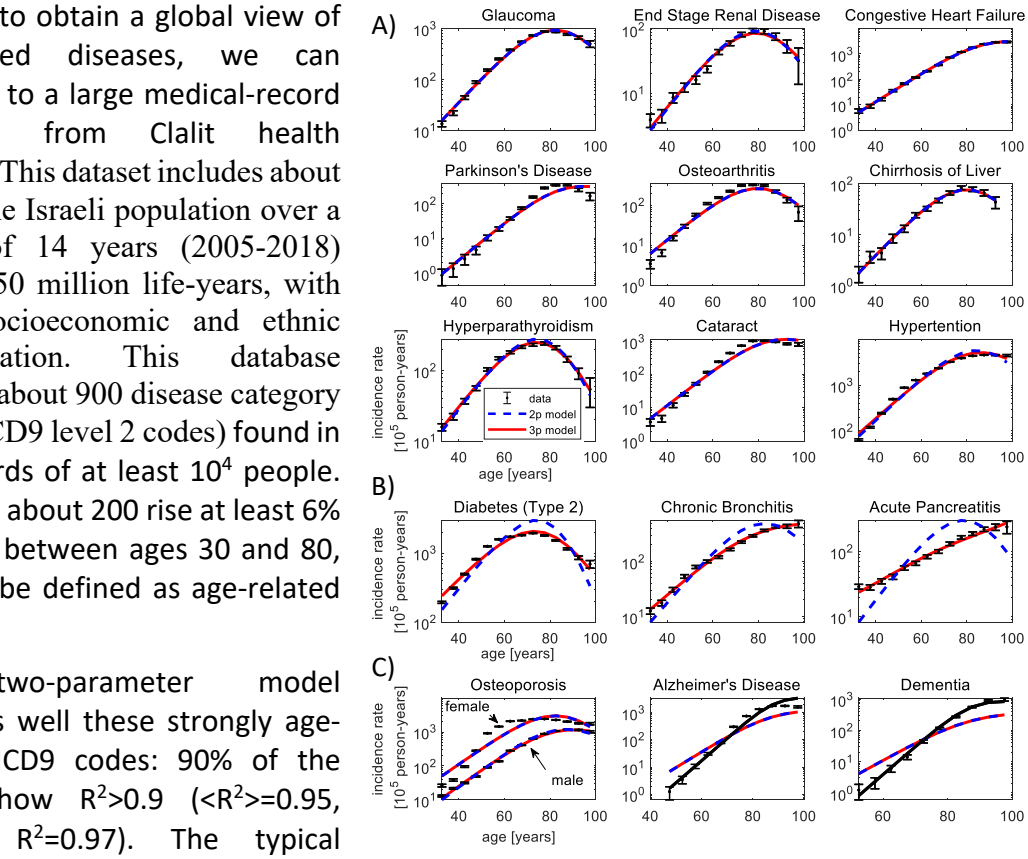

Figure 11.7

The two-parameter model describes well these strongly age-related ICD9 codes: 90% of the codes show $R^2>0.9$ ($\langle R^2\rangle=0.95$, median $R^2=0.97$). The typical disease threshold values X_c range between 12 and 16 (compared with X levels of about 1 in young individuals, and a death threshold of $X_{death} = 17$). These diseases include some of the most common age-related conditions such as Parkinson's, glaucoma, congestive heart failure, end-stage renal disease, liver cirrhosis, cataract, hypertension and osteoarthritis (Fig 11.7).

The model does not describe well the incidence of a few common age-related diseases. A notable example is osteoporosis in women (Fig 11.7C). The incidence curve rises sharply after age 50, in a way that the model cannot capture. Interestingly, osteoporosis in men is well described by the model (Fig 11.7C). This suggests that effects such as menopause-related changes go beyond the current framework.

Another case in which the model does not capture the incidence curve are Alzheimer's disease and dementia. These diseases have an exceptionally large slope of about 20% per year. The model can only explain this large slope with a disease threshold X_c that exceeds the threshold for mortality. Fig 11.7C shows the best fit with the maximal X_c values equal to that of mortality ($X_{death} = 17$), showing an underestimate of the slope. This suggests that the age-related factor X in the brain might be distinct from total body senescent cells, and has distinct dynamics with a different X_c for mortality. A better fit is achieved when allowing X_c to exceed 17 (black lines in Fig 11.7C).

We next focus on three classes of pathologies and provide, for each case, a specific interpretation of ϕ and a specific mechanism for the threshold-crossing assumed in the model.

To demonstrate this theory, we will begin with cancer and COVID-19. We then consider an age-related disease in which lungs fail, called IPF. Its fundamental cause is a mystery. We will attempt to explain this disease as an outcome of fundamental principles of tissue homeostasis. We will then show that a seemingly completely different disease, osteoarthritis, belongs to the same class as IPF.

Cancer incidence can be explained by threshold-crossing of the ratio of cancer growth rate to removal rate

Most cancers incidence curves have the universal exponential rise with age and reduction at very old ages. To explain this, we need to find the physiological parameter ϕ might provide the incidence curves for different cancers.

Cancer cells arise continuously in the body due to accumulation of mutation. The mutant cells are removed by immune surveillance, primarily by the innate immune cells such as NK cells and macrophages, and at later stages by adaptive immunity including T-cells. If the cancer cells manage to grow to a critical amount of roughly 10^6 cells, they organize a local microenvironment that downregulates further immune clearance.

A classic explanation for the age-dependence of cancer is called the **multiple-hit hypothesis**: the need for several mutations in the same cell to turn it into a cancer cell. Most cancers require a series of mutations to knock-out several pathways that protect the cell from growing out of control. Such a multiple-hit process has a likelihood that rises roughly as the age to the power of the number of mutations. Cancer in the young often occurs because one of the mutations is already present in the germline and thus in all cells of the body. This 'multiple hit' hypothesis, however, cannot explain why cancers which require a single mutation, such as some leukemias, also have an exponentially rising incidence with age. Nor does it explain why incidence drops at very old ages.

The present theory can provide an answer. Consider cancer cells that proliferate at rate p, and are removed at rate r (Fig 11.8). The rate of change of the number of cancer cells C is:

$$\frac{dC}{dt} = pC - rC$$

Cancer grows if proliferation exceeds removal, $p > r$. We can thus define the relevant physiological parameter as the ratio between growth and removal rates: ϕ=p/r. The critical threshold for cancer onset thus occurs at ϕ_c=1. At this threshold, growth equals removal.

The parameter ϕ is increased by senescent cells, which affect both p and r (Fig 11.8). With age, rising senescent cells levels inhibit the immune removal capacity of cancer. For example, NK cells remove senescent cells, and thus are occupied with senescent cells and can presumably do less of their

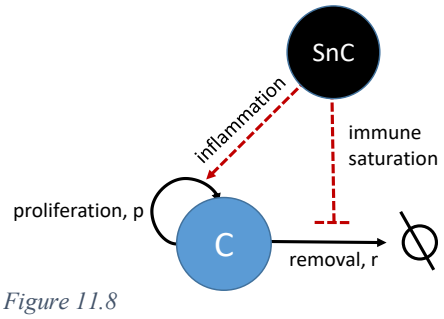

Figure 11.8

cancer removing roles. The garbage trucks are overloaded. Note that NK cell numbers do not significantly change with age. Thus, removal rate r drops with senescent cell level X, $r = r(X)$.

Other effects of senescent cells, such as chronic inflammation, also raise mutation rates due to reactive oxygen species produced by immune cells, and enhance proliferation p for many cancer types. Both effects, raising p and lowering removal r, cause the parameter ϕ to increase with senescent-cell load, $\phi(X) = p(x)/r(x)$. Thus, there exists a threshold X_c at which ϕ exceeds the critical value of 1 and cancer cell proliferation exceeds removal, reaching a clinically detectable pathology (Fig 11.9). Thus, we have criteria (i) and (ii) for the model, with cancer onset when $X > X_c$.

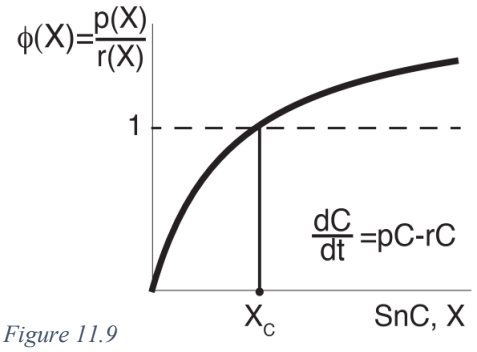

Figure 11.9

Individuals susceptible to a given form of cancer have a low threshold X_c. This low threshold can arise from genetic factors (e.g., BRCA mutations for breast and ovarian cancer) and environmental factors (such as smoking for lung cancer and UV exposure for skin cancer) that generate more occurrences of the cancer cells in the tissue. Each pre-cancerous site has a different proliferation rate p and removal rate r depending on the local niche as well as the mutational and epigenetic background of the cell. Hence, the more occurrences of cancer cells in the tissue, the higher the maximal ϕ among all occurrences. This lowers the threshold of senescent cells needed for cancer onset. A low Xc in an individual can often be simply due to bad luck, a certain rare combination of mutations that arise in a cell (usually a stem cell). Cancer incidence is well documented, allowing a good test for this theory. A great database is called SiteSEER, with incidence curves of 100 cancer types. Of these cancers, 87 are at least mildly age-related as defined above, with a mean slope of more than 3% per year between age 30 and 80. Of these 87 age-related cancers, 66 are well described by the two-parameter model (R^2>0.9) (Fig 11.10). The typical values of X_c are 13-15, and the susceptibilities for different types of cancers, s, range from 10^{-4} to 0.1.

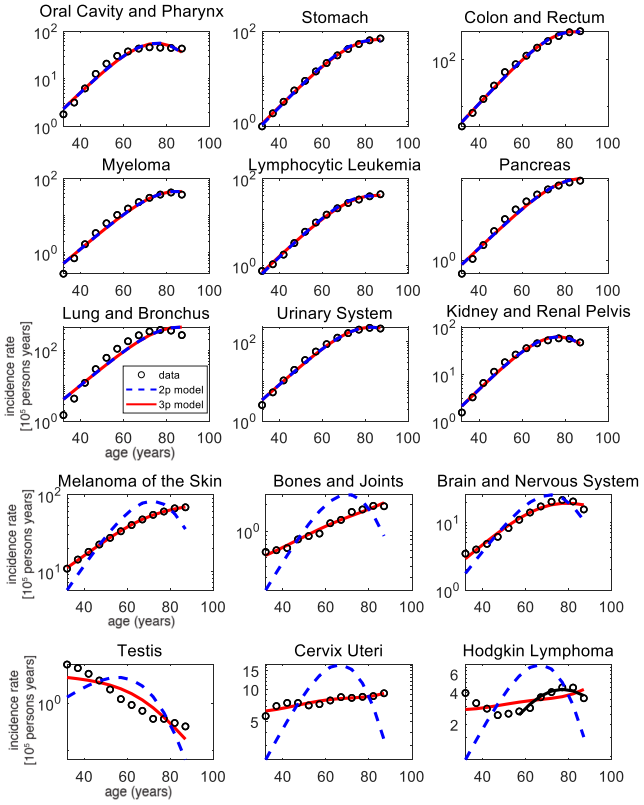

Figure 11.10

An extension of the model can provide a range of Xc for different people. It assumes Xc is distributed between susceptible people by a Gaussian distribution with standard-deviation of sigma. This parameter, sigma, adds a third parameter to Xc and s. The three-parameter model improves significantly on the two-parameter model in 15 type of cancer, and describes well 81 cancer types (R^2>0.9). In these 15 cancers, the slope of incidence with age is relatively low (mean 3%, only mildly age-related). The width of the X_c distribution is about σ=3 for these cancers. Examples of incidence curves are shown in Fig 11.10. Interestingly, skin cancers including melanoma are among the cancers predicted to have a wide range of X_c in the susceptible population. One explanation is the relatively wide range of UV exposure in the US population included in the database due to the variety of climates within the US, which potentially creates different thresholds in different individuals.

Other cancers described better by the three-parameter model include those with sizable incidence at young ages. This includes cancers of bone and nervous system. This young onset contribution effectively decreases the slope of incidence with age, which is captured by the model as a wide range of X_c.

There are several types of cancer that are not fit well by either the two- or three-parameter models. These includes cancers which are most common at young ages, such as testicular cancer whose occurrence drops with age, and cervical cancer, which has a viral origin. The rest of the cancers that are poorly fit have a bimodal age distribution, with a peak at young ages and then an age-related rise above middle age. These include lymphomas such as Hodgkin's lymphoma. The model in this case does not capture the early peak but describes incidence well if the fit is done only at old ages (>50) (R^2>0.9, Fig 11.10 lower panel, black line).

Many infectious diseases, including COVID-19, have age-related mortality

The mortality of COVID-19 also rises exponentially with age (Fig 11.11). This is typical of many infectious diseases such as pneumonia and flu, although many also have a component at very young ages which COVID thankfully lacks.

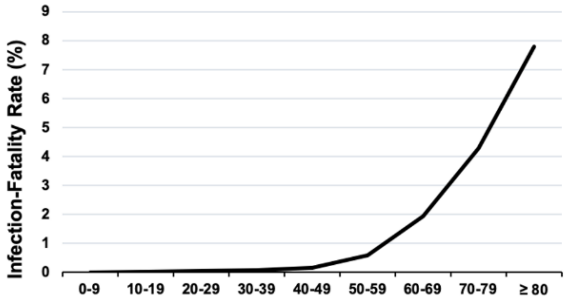

Figure 11.11

There can be at least two reasons for the exponential age-dependence of COVID-19 within our framework. The first has to do with the virus establishing itself in the respiratory tract. The virus v has proliferation rate p and removal rate r, and thus follows the same equation as for cancer cells, $dv/dt = (p - r)v$. It grows exponentially if $p > r$, or equivalently if $\phi = p/r > 1$. Senescent cells raise phi because they inhibit removal: the NK cells that kill virus infected cells are busy killing senescent cells. Thus, the virus removal r drops with X. At a critical level, Xc, virus that would otherwise be removed grows.

The second possibility has to do with the way that COVID-19 kills many of the patients. Beyond damaging cells, the severe symptoms are due to over-reaction of the immune system, also called a **cytokine storm**. One component is macrophages which are activated

by the damage caused by virus. Macrophages can enter a vicious cycle: they close a positive feedback loop by causing more damage and secreting cytokines that activate themselves. This positive feedback creates bistability. Cytokine storm results if a separatrix is crossed and the system locks into a hyperactive state. The inflammation caused by senescent cells can help tip this system to cross the separatrix.
Generally, the immune system shifts with age towards innate immunity (e.g. macrophages) and away from adaptive immune system (T-cells). One reason for this shift may be signals from senescent cells that shift the formation of white blood cells towards the cell types that remove senescent cells. This 'myeloid' shift impairs the ability to combat viruses and bacteria. T-cell production also drops with age due to reduction in the thymus.

Theory for IPF, a disease of unknown origin:
IPF stands for **idiopathic pulmonary fibrosis**. Breaking this down, 'idiopathic' means disease of unknown cause, 'pulmonary' means of the lungs, and 'fibrosis' means excess scarring. In IPF, lung capacity is progressively lost due to the scarring of tissue that is essential for breathing. Lung capacity is progressively lost, and patient dies within 1- 3 years. IPF is a chronic progressive disease that has no cure. The lifetime prevalence of IPF is about 10^{-4}, and its incidence rises exponentially with age, and drops after age 80 (Fig 11.1).
To understand IPF, let's survey the relevant tissue structure. The lung is made of branching tubes that end in small air sacks called **alveoli** (Fig 11.12) The alveoli function to move oxygen from the air to the blood, and to let $C0_2$ from the blood out into the air. The alveoli are made of two layers- an inner epithelial layer that is one-cell thick, and an interstitial layer. IPF scarring occurs in the interstitial layer surrounding the alveoli (Fig 11.13).
The epithelial layer is made of two types of lung cells called alveolar type-1 and-2 cells (AT1, AT2) (Fig 11.14). We will call the first cell type, which are large flat barrier cells, the differentiated cells D. The second type are smaller stem cells we will call S. These stem cells can divide to form new S cells, or to form new D cells. The S cells also secrete a soapy surfactant that shields the cells from the air, protects the cells from air particles and prevents collapse of the alveoli when we exhale.

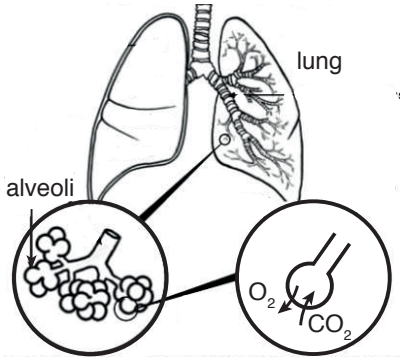

Figure 11.12

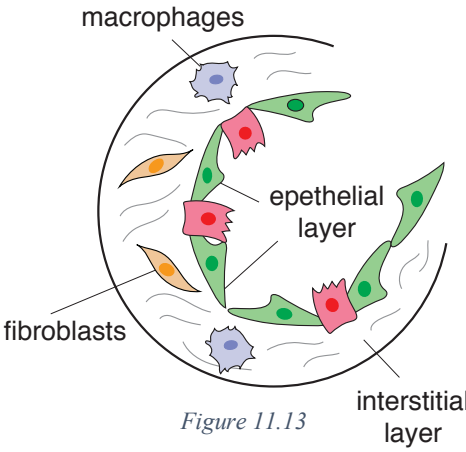

Figure 11.13

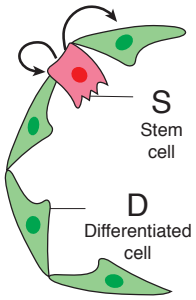

Figure 11.14

The interstitial layer around the alveoli is made of elastic fibers that provide mechanical strength to the alveoli. This layer contains two other cell types, fibroblasts and macrophages, the stars of lecture 8 on fibrosis. Macrophages are ready to gobble up bacteria

and particle if they make it through the epithelial layer of S and D cells. The fibroblasts produce the fibers which make the elastic sheath around the alveoli.

When there is injury to the D cells, they signal (using molecules such as TGF-beta) to S cells to differentiate into new D cells (Fig 11.15). The injury signal also causes S cells to activate inflammation in the interstitial layer around the alveoli to start a healing process. The S cells signal the fibroblasts to become activated myofibroblasts, proliferate and secrete extra fibers. In normal healing, once the new D cells are made, the excess fibroblasts commit programmed cell death and the extra fibers are removed. S cells divide and renew the tissue, and the injury is repaired.

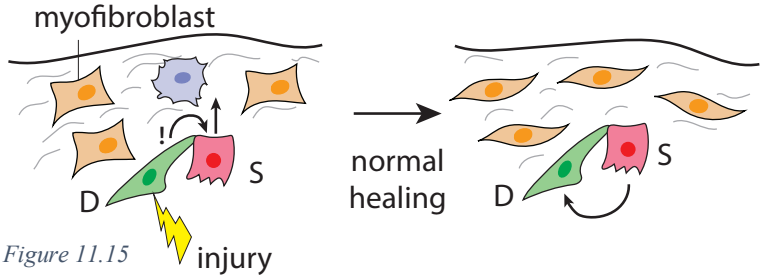

Figure 11.15

In IPF, an unknown factor causes an ongoing injury. The S cells multiply and reach higher numbers than in normal alveoli (Fig 11.16). They activate the fibroblasts to multiply and lay down excessive fibers. These excess fibers cause fibrosis. The interstitial tissue around the alveoli becomes a thick scar that reduces the ability of oxygen to flow from the lung to the blood, and the ability of CO_2 to be ventilated out. It makes the alveoli stiff and less able to expand and contract. Eventually more and more alveoli become dysfunctional, leading to lung failure.

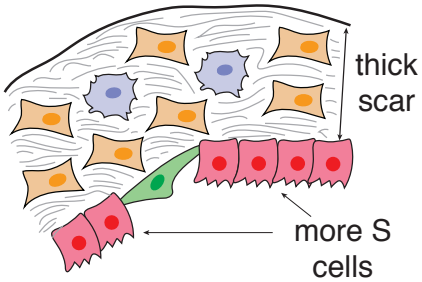

Figure 11.16

A major unknown in IPF is the origin of the injury. We can use what we have learned so far to make a theory to address the source of the injury, and explain why the risk of IPF rises exponentially with age, and why it occurs in only a small fraction of the population. We rely on recent work that shows that senescent cells are important for IPF: removing senescent cells improves IPF in a mouse model (IPF induced by Bleomycin). We will thus explore how the accumulation of senescent cells might cause IPF.

The main idea is that senescent cells slow down the rate of stem cell proliferation; when proliferation drops below the stem-cell removal rate, the alveolar tissue first enriches with S cells, and then locally crashes. The ratio of removal and production will be our physiological parameter phi, which rises with senescent cell levels.

In labile tissues, stem cells must self-renew and also supply differentiated cells

To understand IPF, we thus need to understand how stem cell-based tissues work. Such stem-cell tissues are different from the tissues we discussed in the first part of the course. There, we considered **stable** tissues in which a cell-type divides to make more of itself. For example, beta cells give rise to new beta cells (Fig 11.17).

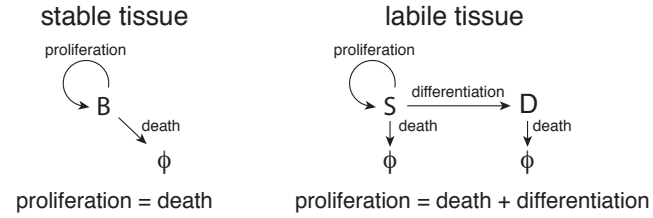

Figure 11.17

But many other tissues, called **labile tissues,** have a different strategy to renew their cells. They use stem cells which renew and generate and differentiated cells**.** Labile tissues are often found in organs, called barrier tissues, exposed to the outside world like the lung, intestine and skin. Because of this exposure, cells can be damaged and need to be replaced. These tissues divide labor: the majority of cells D do the main tissue work, and the minority (1-5%) are stem cells S who divide to regenerate the D cells and themselves. Thus $S \rightarrow D$. In some labile tissues, such as blood and skin, there is a series of differentiated cells $S \rightarrow D_1 \rightarrow D_2 \rightarrow \ldots \rightarrow D_n$. Some of these intermediate cell types can undergo a limited number of divisions, and are called 'transient amplifying cells'. The transient amplification reduces mutational load on the stem cells: each stem cell division can result in thousands of differentiated cells.

This elaborate structure does not seem to exist in the alveoli, which have one kind of differentiated cell, AT1, which does not undergo transient amplification.

Recall that in stable tissues such as beta cells, steady-state requires that cell proliferation rate equals cell death rate, otherwise the tissues grows or shrinks. In contrast, in labile tissues S proliferation must *exceed* S death, because some of the S divisions are needed to make the D cells. For stem cells, therefore, proliferation must balance two processes: death plus differentiation.

Stem cell removal rate, in many labile tissues, is relatively low because the stem cells are in a **protected niche**, where they are shielded from damage. Examples include the blood stem cells hidden in the bone marrow, skin stem cells in the deep epithelium, and the gut stem cells tucked away at the bottom of crypts (Fig 11.18).

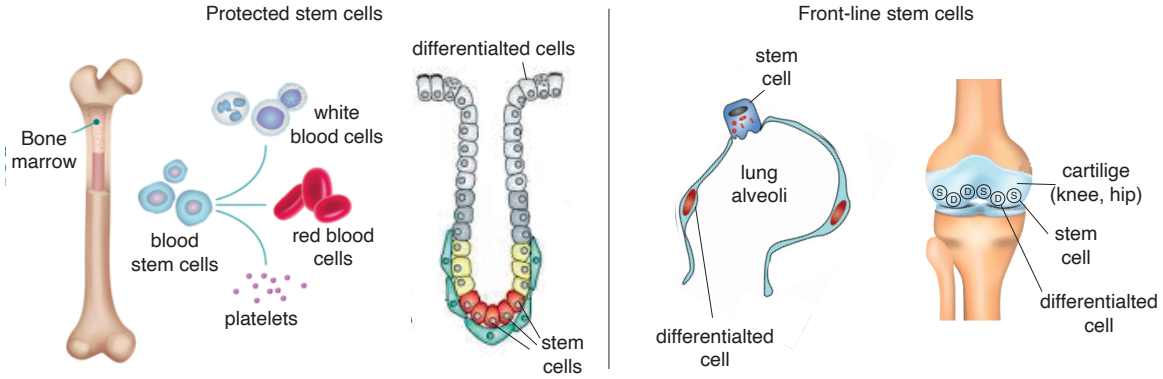

Figure 11.18

In contrast, the lung alveoli are an example of a labile tissue where both S and D are on the **front lines**. Both are equally exposed to damage, such as air particles, pathogens and the mechanical stress of breathing. There is no other choice: the alveoli must be thin to allow diffusion of gases, and can't afford a deep layer for the stem cells.

We are now ready to propose a mechanism for IPF.

Incidence of idiopathic pulmonary fibrosis and osteoarthritis can be explained by threshold-crossing of the ratio of progenitor cell removal to proliferation rates

In front-line tissues, homeostasis is a bit harder to achieve than in tissues in which stem cells are protected, because of the higher rate of removal of stem cells. We prove in the methods section that no matter what the feedback circuits for homeostasis are, a catastrophe happens when stem-cell removal rate r_1 exceeds their maximal proliferation rate p. In this case, there are not enough stem-cell divisions to populate the tissue and the tissue collapses (Fig 11.19). The rate of this collapse depends on the removal rates of the cells. After the collapse, tissue repair cannot proceed by regeneration and instead has to rely on processes such as fibrosis, migration and metaplasia, but this repair reduces tissue function and pathology occurs.

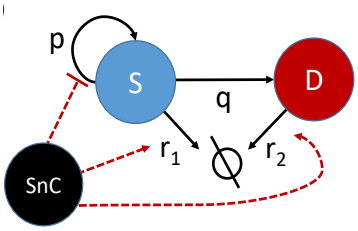

Figure 11.19

The relevant physiological parameter is thus $\phi = r_1/p$, the ratio of removal and proliferation rate of the progenitor cells. Disease onset occurs when ϕ exceeds $\phi_c = 1$ (Fig 11.20). This is criterion (i) of the model.

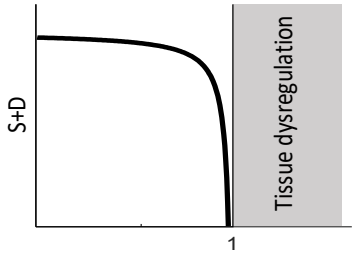

Figure 11.20

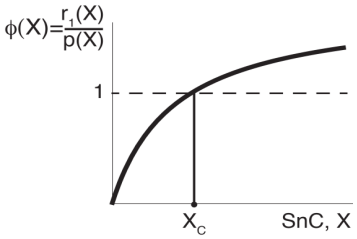

Figure 11.21

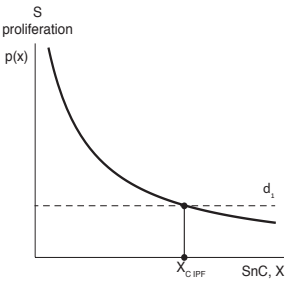

Figure 11.22

Senescent cells affect proliferation and removal in a way that tends to increase ϕ (Fig 11.21). Senescent cells slow down progenitor proliferation due to the factors in the SASP from both local and systemic senescent cells (Fig 11.22). Senescent cells can, in some tissues, also disrupt the extracellular matrix and increase removal rate r_1. Thus, when senescent cells cross a threshold X_c, tissue collapse is predicted to occur in the susceptible population (Fig 11.23). Such a collapse is seen in simulations of tissue homeostasis circuits coupled with stochastic Senescent cells dynamics (Fig 11.23). This is criterion (ii) for the model, providing a basis for disease onset when $X > X_c$.

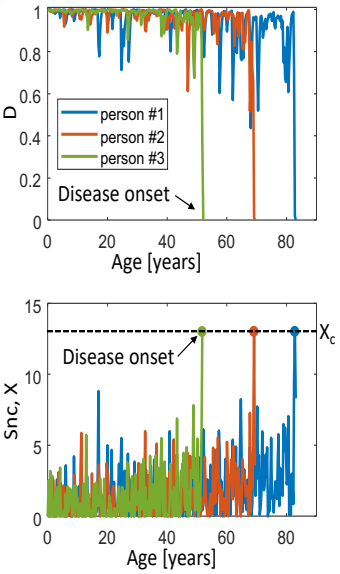

Figure 11.23

Senescent cells slow down proliferation, and cause alveoli crashing when they cross a threshold At this point, senescent cells come into the picture. Senescent cells slow down the rate of stem cell renewal p, because of their secreted

protein profile (SASP). For example, SASP contains proteins that bind and inactivates an important growth factor for stem cells, IGF1. Thus, there is a critical senescent cell level where p drops below r1, at which both S and D crash. We will assume here that the main factor is SASP coming in the circulation from all the senescent cells in the body. Local Senescent cells in the alveoli probably also play a role.

Suppose the proliferation rate of S drops with Senescent cells level X, such that $p = p(X)$. Thus, p reaches its critical value $p = r_1$ when X reaches a threshold $X_{c,IPF}$ (Fig 11.24). In most people, $X_{c,IPF}$ is high so that X never reaches it. Unfortunately, some people are susceptible, and have a lower $X_{c,IPF}$, as we will discuss below. In youth, X starts low, and rises over the decades. When X approaches$X_{c,IPF}$, S cells rise causing fibrosis and eventually tissue collapse. As we will see in the next lecture, once fibrosis is activated, it is generally irreversible and matures over several months. Thus, IPF incidence is akin to the first-passage time to the threshold $X_{c,IPF}$. Thus, in this picture, onset of IPF is a threshold-crossing phenomenon.

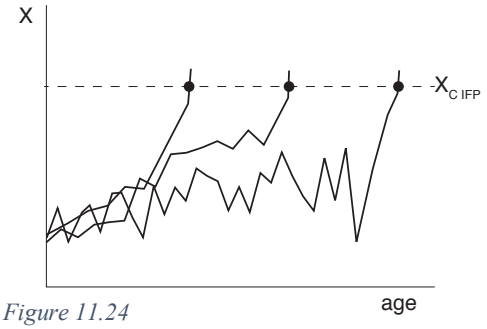

Figure 11.24

To calculate the incidence, which is the probability of crossing the threshold at a given age, the math is the same as in the previous lecture (Fig 11.24). The threshold $X_{c,IPF}$ replaces the death threshold Xc. The hard work we did in the last lecture pays off! The incidence of the disease follows a Gompertz-like law, with exponent $\alpha = \eta\,(X_{c,IPF} + k)/\epsilon$. Incidence is thus exponential with age (Fig 11.25). The observed slope of the incidence curve suggests that $X_{c,IPF}$is about 50% of the threshold Xc for mortality in the previous lecture.

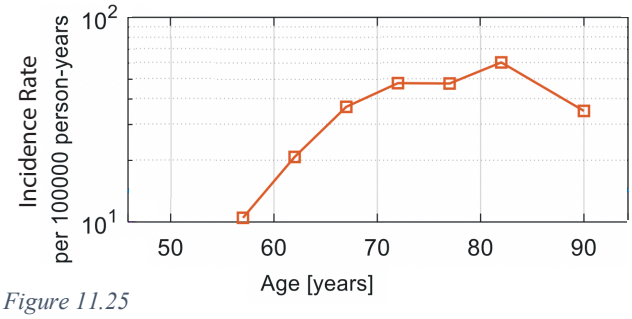

Figure 11.25

What explains the drop-in incidence at old ages? One simple reason is that at old ages, everyone who is susceptible has already gotten sick, and there few susceptible people left. Let's understand the susceptibility to this disease.

Susceptibility to IPF involves genetic and environmental factors that increase stem cell death Who is susceptible? Those with a particularly low threshold, $X_{c,IPF}$, smaller than the threshold for mortality X_c. To understand this, we can examine the genetic risk factors for IPF. Many IPF cases cluster in families (estimated at 15% of the cases). First-degree relatives of a patient have a 5-fold higher risk of contracting IPF. The gene variants in these families have been studied extensively.

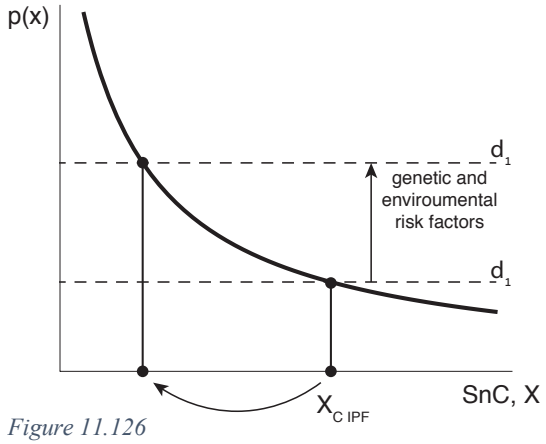

Figure 11.126

There are two classes of gene variants that increase the risk of IPF. The first class is in the surfactant genes expressed by S cells. These variants produce unfolded surfactant proteins that damage S cells and increase S cell death, d1. Furthermore, since surfactant is protective, reduced surfactant may also increase cell death rates. Increasing death rate d1 lowers the IPF threshold $X_{c,IPF}$ (Fig 11.26). Thus, these gene variants act to decrease the IPF threshold, making the disease much more likely.

The other class of variants also affects S cells. These are **telomerase** genes. Telomerase is important to allow stem cells to divide many times. In each cell division, the DNA ends called **telomeres** become shorter. When DNA becomes too short, the cell stops dividing and becomes senescent- this was how senescent cells were first discovered by Hayflick in the 1960s, a process now called replicative senescence. Stem cells have an enzyme called telomerase that adds back the missing DNA ends allowing stem cells to divide indefinitely. Thus, the telomerase variants reduce S cell proliferation rate p and increase their death rate d_1 (or equivalently their removal by becoming senescent). This also raises the possibility that local senescence in the alveoli might be at play, in addition to the SASP form the systemic senescent cells throughout the body.

IPF also has environmental risk factors, such as smoking that increases the risk of IPF by 2-fold. Smoking is mutagenic, increasing the rate of local senescent cell production, and also increases the removal rates r1 and r2. Exposure to toxins such as asbestos also increases r_1 and r_2.

Thus, both the genetic and environmental factors tend to lower $X_{c,IPF}$ and increase the risk of IPF.

To sum up, homeostasis front line tissues, such as the alveoli, is fragile to a reduction in stem cell proliferation. As proliferation drops towards stem cell death rate, the fraction of stem cells in the tissue rises and sets off irreversible fibrosis. Such a reduction in proliferation is caused by senescent cells that accumulate with age. The statistics of senescent-cell fluctuations explain the exponential rise of IPF incidence with age. The drop of incidence at very old ages occurs as all those susceptible due to genetic and environmental factors have already got the disease.

IPF may be mathematically analogous to another age-related disease, osteoarthritis. The analysis of IPF raises the possibility that the exponential incidence of other age-related diseases might also be caused by a threshold crossing of senescent cells. To make progress,

we need to analyze each disease and understand its biology. It is likely that there will be several classes of diseases with different reasons for the threshold.

An age-related disease that might be in the same class as IPF is **osteoarthritis**. Osteoarthritis is a very common condition that occurs in about 10% of those over 60, in which the protective cartilage that cushions the ends of the bones wears down over time. Although **osteoarthritis (OA)** can damage any joint, the disorder most commonly affects joints in hands, knees, hips and spine. The main symptoms are pain and stiffness in the joints. It is a progressive disease with no cure, except joint-replacement surgery.

The joint is made of a tough fibrous cartilage. The business end of the cartilage is the very smooth edge region where two parts of the joins meet. This is the front line of the tissue, and where the wear-and-tear occurs. The cartilage is constantly remodeled by chondrocytes D that make the fibers for strength and elasticity, including collagen 2. These D cells are generated by stem cells S called progenitor cells. The stem cells in the joint are at the front line, just like in the alveoli. The reason is that cells have a hard time moving through the cartilage, and thus S cells need to be where new D cells are needed, namely at the front line.

The joints suffer a lot of mechanical stress, especially in regions that support the body's weight. In the young, this stress doesn't do much and the joints are fine for 50 or more years. But at old ages, osteoarthritis can set in. In a process that takes a few years, cartilage is lost, D cell number reduces, and the fraction of S cells increases. The S cells make tougher fibers than in normal cartilage, such as collagen-1 instead of collagen-2, making the tissue stiffer and less elastic [https://link.springer.com/chapter/10.1007/978-3-319-53316-2_3]. As a result, cracks form, leading to a hole that goes right down to the bone. This hole occurs in the part of the joint that bears the most weight, and thus has the highest cell removal rates (Fig. 11.27).

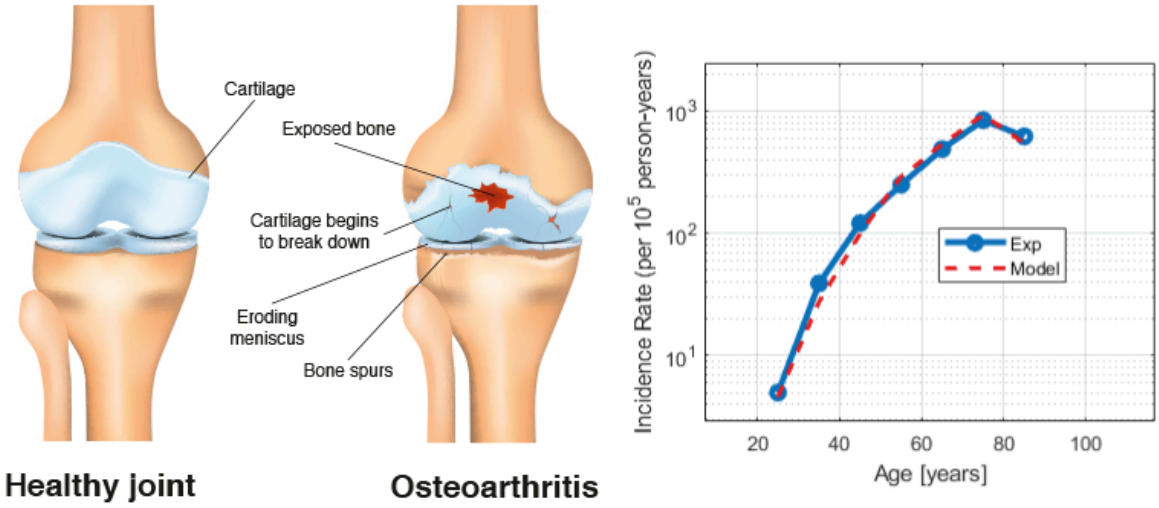

Figure 11.27

Thus, the two diseases have a **mathematical analogy.** The removal rate of both stem and differentiated cells is high because both are at the front line. The removal rate varies across the tissue and is highest where the most pressure occurs. Reducing the proliferation rate of S cells down towards their death rate leads to a rise in the stem cell fraction S/D, secreting more collagen-1, and eventually the cells are lost altogether. This reduction in S

proliferation can be caused by SASP secreted by the senescent cells in the body, as well as local senescent cells in the joint. Indeed, removing senescent cells alleviates OA in mice models. This picture thus suggests that OA occurs at a senescent-cell threshold $X_{c,OA}$.
Susceptibility to OA means a low threshold$X_{c,OA}$, as in IPF. Such a low threshold can be due to genetic and environmental factors. Environmental risk-factors for OA include being overweight, which increases the load on the joints and hence increases death rates and lowers the threshold. The higher the body-mass index (mass divided by height squared), the larger the susceptible fraction s (Fig 11.28); BMI does not seem to affect the threshold Xc.

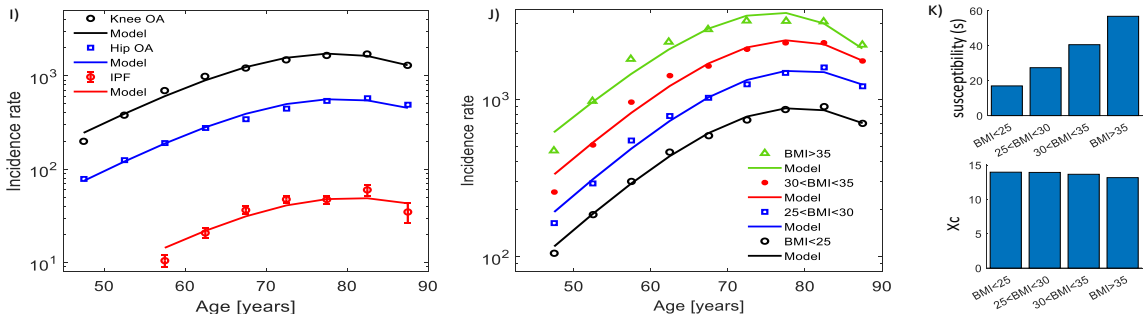

Figure 11.28

Genetic factors are also important, as OA has about a 50% heritability. Affected genes include fiber components like certain collagens (including collagen-2) and other cartilage components, as well gene-variants for the signaling molecules IGF1 and TGFbeta relevant to the feedback circuit [https://doi.org/10.1016/j.joca.2003.09.005].
It is fun to think that diseases as different as a lung disease and a knee disease might have common fundamental origins.

Other age-related diseases show diverse links with senescent cells and age
Most age-related diseases tested so far are alleviated by removing senescent cells in mice. For example, type-2 diabetes (T2D) is an age-related disease that has a threshold-like mechanism. As we saw in lecture 3, late-stage T2D involves loss of beta cells when the glucotoxicity threshold is crossed. With age, the proliferation rate of beta cell goes down, and this threshold drops lower and lower. Genetic factors that affect glucotoxicity can further lower the threshold. Inflammation due to senescent cells causes insulin resistance, as do lack of exercise and obesity. Insulin resistance can push the system beyond its ability to compensate, causing prediabetes, increasing the risk of crossing the threshold for T2D.

A grand project is thus to find mathematical classes of diseases, to understand the ways in which disease incidence rises with age, and to provide clues for treatment.

Removing senescent cells can reduce the incidence of age-related diseases
Age-related diseases are currently treated one at a time. A change of paradigm would be to treat them all at once by treating their core underlying risk factor- ageing itself. With our mathematical picture in hand, we can evaluate potential treatments for ageing as a core process. We can ask what happens if senescent cells are removed. In the previous lecture we mentioned three treatment strategies: reduction of senescent cell production by

inhibiting the mTor pathway, senolytic drugs that kill senescent cells, and immune therapy that targets senescent cells.
Suppose a 60-year-old start taking a drug once per month that removes senescent cells. The SR model suggests a rejuvenation on the order of decades: the incidence curve shifts within a couple of months to the curve of a younger population (dashed line in Fig 11.29). Even killing only half of the senescent cells once every 45 days rejuvenates by a decade. This works even if we assume, as in Fig 11.30, that senescent cells account for only 25% of the damage responsible for the age-related disease, and the rest is due to currently unknown forms of damage.

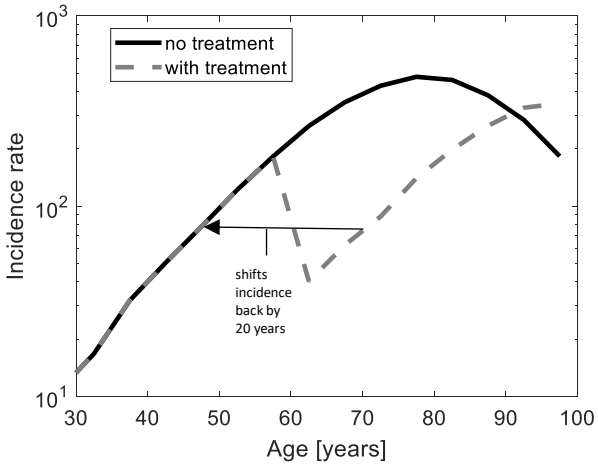

Figure 11.29

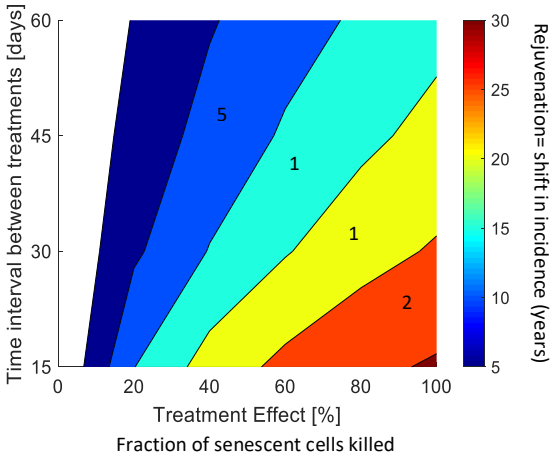

Figure 11.30

A non-pharmacological approach for such rejuvenation is the triad of exercise, heathy diet, and taking care of the mind by psychotherapy, moderation and/or spiritual practice. Exercise has coordinated beneficial effects including lowering insulin resistance, and reducing fat in tissues that causes inflammation. Healthy diet likewise reduces fat and insulin spikes. Easing the mind reduces chronic stress (HPA axis, sympathetic nervous system) which positively impacts insulin resistance, blood pressure and inflammation.
One might say that some age-related disease come from a mismatch between the diet and amount of physical activity we evolved for and that offered by modern lifestyle. Such mismatches are nicely described in one of the inspirations for this course, Medzhitov and Stearns book “Evolutionary medicine”.

Hallelujah Alveola

When I take a breath of air,
Alveoli - glad they’re there!
They let oxygen inside
And take out the carbon dioxide
Every time you take a breath of air

They are nicely elastic
And their coated with surfactant ick
They have stem cells and worker cells

In a single layer, working well
Every time you take a breath of air

So, let's thank our alveoli
Oh, without them we will die
They let our oxygen inside
And take out the carbon dioxide
Every time -we –take- a –breath- of- air

Appendix - Solved example 11.1: Stem-cell feedback circuit crashes when removal rate exceeds maximal proliferation

Let's first write down the basic equations for a labile tissue. These equations account for stem-cell S proliferation at rate p, and their differentiation to make differentiated cells D at rate q. The removal rate of S cells is r, and of D cells is r_2:

$$(1)\ \frac{dS}{dt} = pS - r_1 S - qS$$

$$(2)\ \frac{dD}{dt} = qS - r_2 D$$

Note that differentiation means a loss of a S cell and a gain of a D cell. As a result, the -qS term in the first equation shows up as a +qS term in the second. At steady state, setting Eq. 2 to zero, $S_{st}/D_{st} = r_2/q$. From Eq. 1 at steady state $q = p - r_1$, (or S=0 which is loss of tissue) and thus

$$(3)\ \frac{S_{st}}{D_{st}} = \frac{r_2}{p - r_1}$$

There are additional subtleties of whether each stem-cell division is symmetric (yielding two S or two D cells) or asymmetric (yielding an S and a D cell). These subtleties do not matter for the present discussion (exercise 11.5).

In order to keep the tissue at homeostasis, and in particular to maintain a proper concentration of D cells, labile tissues need and have an additional feedback loop. In this feedback loop, the cells D and S signal to each other by secreting molecules that affect differentiation and proliferation rates. If there are too few D cells, for example, these signals act to increase D cell production and restore homeostasis.

In a typical feedback loop found in the lung and skin, D secretes a signaling molecule that increases S differentiation (one such molecule is TGF_β, a strong signal for differentiation). Similarly, S cells secrete factors that increase their own differentiation rate. Thus, differentiation rate is an increasing function of D and S concentrations, $q = q(S, D)$.

Let's see how this feedback works. Suppose there is a loss of D cells (Fig 11.31). Since D cells signal to increase differentiation, less D cells mean lower differentiation rate q.

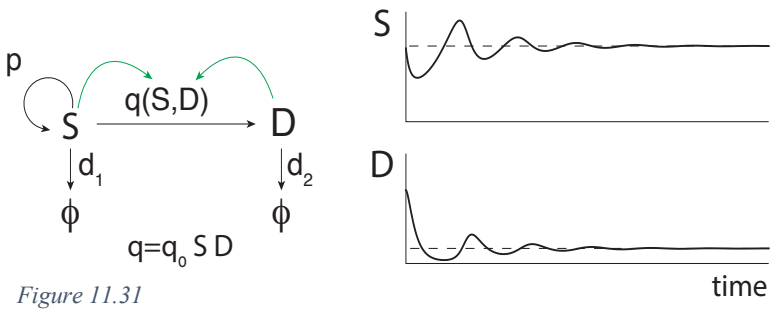

Figure 11.31

Thus, at first there are even fewer D cells. This seems paradoxical. But the reduction in differentiation means that more S divisions go to making new S cells instead of D cells. S levels rise, and eventually the larger S cell population supplies more differentiation events per unit time than before. D levels rise back. The timescale in the alveoli is months, due to the turnover rate of about a month of alveolar epithelial cells. In joints, turnover time is probably much slower.

This feedback process shows damped oscillations and settles down to a proper steady state. As an aside, we can predict, as in chapter 4, that such damped oscillations might entrain to the seasons and lead to seasonal changes in alveolar composition, with more S cells and thus more surfactant in some seasons and less in others.

In Fig 11.31, by the way, we used a concrete example of such as feedback loop, in which $q(S,D) = q_0\, S\, D$. Let's see what happens when maximal proliferation rate drops to approach stem cell removal r_1. To keep homeostasis, the number of S cells rises to compensate the reduction in their proliferation rate. The ratio of stem to differentiated cells, $\frac{S_{st}}{D_{st}} = r_2/(p - r_1)$, rises with cell removal rate r1 (11.32). In typical healthy alveoli tissue (16% AT2 cells, 8% AT1 cells but AT2 cells 7% of surface area (*Am Rev Respir Dis*. 1982), $S/D = 2 = 1/(p/r - 1)$ thus p/r~1.5. The rise in S cells buffers the decrease in D cells due to the rise in removal r (Fig 11.33).

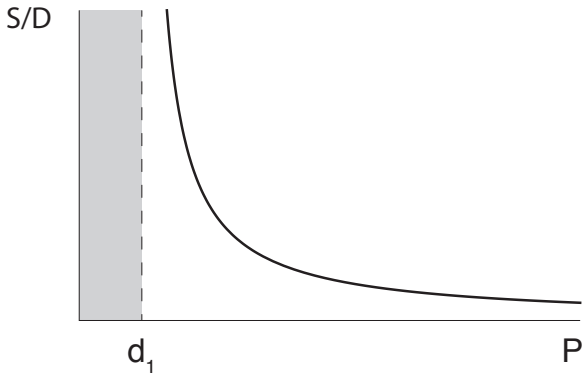

Figure 11.32

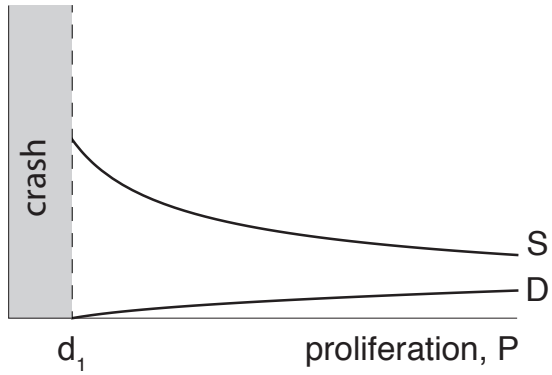

Figure 11.33

The basic equation structure for labile tissue with sizable stem cell removal has a fragility. When proliferation rate of stem cells drops below their death rate, $p < r_1$, a catastrophe happens- the tissue collapses. To see this, consider Eq 3

$$\frac{S_{st}}{D_{st}} = \frac{r_2}{p - r_1}$$

Thus, the fraction of S cells in the tissue diverges as proliferation drops towards the S-removal rate r_1 (Fig 11.33). There are more and more stem cells relative to D cells, to supply the needed amount of D cells, as well as their own renewal. Elegantly, the rising amounts of S cells also lead to more surfactant that protects the alveolus. In IPF, this is a doomed attempt to prevent tissue collapse.

The ability of S cells to produce the needed amount of cells for the tissue breaks down when proliferation p falls below the death rate r1. The cell population crashes to zero.

To see this mathematically, we take our equation, and bound it by a simpler equation which crashes. We first increase the right-hand-side by using the smaller of the two removal rates (let's say without loss of generality $r_1 < r_2$)

$$\frac{d(S+D)}{dt} = pS - r_1 S - r_2 D < pS - r_1(S+D)$$

We can further increase the right-hand-side by changing S to S+D because D is always positive

$$\frac{d(S+D)}{dt} < p(S+D) - d(S+D) = (p-r_1)(S+D)$$

We end up with a simple linear equation for total number of cells T=S+D which goes as

$$\frac{dT}{dt} = (p-r_1)T.$$

Thus, when the maximal proliferation rate falls below removal, $p < r_1$, the total cell number is bounded below an equation that goes to zero exponentially fast with time. This makes sense: in each unit time, addition of new cells goes as S renewal, and removal of cell mass goes as death. Renewal rate must not go below death rate or there is exponentially fast loss of cells.

Exercises:

11.1 Stem cell feedback that keeps constant S: Consider the following feedback loop in a labile tissue. Both stem cells and D cells secrete factors that increase differentiation rate. The differentiation rate is $q(S,D) = q_0 SD$.

(a) Write down the equations for this circuit.

(b) Simulate this circuit (or use linear stability analysis) and test whether the steady-state is stable.

(c) Show that the steady-state concentration of S cells is independent on S proliferation, p.

(d) What is the concentration of D cells as a function of p?

(e) Is the effect of this feedback biologically useful?

11.2 Oscillations in a labile tissue circuit: consider a feedback loop with a single interaction in which D increases differentiation rate $q(S,D) = q_0 SD$.

(a) Write the equations and simulate them.

(b) Explain the resulting oscillations in S and D numbers intuitively.

(c) Read about the predator-prey model in ecology called the **Lotka-Volterra** model. What is the analogy?

(d) Why are ecology population models for species population an interesting resource for modelling cell circuits?

11.3 Protected stem cells: Consider a tissue in which the stem cell removal rate r1 is negligible, whereas the D cells have a sizable removal rate r2.

(a) Suppose that a feedback loop provides a stable-steady state. What happens to the S/D ratio as S proliferation p is lowered? Is there a point of collapse?

(b) What diseases might characterize such tissues, more often than tissues with stem cells at the front line (high r1)?

(c) Design a feedback loop that provides D levels that are insensitive to variations in stem-cell proliferation p.

11.4 NK cell homeostasis circuit: NK cells are constantly produced by stem cells in the bone marrow. They have a high removal rate r2, with a lifetime of hours, unless they go into the bodies tissues and find cells that make a survival signal (IL15-IL15R). Most cells of the body produce this survival signal. When NK cells touch the donor cells, they receive the signal, and their death rate drops to zero. NK cells constantly patrol the body and go into and out of the blood stream and into the tissues.
(a) Write equations for NK cell numbers.
(b) What determines the NK cell lifetime of about a week in humans?
(c) NK cells were introduced into a mouse mutant that cannot produce its own NK cells. These cells lasted for at least six months. Explain this result.
(d) Explain how this homeostasis mechanism ensures that the number of NK cells matches the number of cells in the tissues that require NK cell surveillance.

11.5 Stem cell symmetric and asymmetric divisions: Consider the case where a stem cell can divide to form either two stem cells or two differentiated cells, 2S or 2D. This is called symmetric division. Asymmetric division is the case where there is also a third possibility, of dividing to form one D and one S cell.
(a) What is the difference in the mathematical equations for the S and D populations in the two cases?
(b) How does this affect the S/D ratio as proliferation p approaches removal r_1?

11.6 Two disease thresholds: Consider two age-related diseases with senescent cell thresholds Xc,1 and Xc,2. Suppose the two diseases can occur in the same person (the person is susceptible to both diseases). What would you expect about the relative timing of the diseases in the same person? How would you test this hypothesis? What are some confounding factors?

11.7 Osteoarthritis: Explain why osteoarthritis occurs in certain regions of the joint. In the hip it occurs in the top part of the joint. In the knee it occurs at the inside rim in people with legs oriented slightly as an X-shape, and at the outside rim of the knee in people with a bowlegged, O-shaped configuration.

11.8 Removal rates: In healthy alveoli tissue there are approximately twice as many AT2 cells (S) than AT1 cells (D). Since S cells are smaller they make up only 7% of the surface area *Am Rev Respir Dis*. 1982). Estimate using the simple calculations in the lecture what is the ratio between S proliferation and removal rates. In the knee joint, progenitor cells (S) amount to about 4% of the total cell population, rising to about 8% in OA. What is the ratio of proliferation to removal rates?