

Systems medicine Lecture notes

Uri Alon (Spring 2019)

<https://youtu.be/XIRnAHN-SZU>

Lecture 3

Autoimmune disease as a fragility of surveillance against hyper-secreting mutants

[Yael Korem, Avi Mayo, Avichai Tandler, Nir Friedman and Uri Alon, 2019]

Introduction:

Type-1 diabetes (T1D) is an auto-immune disease, in which the immune system attacks and kills beta cells. The origin of auto-immune diseases such as T1D is currently unclear – why do they exist? In this lecture we will discuss how type-1 diabetes and other common autoimmune diseases might arise from first principles. Here is the main idea: As we saw in the last lecture, the circuit that is essential for tissue size control and homeostasis has a fragility to mis-sensing mutants. To avoid mutant take-over that can be lethal, we will explore the hypothesis that the body uses the immune system to remove the mutants. These auto-immune cells thus serve an essential role, but create a fragility to auto-immune disease. Thus, there is a tradeoff between risk of autoimmune disease and risk of diseases of hyper-secreting mutant expansion. Different tissues choose among these two evils according to the evolutionary costs and benefits, providing rules for which tissues get autoimmune diseases versus mutant-expansion diseases.

Type-1 diabetes is a disease in which the immune system kills beta-cells

In type-1 diabetes, beta-cells are attacked and killed by the body's own immune system. When enough beta-cells are killed, insulin levels in the blood are insufficient and glucose can't get into the cells from the blood. The cells starve, and switch to metabolizing fats, leading to acidification of the blood (going below the normal pH range of 7.35-7.45), which is deadly.

Thus, T1D is a lethal disease - until the 1920s, it was a death sentence for about 1% of the world's children. Then, since the discovery of insulin by Banting and Best, T1D patients can survive and thrive by injecting insulin at the proper doses and times. But T1D still causes a lot of suffering and morbidity, and is not easy to control. It is not known how to prevent T1D, causing special concern for people at risk, such as those with a family member who has T1D.

It is remarkable that T1D is so prevalent and has such a young age of onset (peaking around age 14), because this is a huge evolutionary cost. Natural selection should have eradicated this disease, especially the relatively common gene variants that make one susceptible (MHC class 2

gene variants such as HLA DR3 and DR4). The fact that these genes variants are not eliminated suggests that the disease is the dark side of an important physiological process.

How can the immune system attack our own body cells? The immune system is designed to protect us against pathogens like bacteria and viruses, and to eliminate cancer cells. It has killer cells, called **T-cells**, that monitor the cells of the body to see if they make proteins that belong to viruses or mutated cancer proteins (Fig 3.1). All cells present parts of their proteins on special molecular “platters” called MHC on the cell surface, where they can be read by T-cells. Each cell has many MHC molecules presenting pieces of their proteins.

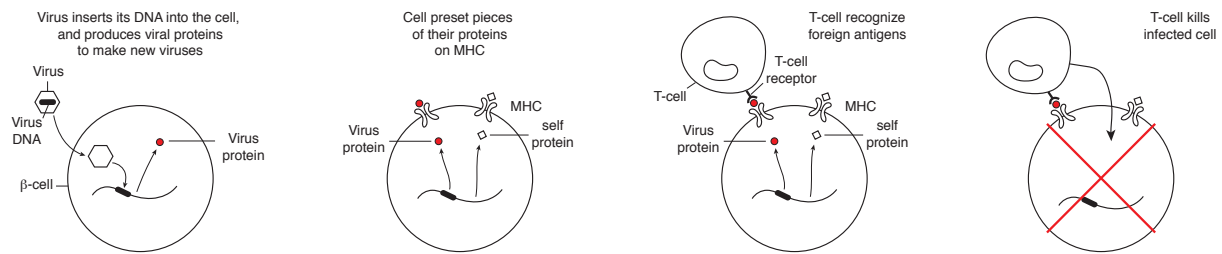


Figure 3.1

There are billions of types of T-cells in each person. Each T-cell has a unique T-cell receptor that can recognize (bind to) a different protein fragment presented on the MHC. The recognized protein fragment is called the **antigen**. If the T-cell binds to a foreign antigen, it multiplies and attacks the cell, killing it. Thus, T-cells eliminate cells infected with a virus, thanks to the foreign protein antigens produced by the virus inside the cell and presented on the cell surface in the MHC.

Most of the antigens presented on the MCH are fragments of healthy proteins normally made by cells. These are called **self-antigens**. A huge question in immunology is how self-antigens do not lead to immune attack, which would destroy the cells of our healthy tissues. *How can the immune system tell self from non-self?*

The main concept is that T-cells that react to self-antigens are eliminated. T-cells develop in an organ near the lungs called the thymus. Each T-cell has a unique T-cell receptor, and some T-cells can recognize self-antigens. In the thymus, the new T-cells are presented with virtually all types of self-proteins in a safe environment. T-cells that bind self-antigens too tightly kill themselves. This process is called central tolerance. Self-reactive T-cells that escape this process can still be ‘caught’ in the other tissues of the body. In the lymph nodes found throughout the body, if T-cells recognize an antigen but there is no “alarm signal” at the same time, the T-cell usually also kills itself (processes called clonal deletion and clonal anergy).

Still, these processes do not eliminate all self-reactive T-cells: there are self-reactive T-cells in all healthy people. How these self-reactive T-cells sit quiet and what is their function is not understood (Madi et al., 2014; Semana et al., 1999; Yu et al., 2015). (Culina et al., 2018). Mainstream thought is that self-reactive T-cells are errors in the elimination mechanisms. A different line of thought in immunology is that that *self-reactive T-cells play maintenance roles in*

the body [Kracht et al., 2016; Schwartz and Cohen 2000, Schwartz Raposo, 2014]. We will go with the latter line of thought.

T-cells can help to remove hyper-secreting mutants

In this lecture, we will consider the idea that the immune system can help to remove mis-sensing beta-cell mutants (Korem et al, 2019). The immune system can thus solve the problem of the

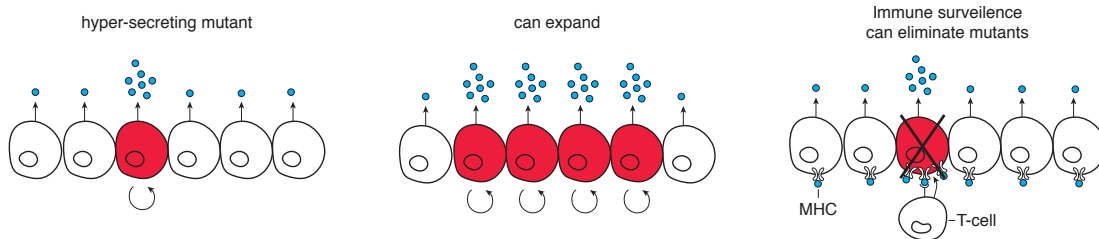


Figure 3.2

range of mild mutants in Fig (2.17) of the previous lecture. Recall that such mutants can expand and lead to hyper-secretion of insulin and thus lethally low levels of glucose.

To eliminate these mutants, we need a surveillance mechanism, which we will call **Autoimmune Surveillance of Hypersecreting Mutants (ASHM)**. ASHM requires three main features. First, it needs to detect the hyper-secreting cells. Thus, the antigens it detects must be in the secretion pathway of insulin. Indeed, the antigens in T1D (called **auto-antigens**) are all pieces of proteins in the insulin secretion pathway. For example, a major antigen is pre-proinsulin, the protein in the cell which is cleaved to make insulin. Other major T1D auto-antigens are also proteins in the secretion pathway of insulin (Table 1).

Second, the T-cells against these auto-antigens need to be present in healthy people, not just in people with T1D. Indeed, T-cells that recognize pre-proinsulin and other secretion auto-antigens are found in the T-cell repertoire shared by all people, called the **public T-cell repertoire**. We all have self-reactive T-cells against beta-cells.

Thirdly, the T-cells need to tell which beta-cell makes more antigen than its neighbors. In this way they can preferentially kill hyper-secreting beta-cells. Such differential sensitivity is indeed a feature of T-cells. Experiments tested the relation between the amount of a certain antigen that a cell presents and the probability that it is killed by a T-cell that recognizes that antigen. The probability of killing is a steep function of the number of MHCs on the cell surface that present the antigen (Fig 3.3) (Martin-Blanco et al., 2018). (Halle et al., 2016). The killing rate $h(x)$ goes approximately as a power law of antigen level x

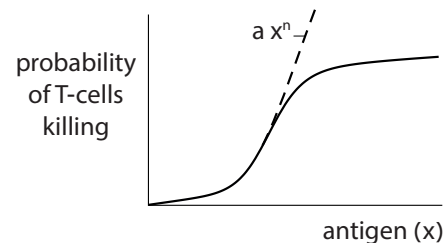


Figure 3.3

$$(1) h(x) \sim ax^n,$$

with large exponent $n=7-10$, signifying a steep relationship (such steep relationships in biology are often called ‘**cooperativity**’, because multiple T-cell receptors in the same T-cell can cluster together and cooperate to make each other more active) .

Another important property of the immune system is that it can adapt to a background level of antigen, and only respond to temporal changes in antigen. This is seen for viruses, for example, which are tolerated if they sit quiet, but set off a strong response when they begin to expand exponentially. Mechanism for this adaptation to background is provided by **regulatory T-cells**. When a T-cell is activated, it starts to multiply, and makes killer T-cells but at the same time it also produces regulatory T-cells, T-regs, which inhibit the killers. This creates an incoherent –type 1 feedforward loop circuit (see exercise 3.7 for an explanation of this circuit) that has the capacity to adapt to a constant input signal (antigen level), and to respond to exponentially increasing antigen threat (Sontag, 2017). Other mechanisms exist to help the T cells adapt, such as molecular ‘switches’ on the T-cell that make them less active if they kill too often. The result of this adaptation is that killing rate goes according to the ratio of antigen relative to the mean antigen presented by all cells, $x/\langle x \rangle$, so that

$$(2) \quad h(x) = a \left(\frac{x}{\langle x \rangle} \right)^n$$

This killing function has two parameters: the rate a and the cooperativity n .

Autoimmune surveillance can eliminate any mutant, and can do so with a low killing rate

In order to work well, ASHM needs to eliminate any possible hyper-sensing mutant, and to do so without killing too many healthy beta-cells. To understand how this might work, let’s analyze a mathematical model for ASHM.

We begin with the growth equation for beta-cells from lecture 2, whose growth rate $\mu(G)$ is controlled by glucose G :

$$(1) \quad \frac{dB}{dt} = \mu(G)B$$

We will consider situations near the stable fixed-point $G = G_0 = 5mM$. Recall that the growth rate is zero at G_0 , so that proliferation equals removal and beta-cell numbers are at steady-state.

Near G_0 , we can approximate the growth rate as a line with slope denoted μ_0 , so that $\mu(G) = \mu_0(G - G_0)$ (gray line in Fig 3.4). This approximation is not essential, but makes the math easier and is sufficiently accurate for our purposes. Thus

$$(2) \quad \frac{dB}{dt} = \mu_0(G - G_0)B$$

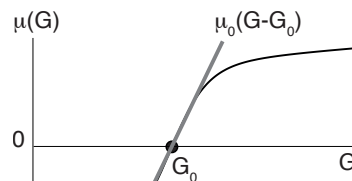


Figure 3.4

Now let's add ASHM, in which beta-cells are killed by T-cells. We begin with the case in which there are only non-mutant beta-cells, called **wild-type** cells. Each cell makes x copies of antigen, and on average a cell has $\langle x \rangle$ copies. The antigens are in the secretion pathway and hence proportional to the insulin production rate per cell, $qf(G)$. Adding the killing term from Eq. 2 to the growth equation, we find

$$(3) \frac{dB}{dt} = \mu_0(G - G_0)B - a \left(\frac{x}{\langle x \rangle} \right)^n B$$

Since all cells are wild type cells, $\langle x \rangle = x$, and the killing term is just equal to $a 1^n = a$. Thus, at steady state,

$$(4) \frac{dB}{dt} = 0 = \mu_0(G - G_0) - a$$

whose solution is the steady state glucose level that is slightly shifted upwards from G_0 due to the effect of beta-cell killing:

$$(5) G_{st} = G_0 + a/\mu_0$$

The higher the killing rate a , the higher the glucose because more beta-cells are killed per unit time, and hence less insulin, and thus more glucose. In extreme cases, where a is very large, killing is widespread and we have very high glucose levels- this is the situation in T1D.

Now let's consider a mutant beta-cell that mis-senses glucose. It acts as though the true glucose level G is actually uG , where u is the **mis-sensing factor** (Fig 3.5). Such mis-sensing mutants were discussed in the last lecture. The mutants can, for example, have a mutation causing them to pump in too much glucose (James et al., 2009; Matschinsky, 2002), and as a result their insulin secretion, proliferation and removal all act as if blood glucose is higher than it actually is. In the equation for such a mutant we need to replace all occurrences of G by uG . The equation for the growth of the mutant population B_m is therefore

$$(6) \frac{dB_m}{dt} = B_m \left[\mu_0(uG - G_0) - a \left(\frac{x_m}{\langle x \rangle} \right)^n \right]$$

where the ASHM killing term contains the mutant antigen level x_m . Initially, there is a single mutant that arises in a wild-type tissue. Since there is only one mutant, the average antigen $\langle x \rangle$ is virtually unaffected by the mutant so that $\langle x \rangle$ can be approximated by the wild-type level of antigen. Similarly, glucose level G is not affected by the mutants as long as they are few.

The antigen level of the mutant is determined by its insulin production rate, $x_m = qf(uG)$. Using $f(G) \sim G^2$, we find that $x_m = qu^2G^2$, whereas the wild-type antigen level is $\langle x \rangle = qG^2$, because $u=1$ for the wild-type cells. Thus, the mutant killing term $a \left(\frac{x_m}{\langle x \rangle} \right)^n$ depends only on the mis-sensing factor u , because the factors q and G^2 cancel out, leaving $a(u^2)^n = au^{2n}$. Thus:

$$(7) \frac{dB_m}{dt} = B_m [\mu_0(uG - G_0) - au^{2n}] = \mu(u)B_m$$

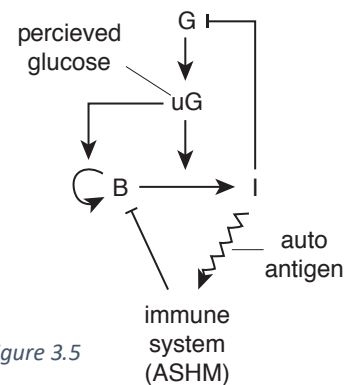


Figure 3.5

We conclude that the mutant has a growth rate that is determined by its mis-sensing factor u :

$$(8) \quad \mu(u) = \mu_0(uG - G_0) - au^{2n}$$

In order for ASHM to work perfectly, we need the wild type cells ($u = 1$) to have the highest growth rate among all possible mutants (Fig 3.5). The wild-type cells should have zero growth rate (proliferation equal removal and thus a steady population size) and all other mutants should have negative growth rate and vanish. This is called an '**evolutionary stable strategy**' (ESS): a mechanism which cannot be invaded by any single mutant. We therefore need to find a condition such that $\mu(u)$ is maximal at $u = 1$ (Fig 3.6). This occurs when

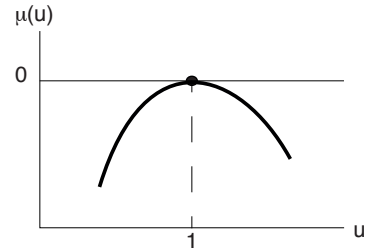


Figure 3.6

$$(9) \quad \frac{d\mu(u=1)}{du} = 0 \quad \text{condition for evolutionary stable strategy}$$

Taking this derivative in Eq.8, we find

$$(10) \quad \mu_0 G - 2nau^{2n-1} = 0$$

The glucose level G is just the glucose level for the wild-type case (Eq.5), because a single mutant can't affect glucose levels. Plugging in G_{st} from Eq.5, we find the condition for ESS:

$$\frac{a}{\mu_0 G_0} = \frac{1}{2n - 1}$$

Interestingly, the higher the T-cell cooperativity (steepness) parameter n , the lower the killing rate a that is required for ESS. Since the cooperativity of immune recognition is high ($n \sim 10$), killing rate should be small, about 5% of the natural turnover rate $\mu_0 G_0$. Thus, these secret-agent T-cells work very subtly and with high precision (Fig 3.7). Only 5% of the removals of beta-cells are due to ASHM, and the rest to natural turnover.



Figure 3.7

Autoimmunity can develop in a scenario of mutant expansion

How can the AHSM mechanism lead to autoimmune disease? We don't know for sure, but there are several plausible scenarios. In one scenario, AHSM works too weakly (a is too low). A mutant arises and begins to expand exponentially. The immune system sees an exponentially rising amount of antigen. An exponentially rising level of antigen is an alarm signal for the immune system, because it is a sign of bacterial or viral infections. If this mutant expansion also happens to coincide with a real viral infection, the immune system gets a double alarm. It concludes wrongly that the self-antigen, such as pre-proinsulin, is actually of viral origin. This sets off the heavy guns – an army of **B-cells** that produce antibodies against the antigen. The antibodies are secreted by the B-cells, and coat the beta-cells, leading a large number of immune cells to attack the beta-cells aggressively, thinking that they have virus inside them (Figs 3.8-3.9).



Figure 3.8

Normally such an antibody response would stop when the virus is eliminated and the foreign antigen is gone. But in T1D, beta-cells are attacked and killed continuously, and the immune response is not turned off. In fact, long lasting memory B-cells and T-cells are formed which are easily triggered by the antigen. When about 90% of the beta-cells are killed, insulin production drops so low that clinical symptoms set in. A balance of beta-cell proliferation and killing is reached in T1D patients, with very low numbers of dysfunctional beta-cells persisting for decades and a continual B-cell response (Keenan et al., 2010; Liu et al., 2009)(Rui et al., 2017).

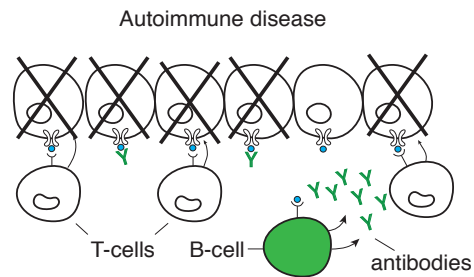


Figure 3.9

Such a route to T1D explains why T1D often occurs after viral infections. Moreover, in mice models of T1D, the disease is preceded by a phase of hyper-insulin secretion, suggesting that an expanding mutant might be at play.

Whatever the precise route to T1D, the presence of auto-reactive T-cells creates a fragility to autoimmune disease.

ASHM can stabilize other hormone-secreting organs and explain their auto-immune diseases

Autoimmune diseases are classified into systemic diseases that attack many organs (like lupus and rheumatoid arthritis), and organ-specific diseases such as T1D. Here we focus on organ-specific diseases. These diseases happen primarily in hormone-secreting organs (endocrine organs). There is a range of such disease for different endocrine organs. A very common autoimmune disease is called Hashimoto's thyroiditis (about 5% of the population) in which the body attacks the cells of the thyroid gland that make thyroid hormone. Killing the thyroid cells makes the person have too low thyroid hormone, and hence pathologically low metabolism. Other common diseases are Addison's disease of the adrenal cortex, vitiligo of the skin, and gastritis of the stomach parietal cells. The origin of all of these diseases is currently unknown: they are said to be a combination of genetic and environmental factors.

All of these organs have the same regulatory motif as the beta-cells, as discussed in the previous lecture (Fig 2.12). In this feedback motif, a signal causes the cells both to secrete a hormone and to proliferate. All of these tissues are thus sensitive to mutants that mis-sense the signal. Such mis-sensing mutants can expand and cause loss of homeostasis. It is thus plausible that these organs have an ASHM mechanism in order to eliminate the mutants.

Indeed, one hallmark of ASHM that we discussed is that the auto-antigen lies in the secretory pathway of the hormone. This feature is found in all of these diseases: the auto-antigen in Hashimoto's is the protein cleaved to make thyroid hormone (called thyroglobulin Tg, the analog of pre-proinsulin), or the key enzyme that modifies this protein to make the hormone (TPO). In Addison's, the auto-antigen is the key enzyme that synthesizes the hormone cortisol (21-hydroxylase). Other examples are shown in (Table 3.1).

Moreover, T-cells that recognize these antigens are found in all healthy people, as evidenced by the presence in the public T-cell repertoire of T-cell receptors that recognize Tg, TPO, and so on.

This is thus a theory for the fundamental reason for organ-specific autoimmune disease: an essential circuit for hormone glands which provides size control and dynamic compensation, is unavoidably sensitive to mis-sensing mutants, making it necessary to have an autoimmune surveillance to get rid of these mutants, providing the possibility of descent into organ-specific auto-immune disease.

Some endocrine tissues almost never get auto-immune disease, but instead are prone to diseases of mutant expansion

Strikingly, other endocrine cells and organs only very rarely have autoimmune diseases - less than 1 in $10^5 - 10^6$ people (Fig 3.10). These organs include the parathyroid (PT) gland, a tiny gland that sits on top of the thyroid. Its job is to secrete the hormone PTH in order to control blood calcium, which needs to be in a tight range around 1mM. PTH helps dissolve bone, which is made of calcium phosphate, in order to increase blood calcium.

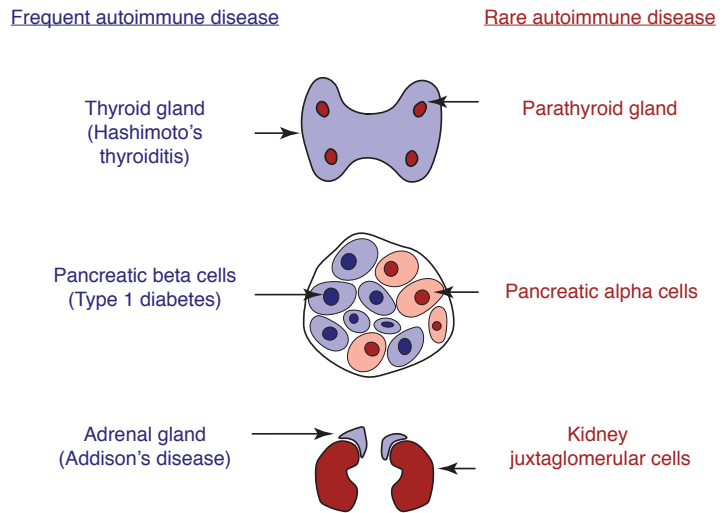


Figure 3.10

The PT gland has a circuit that is sensitive to take-over by mis-sensing mutants. The circuit is essentially the same as in the other glands, except for a sign reversal. In this circuit (Fig 3.11), the signal, calcium, inhibits both the proliferation of PT-cells and secretion of PTH. Because the signs in the circuit are opposite to those of the other systems, a loss of PT-cells means low levels of calcium. A mutant that mis-senses too little calcium (hypo-sensing mutant) is the dangerous culprit: such a mutant would expand and hyper-secrete PTH, and if it takes over, lead to too high calcium.

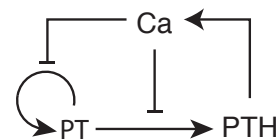


Figure 3.11

The lack of autoimmune disease in this gland suggests that it has no ASHM or perhaps a very weak version. **This predicts that the gland is prone to takeover by hypersecreting mutants.** Indeed, this is a very common disease with the long name *primary hyperparathyroidism*. It afflicts about 1/50 women after menopause. A hypersecreting mutant grows exponentially and becomes a small tumor in the gland, pushing calcium levels up. The over-high calcium comes at the expense of bones, and the symptoms include loss of bone mass and neuronal problems. Treatment sometimes requires surgically removing the tumor.

Thus, a tradeoff seems to exist between two evils: autoimmune disease and diseases of hypersecreting mutant expansion. This allows one to predict which organs will get which diseases. For example, alpha cells in the pancreas sit next to beta-cells, but unlike beta-cells, they almost never get auto-immune disease. This predicts that alpha cells should show frequent mutant expansions that hyper-secrete their hormone, glucagon, leading to excess glucose production. Such growths are indeed reported and associate with type-2 diabetes (Feng et al., 2017; Liu et al., 2011; Unger and Cherrington, 2012).

What rules might determine if a tissue gets autoimmune disease or diseases of mutant expansion? One possibility is based on the evolutionary cost of these diseases: it pays to set things up so that the less severe disease occurs (Fig 3.12). In beta-cells, a hypersecreting mutant expansion is lethal, because it causes low glucose. Thus, it makes sense to sacrifice 1% of the population to T1D, to save a higher fraction of the population from lethal mutant expansion disease.

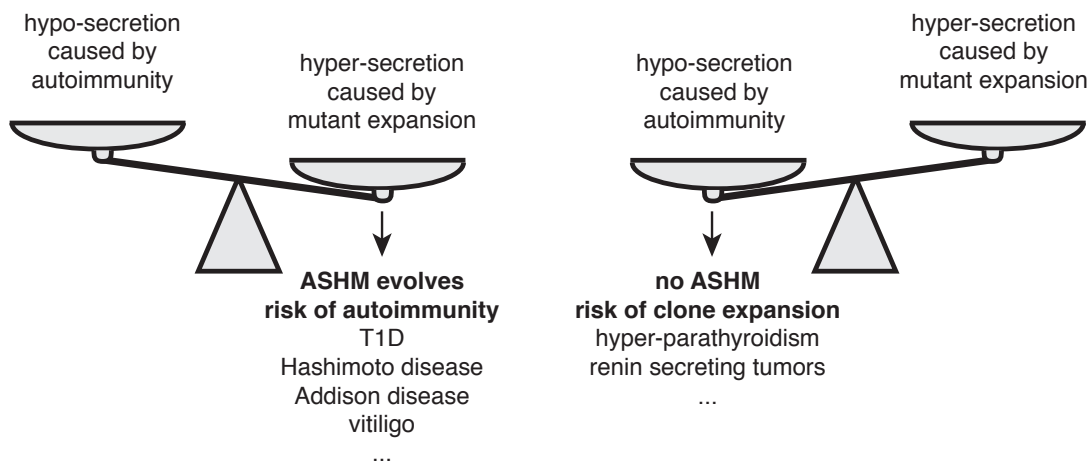


Figure 3.12

In the PT gland, in contrast, high levels of calcium caused by mutant expansion are bad but not lethal. This gland has a biphasic mechanism to protect against strong hyper-secreting mutants. The mild mutants that take over cause high calcium, but below the lethal calcium level of roughly 4 times the normal level. But even a slight reduction in calcium, as would be caused by an over active ASHM, can push calcium down to lethal levels: even a 20% reduction is lethal (below 0.9mM compared to the normal level of 1.1mM). Thus, it makes sense that ASHM does not evolve in the PT gland, to avoid the risk of low calcium. We pay the price of a less severe mutant expansion disease with a late age of onset.

I like the prospect of such 'rules' for diseases, maybe pointing towards a future Mendeleev table of diseases. It is fun to consider the 'diseases that might have been and are not' (such as autoimmune disease of alpha cells), and to explain them based on first principles.

Exercises:

3.1 **Molecular mimicry:** read about the hypothesis of ‘molecular mimicry’ for autoimmune diseases. Discuss its pros and cons.

3.2 **Childhood mutations:** When the embryo develops from an egg to a baby, a single cell divides to form all the cells in the body. Among these are about 10^9 beta-cells, and so there are 10^9 divisions to make them.

- Explain why in many cases there are mis-sensing mutants present already at birth.
- Consider what happens if a mis-sensing mutation occurs early in the process of beta-cell formation, as one beta-cell divides to make two, four, eight and so on. Use this to explain why some babies are born with hyper-insulinemia (too much insulin), secreted from a part of their pancreas. Use the concept of ASHM to explain why this condition usually goes away spontaneously after a few weeks (Ackermann and Palladino, 2015).
- In many people, the thyroid shows masses of cells that hyper-secrete thyroid hormone (called hot nodules, visible by ultrasound). These nodules usually disappear by themselves over months. Explain using the concept of ASHM.

3.3 **Route to autoimmune disease:** If a mutant manages to somehow escapes ASHM and start expanding, it can reach a size that overcomes the ASHM. This happens when average antigen $\langle x \rangle$ starts changing due to the mutant hyper-secretion. When the entire tissue is mutant, ASHM can no longer distinguish between cells, and the tissue is not attacked. Thus, ASHM is a ‘**frequency dependent**’ mechanism, where frequency means the fraction of mutants in the cell population.

- Estimate the number of mutants relative to wildtype cells needed to tip the balance and overcome elimination of the mutant by the ASHM.
- Fig 3.13 shows the flow of cells in the case of a mutant with $u = 2$ competing with wild-type cells. The panels go from left to right with increasing AHSM strength parameter a . Explain the figure.
- In rare cases, children are born a hyper-sensing mutation in their genome (germline), so that all their beta-cells have $u > 1$ and hyper secrete. This is called congenital hyper-

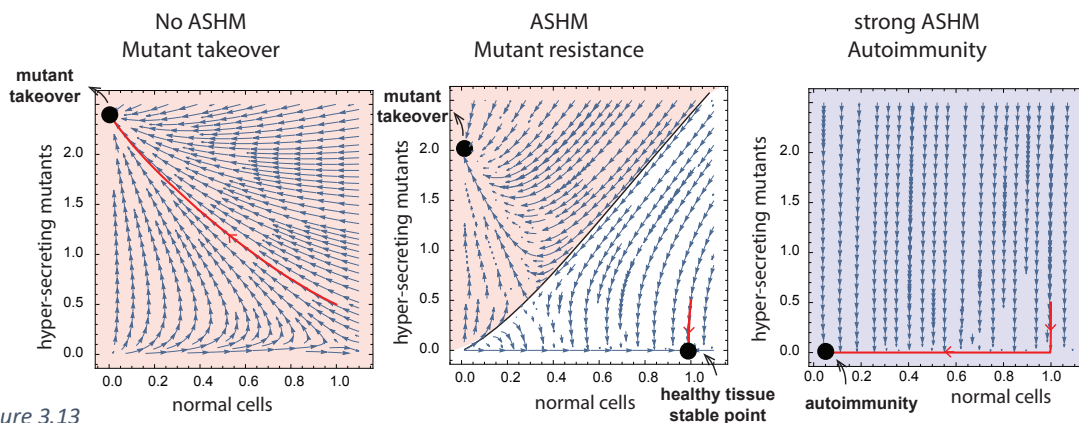


Figure 3.13

insulinism (prevalence of about 10^{-5}). Unlike question 3.2 in which only some cells hyper-secrete, this disease does not go away on its own. It requires sometimes removing the pancreas to avoid lethally low glucose (hypoglycemia). Explain using part a, b of this question.

3.4 range of parameters for ASHM: Estimate the range of parameters a and n that provides protection against all mutants with $u > 2$, and kills less than 50% of the wild-type cells. Compare to Fig (3.14).

3.5 Biphasic mechanism and ASHM: If ASHM is good at eliminating mutant T-cells, why is the glucotoxicity mechanism also present, with its attendant risk of T2D?

3.6 Link between two rare diseases: Explain how ASHM might offer a link between two rare diseases. The first is polyglandular autoimmune disorder (PGAD), in which several endocrine glands show autoimmune disease in the same patient. This disorder is caused by a germ-line mutation (that is, a mutation in the fertilized egg which is present in the DNA of all cells of the body) in the thymus selection gene AIRE, responsible for eliminating self-reactive T- cells. The second disorder is called multi-endocrine neoplasm (MEN). It shows mutant expansions in multiple endocrine glands, with hormone hyper-secretion. These growths are typically non-cancerous, and are caused by germline mutations in a T-cell related gene, MEN1.

3.7 Sensing relative antigen changes by T-cells: An antigen x causes production of killer T-cells K , and regulatory T-cells, R , that inhibit the production of killer T-cells. A very simplified model, based on an analysis by Eduardo Sontag (2017), is

$$\frac{dR}{dt} = x - \alpha_1 R$$

$$\frac{dK}{dt} = \frac{x}{R} - \alpha_2 K$$

- Explain the biological meaning of these equations and parameters. Solve the steady state levels of R and K for a given constant antigen level x .
- Simulate this model for a case of a step of antigen, in which $x = 0$ before time $t = 0$, and then $x = 1$ for $t > 0$, starting from steady-state initial conditions. Use $\alpha_1 = \alpha_2 = 1$.
- Show that the number of killer T-cells, $K(t)$, first rises and then returns to baseline. Explain how this might relate to the phenomenon of immune tolerance of a virus that does not increase in number.
- Simulate this model for an exponentially growing amount of antigen $x(t) = x_0 e^{ct}$. Does the amount of killer cells K go back to baseline? How does the deviation from baseline

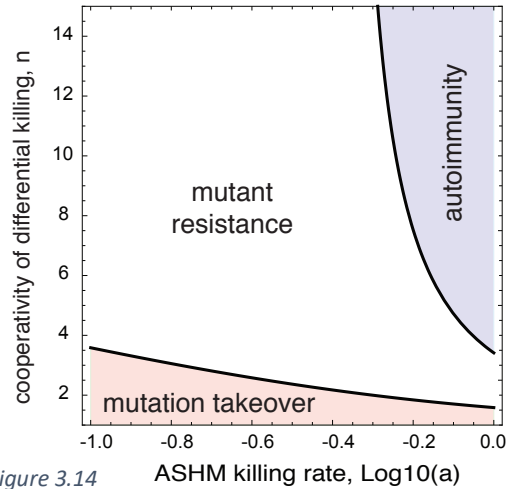


Figure 3.14

depend on the rate of antigen exponential rise, c ? Explain how this phenomenon might allow the immune system to detect exponentially growing threats.

Table 3.1: Endocrine autoimmune diseases

Disease	Cells	Prevalence in population	Input	Secreted factor	Auto-antigens	Role of autoantigen
Type 1 Diabetes	Pancreatic beta-cells	0.1-1%	glucose	Insulin	Insulin	Insulin
					preproinsulin (PPI)	Insulin precursor
					PTPRN, PTPRN2	Insulin storage and secretion
					ICA69	transport of insulin secretory granules
					zinc transporter 8 (ZnT8)	Insulin production, storage, and secretion
					GAD65	No known role in insulin secretion
Thyroiditis (Hashimoto disease)	Thyroid gland cells (thyrocytes)	0.1-1%	TSH	T3/T4	thyroid peroxidase (TPO)	T3/T4 biosynthesis
					Thyroglobulin (Tg)	T3/T4 precursor
Addison Disease	Adrenal cortex cells	0.01%	ACTH	Cortisol/aldosterone	21-hydroxylase (CYP21A2)	Cortisol/ aldosterone biosynthesis
Vitligo	Melanocytes	0.1-1%	MSH	melanin	PMEL	Melanin synthesis and storage
					Protein melan-A (MART1)	
					Tyrosinase (TYR)	Melanin synthesis
Autoimmune gastritis	stomach parietal cells	0.1-1%	Gastrin	acid	gastric H/K ATPase	Acid production

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