# Hormone Circuits Lecture notes
# Uri Alon (Spring 2021)
# Lecture 10

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

Reference: Yael Korem, Avi Mayo, Avichai Tendler, Nir Friedman and Uri Alon, Immunity (2020)

There's hormone in the thyroid that can make us feel at ease

But the thyroid like a magnet for autoimmune disease

why do we attack ourselves, we'd really like to know

and in this lecture, we explain because I love you so

**Introduction:**

Hormone glands are prime targets for autoimmune attack. We saw how type-1 diabetes (T1D) is an auto-immune disease, in which the immune system, namely T-cells, attacks and kills beta cells. We saw that Hashimotos is an autoimmune disease in which T cells kill the thyroid cells. In both cases, important hormones are lost, insulin and thyroid hormone, and this loss is fatal unless treated. The diseases often occur at a young, reproductive age and are very common, 1% in T1D and upto 5% in Hashimotos. Why did evolution fail to eradicate these diseases? Why does the body attack itself, and why especially these specific cell types and not others? Fig 10.1 Shows how some glands get common autoimmune disease and others very rarely get these diseases. Are there rules for which organ gets attacked and which is spared?

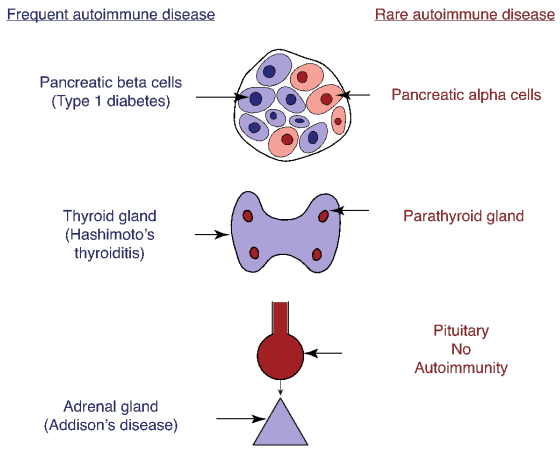



*Figure 10.1*

In this lecture we will discuss from first principles why endocrine autoimmune diseases might arise. Here is the main idea: These glands have a circuit that is essential for tissue size control and homeostasis but has a fragility to mis-sensing mutants. To avoid mutant take-over that can cause a hypersecreting nodule (adenoma) that over-secretes the hormone and 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 in all healthy individuals. In some individuals they 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 (Fig. 10.1).

**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. Since the discovery of insulin by Banting and Best 100 years ago, T1D patients can survive and thrive by injecting insulin at the proper doses and times. But T1D still causes 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. The fundamental reason that the body attacks specific cells- beta cells- is not known. As usual in medicine, when the origin is unknown, it is discussed as a combination of genetic and environmental factors. Relatively common gene variants make one susceptible (such as MHC-class-2 gene variants such as HLA-DR3 and DR4)

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 self-killing cells. The fact that these cells are not completely eliminated raises the possibility that the disease is the dark side of an important physiological process.

**Many endocrine organs have organ-specific autoimmune disease**

T1D and Hashimotos are just two of many autoimmune 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) or in tissues regulated by hormones. There is a range of such diseases. Relatively common diseases with a prevalence of 0.01%-0.1% are Addison's disease of the adrenal cortex, vitiligo of the skin melanocytes, and gastritis of the stomach parietal cells (Fig 10.2). The origin of all these diseases is currently unknown: they are said to be a combination of genetic and environmental factors.

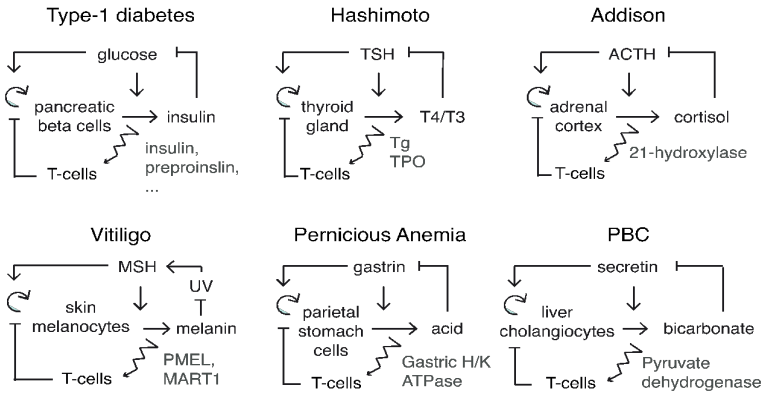



*Figure 10.2*

Equally puzzling is the fact that some endocrine organs virtually never get autoimmune diseases (fig 10.1). These include the pituitary, alpha cells that secrete glucagon, parathyroid cells that secrete a hormone that controls calcium (PTH). We will try to understand why in this lecture.

All these organ-specific diseases are due to T-cells attacking the specific cell type that secretes the hormone. Antibodies from B-cells often also participate in the carnage. Why does 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. As we mentioned in the previous lecture T-cell, monitor the cells of the body to see if they make proteins that belong to viruses or mutated cancer proteins.

The most common hypothesis until recently is that autoimmune diseases are mistakes, failures of **tolerance** mechanisms that eliminate t cells that attack healthy cells. T-cells that detect **self-proteins** are mostly eliminated. This is done right when t cells are made in the thymus. They are compared to a vast library of self in the thymus, and self-reactive cells are eliminated or turned into regulatory T cells which act to reduce T-cell activity. T cells that escape elimination in the thymus can still be eliminated in the rest of the body when they are over-activated by self-proteins or activated out of context in the periphery. The regulatory t cells are important elements to control against autoimmunity; mutations in Tregs often lead to autoimmune attack of multiple endocrine organs. So do mutations that destroy selection in the thymus (AIRE mutations).

Still, these processes do not eliminate all self-reactive T-cells. Research over decades has shown again and again that there are self-reactive T-cells in all healthy people. How these self-reactive T-cells sit quiet is not understood, and neither is their function (Madi et al., 2014; Semana et al., 1999; Yu et al., 2015). (Culina et al., 2018).

Thus, 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.

**We explore the idea that T-cells can help to remove hyper-secreting mutants**

All the organs that get organ-specific autoimmune disease have the same regulatory motif as the beta-cells and thyroid cells. In this feedback motif, a signal causes the cells both to secrete a hormone and to proliferate (Fig 10.2)

All of these tissues are thus sensitive to mutants that missense the signal. Such mis-sensing mutants can expand and cause loss of homeostasis.

Such mutants are well known clinically. Thyroid cells with mutations in the receptor for their signal (TSH) grow into nodules that secrete too much thyroid hormone. These “toxic nodules” cause hyper-thyroidism which can be lethal. Incidentally, these nodules are not cancerous- unlike cancer, they don’t give rise to new growths in other tissues called metastasis. They are instead adenomas which behave like normal thyroid cells, except that the mutant cells” think” there is too much signal. Thyroid cancer typically does not secrete thyroid hormones. Similarly, mutations in beta cells make them think there is too much glucose were described in lecture 3.

These mutants are inevitable. An organ like the thyroid weighs 10g and has $10^{10}$ cells. It thus takes $10^{10}$ cell divisions to make it. Since mutation rate is about $10^{-9}$/base-pair/division, each possible point mutation will be found in about 10 thyroid cells. It is known that at least 50 such mutations cause hyper sensing and hypersecretion leading to toxic thyroid nodules. Thus, every person should develop 10x50=500 toxic thyroid nodules secreting thyroid hormone- which would kill the person. Similarly, the $10^{9}$ beta cells are sure to get enough insulin hypersecreting mutants to kill the person from hypoglycemia. Thus, just to have endocrine organs requires removal of mutants.

In lecture 3 we saw a **biphasic mechanism** for removing such mutants in beta cells: glucotoxicity. Glucotoxicity can cause mutants that “think” glucose is way too high to kill themselves. We noted that this mechanism still leaves the range of mild mis-sensing mutants, between the two fixed points (hatched region in Fig 10.3). Other organs, like the thyroid, do not have

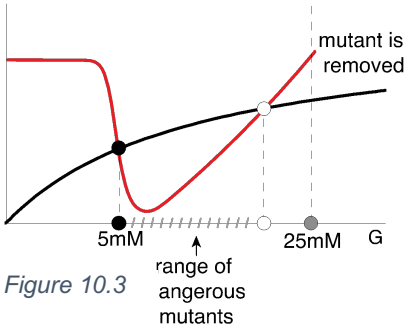


*Figure 10.3*

a mechanism like glucotoxicity at all. There is no TSH toxicity, probably because TSH needs to vary over a 1000-fold range in normal physiology, such as when iodine levels in nutrition change. Thus, we need another mechanism to remove mutants.

In this lecture, we will consider the idea that T-cells can help to remove mis-sensing mutants (Korem et al, 2020). To eliminate these mutants, we need a surveillance mechanism, which we will call **Autoimmune Surveillance of Hypersecreting Mutants (ASHM)** (Figs 10.4, 10.5). This is a theory we developed with PhD student Yael Korem and systems immunologist Nir Friedman at Weizmann (Fig. 10.6). This lecture is in memory of Nir Friemdman, who passed away this year. A noble and gentle clear thinker.

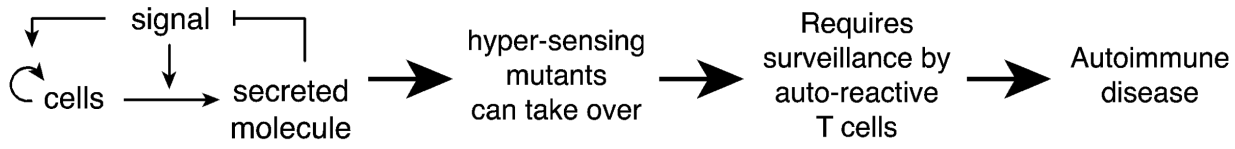



*Figure 10.4*

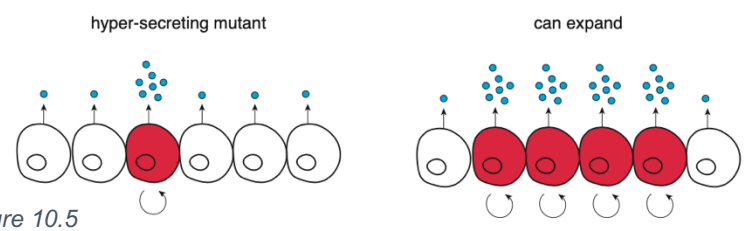



*Figure 10.5*

*Figure 10.6*

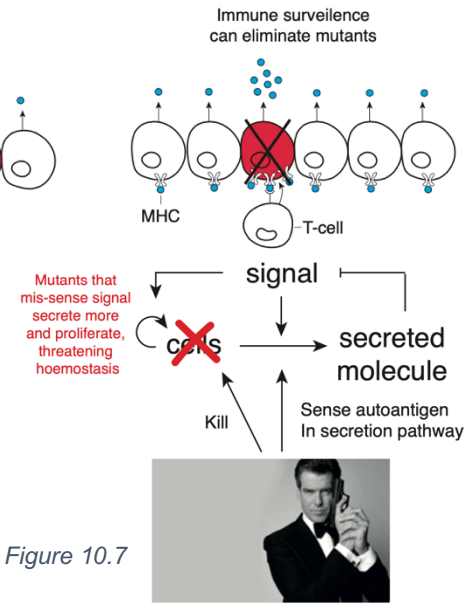



*Figure 10.7*

ASHM requires three main features. First, it needs to detect the hyper-secreting cells in order to eliminate them. Thus, the antigens it detects must be in the secretion pathway of the hormone, made by the cells (Fig. 10.7). The best idea is to have the antigens in the very end of the production process of the hormones, to minimize the number of self-antigens that are dejected.

Indeed, the antigens in T1D (called **autoantigens**) are all pieces of proteins in the insulin secretion pathway. For example, a major antigen is pre-proinsulin, the very last protein in the production pipeline, 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.

This feature is found in all the organ-specific diseases: the autoantigen in Hashimoto's thyroiditis 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 autoantigen is the key enzyme that synthesizes cortisol (21- hydroxylase). Other examples are shown in

Figure 10.2 and in (Table 10.1).

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**.

| Autoimmune disease | Auto-antigens | Role of autoantigen |
|---|---|---|
| Type 1 diabetes | Insulin, preproinsulin, PTPRN, PTPRN2, islet cell antigen-69, ZnT8, GAD65 | Insulin synthesis, storage and secretion |
| Hashimoto's thyroiditis | Thyroid peroxidase, thyroglobulin | T3/T4 biosynthesis |
| Addison's disease | 21-hydroxylase | Cortisol/aldosterone biosynthesis |
| Vitiligo | PMEL, MART1, tyrosinase, tyrosinase related proteins 1 and 2 | Melanin synthesis and storage |
| Autoimmune gastritis | Gastric H/K ATPase | Acid production |
| Primary Biliary Cirhosis | PDC-E2 pyruvate/oxo-glutarate | Bicarbonate production |

*Table 7.1*

**T-cell can tell the difference in antigen between neighboring cells**

For immune surveillance to work, the killer T-cells need to tell which cell makes more antigen than its neighbors. In this way they can preferentially kill hyper-secreting 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 10.8) (Martin-Blanco et al., 2018). (Halle et al., 2016).

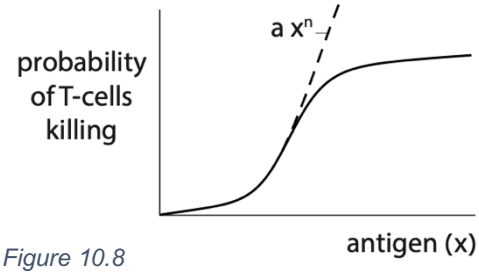



*Figure 10.8*

For very strong binding of antigen, a single antigen presented on a cell is probably enough. Thus, ASHM cannot operate with very strong binding T-cells, because they would not be able to discriminate between hypersecretion and other cells.

Most T cells, however, have only moderate binding to their antigens. For moderate binding, the killing rate *h(a)* goes approximately as a power law of antigen level *a*

$$(1)\ h(a) \approx c\ a^n\ ,$$

with a large exponent n=3-5, signifying a steep relationship. We saw such steep relationships in previous lectures, for example in glucose sensing by beta cells. 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 adaptation to background is provided

by **regulatory T-cells**. $T_{regs}$ provide an incoherent feedforward loop 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, called immune checkpoints. 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, $\mathrm{a}/<\mathrm{a}>$, so that

$$(2)\ h(a) = c\left(\frac{a}{<a>}\right)^n$$

This killing function therefore has two parameters: the rate *c* and the cooperativity *n*.

The relative sensing explains why the T-cells don't severely attack an organ if it simply starts to produce more hormone. For example, when the thyroid starts producing more thyroid hormone due to low iodine or a TSH-secreting tumor, or when beta cells start making more insulin due to a change in diet or insulin resistance. When more hormone is made in all the cells of the organ, more antigen is presented, $T_{regs}$ level rise and compensate by inhibiting the effector T-cells. The immune system thus adjusts to precisely cancel out the rise in antigen – exact adaptation we saw in the previous lecture. It remains sensitive to individual cells that make more antigen than their neighbors.

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

To work well, ASHM needs to eliminate any possible hyper-sensing mutant, and to do so without killing too many healthy cells. To understand how this might work, let's analyze a mathematical model for ASHM. The main conclusion is that ASHM can eliminate mutants and kill healthy cells at a very low rate compared to their natural turnover.

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

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

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 $\mu_0$, so that $\mu = \mu_0(G - G_0)$ (gray line in Fig 10.9). This approximation is not essential but makes the math easier and is sufficiently accurate for our purposes. Thus

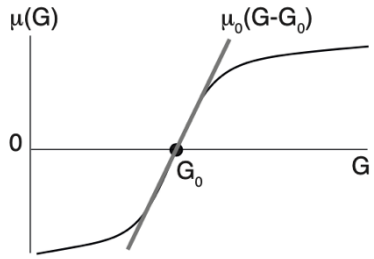


*Figure 10.9*

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

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 presents *a* copies of antigen on its surface, and the average *<a>=a* since we assume all cells are the same. 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

$$(3)\frac{dB}{dt} = \mu_0(G - G_0)B - c\left(\frac{a}{<a>}\right)^n B$$

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

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

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

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

The higher the killing rate *c*, 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 *c* 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 10.10). Such mis-sensing mutants were discussed in lecture 3. 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

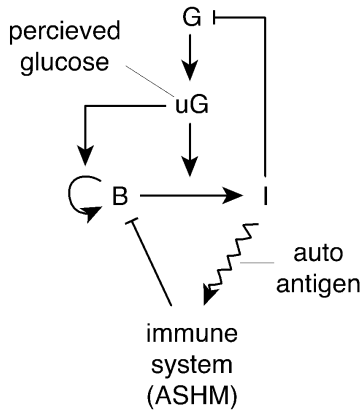



*Figure 10.10*

$$(6)\ \frac{dB_m}{dt} = B_m\left(\mu_0(u\,G - G_0)B - c\left(\frac{a_m}{<a>}\right)^n\right)$$

where the ASHM killing term contains the mutant antigen level $a_m$. Initially, there is a single mutant cell surrounded by wild-type cells. Since there is only one mutant cell, the average antigen <a> is virtually unaffected by the mutant so that <a> can be approximated by the wild-type level of antigen. Similarly, glucose level G is virtually unaffected by the mutants as long as they are few.

The antigen level of the mutant is determined by its insulin production rate, $a_m \sim f(uG)$. Using

$f(G) \sim G^2$ , we find that mutant cell antigen level is $a_m = qu^2\,G^2$ . The wild-type antigen level is $<a> = qG^2$ , because u=1 for the wild-type cells. Thus, the mutant killing term $c\left(\frac{a_m}{<a>}\right)^n$ depends only on the mis-sensing factor u, because the factors $q$ and $G^2$ cancel out, leaving $(u^2)^n = cu^{2n}$ . Thus:

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

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

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

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 10.11). This occurs when

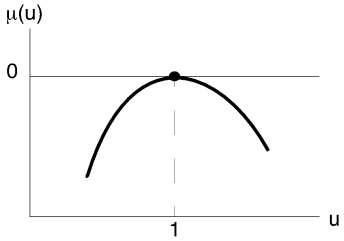


*Figure 10.11*

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

and also, that the second derivative is negative to ensure a maximum. Taking the derivative in Eq.8, we find

$$(10)\ \frac{d\mu}{du} = \mu_0 G\ -\ 2ncu^{2n-1}\ =\ 0$$

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, and u=1, we find the condition for ESS:

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

This equation connects the killing rate c, normalized by the natural turnover of beta cells, to the steepness of the killing function n. Interestingly, the higher the T-cell cooperativity (steepness) parameter *n*, the lower the killing rate *c* that is required for ESS. Since the cooperativity of immune recognition is high ($n \sim 3\text{-}5$), killing rate should be small, about 10-20% of the natural turnover rate parameter $\mu_0 G_0$. Thus, these secret-agent T-cells work subtly and with high precision (Fig 10.12). Only a small part of the removals of beta-cells are due to ASHM, and the rest to natural turnover.


*Figure 10.12*

**Surveillance can descend to autoimmune disease in several ways**

This surveillance mechanism appears to work well in most people. But a small fraction of people unfortunately gets autoimmune disease. The risk has a sizable genetic component. But genetics is not all: the process also has a stochastic component- even identical twins have only about a 50% congruence in term of getting autoimmune disease.

How does the AHSM mechanism fail and descend to autoimmune disease? We don't know for sure. One theory is that a microbial infection damages the tissue, causing release of self-antigen. The infection grows exponentially and provides an inflammation danger signal. This infection may or may not have detectable symptoms. The T–cell system sees an exponentially rising amount of self-antigen in the context of inflammation. It concludes wrongly that the self-antigen, such as pre-proinsulin, is actually of viral origin.

Genetic factors come into play, such as **MHC variants** (HLA-DR3,4) that make the MHC "platters" on antigen presenting cells. The high-risk variant MHCs appear to present the auto-antigens more strongly to immune cells. This may help to set off the heavy guns – an army of **B-cells** that produce antibodies against the antigen. The antibodies 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 10.13-10.14). Another possibility, raised by experiments in mouse, is that these high-risk MHC variants cause $T_{regs}$ to undergo activation-induced cell death at high antigen levels. When tregs are gone, there is less inhibition on effector T cells, unleashing a large auto-immune response.

*Figure 10.13*

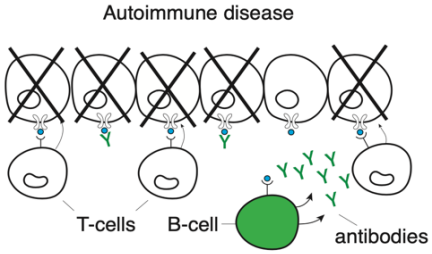



*Figure 10.14*

Note that these pro-autoimmunity genetic factors probably played a beneficial role in some past historical period, perhaps one plagued by a dangerous pathogen. By enhancing B-cell activation or reducing $T_{regs}$ inhibition, such variants may help to better fight the pathogen. This tradeoff may explain why these variants are present in a sizable fraction of the population, about 30%, quite consistently across the world population.

Normally the antibody and T-cell response would stop when the virus is eliminated, and the foreign antigen is gone. In the aftermath of a viral infection, T-cells even kill each other in a process called fratricide. But in autoimmune disease, cells of the targeted tissue are attacked and killed continuously, and the immune response is not turned off. The killing releases more self-antigen, activating more immune cells, making a **vicious cycle**. Long lasting **memory** B- cells and T-cells are formed which are easily triggered by the antigen. When about 90% of the beta-cells or thyroid cells are killed, hormone 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).

Another possible route to autoimmunity may involve rapid growth of the tissue during puberty, coupled with some inflammation. Again, rising self-antigen levels plus alarm signals may fool the T-cells and trigger autoimmune disease, whose peak prevalence is often around puberty.

Whatever the precise route to auto-immune disease, the presence of auto-reactive T-cells provides the basic soldiers that cause a fragility to auto-immune disease.

**Endocrine tissues that rarely get auto-immune disease are prone to diseases of mutant expansion**

We now turn to the question of why certain organs are attacked and others aren't (Fig 10.1). The ASHM theory predicts a tradeoff: if there is little or no surveillance in a tissue, it should get no autoimmune disease. However, it should get diseases of mutant expansion, especially at old ages when mutant cells have had enough time to grow into an adenoma.

We can test this prediction by looking at endocrine cells and organs that very rarely have autoimmune diseases - less than $10^{-5} - 10^{-6}$ lifetime prevalence. These organs include the parathyroid (PT) gland, a tiny gland that sits on top of the thyroid (Fig 10.1). Its job is to secrete the hormone PTH in order to control free blood calcium, which needs to be in a tight range around 1mM. PTH helps dissolve bone, which is made of calcium phosphate, and to regulate calcium intake from the gut, in order to increase blood calcium.

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 takeover occurs. It is a 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 adenoma (non cancerous growth) 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 adenoma.

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 10.15), 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. This circuit also has biphasic mutant protection (low and high calcium kill PT cells). But intermediate hyper-sensing mutants are still dangerous.

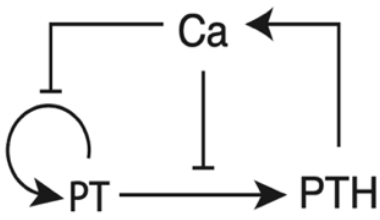
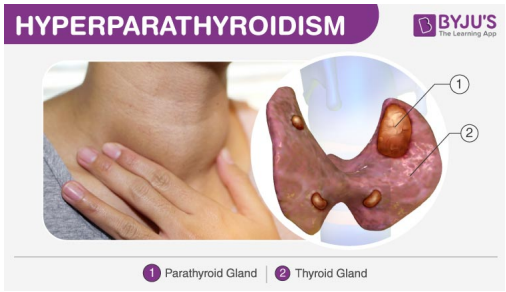


Figure 10.15




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 associated with type-2 diabetes (Feng et al., 2017; Liu et al., 2011; Unger and Cherrington, 2012).

It seems that the parathyroid has at least some immune surveillance because autoimmunity in this organ can be caused by certain drugs. In particular, drugs that enhance immune response against cancer, by blocking immune checkpoints, have parathyroid autoimmunity as a side effect in some patients. Thus, ASHM in this organ may be tuned to low levels that prohibit autoimmune disease under normal conditions.

A particularly clear example of the mutant/autoimmunity tradeoff seems to occur in the HPA axis. There are two glands, the pituitary and the adrenal, A and P. Each has a version of the circuit motif that is fragile to mis-sensing mutants, as we saw. Mutants in the pituitary that hyper-sense hormone $x_1$, for example, grow into nodules that hyper-secrete hormone $x_2$ (ACTH), making the adrenal make too much cortisol (Fig 10.16). This is known as **Cushing's syndrome**, with depression, hypertension, muscle wasting and fat distribution in the face and abdomen. An almost exact type of disorder is caused by adrenal mutants that hyper-sense $x_2$. However, 90% of Cushing's

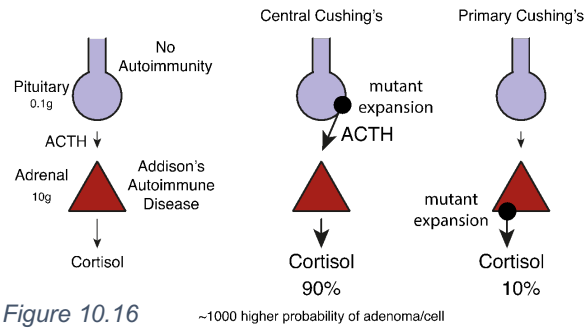


Figure 10.16

syndrome is caused by mutants in P, not in A. This is surprising because the number of cells in P is smaller by a factor of 100 than in A (relevant cells in the adrenal total about 10g, in the pituitary about 0.1g).

Our theory predicts then that the adrenal A is protected from mutants by ASHM, and hence should have autoimmune disease. Indeed, the adrenal A suffers from a relatively prevalent autoimmune disease called Addison's disease which destroys the adrenal by T cells. The pituitary virtually never gets such an autoimmune disease- it seems to lack ASHM. Indeed, is it an immune privileged site. However, it shows relatively frequent mutant-expansion diseases- the most common form of Cushing's syndrome called central Cushing's (Fig 10.16).

Similar pituitary mutant expansion diseases plague other HP-axes. Pituitary mutant cells in the growth axis account for acromegaly and gigantism, and in other pathways to disease of hyper-gonadism and hyper-thyroidism. Again, like the adrenal, thyroid is tilted towards autoimmunity, whereas its pituitary controller cells (thyrotrophs) are tilted to mutant expansion.

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 10.17). 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.

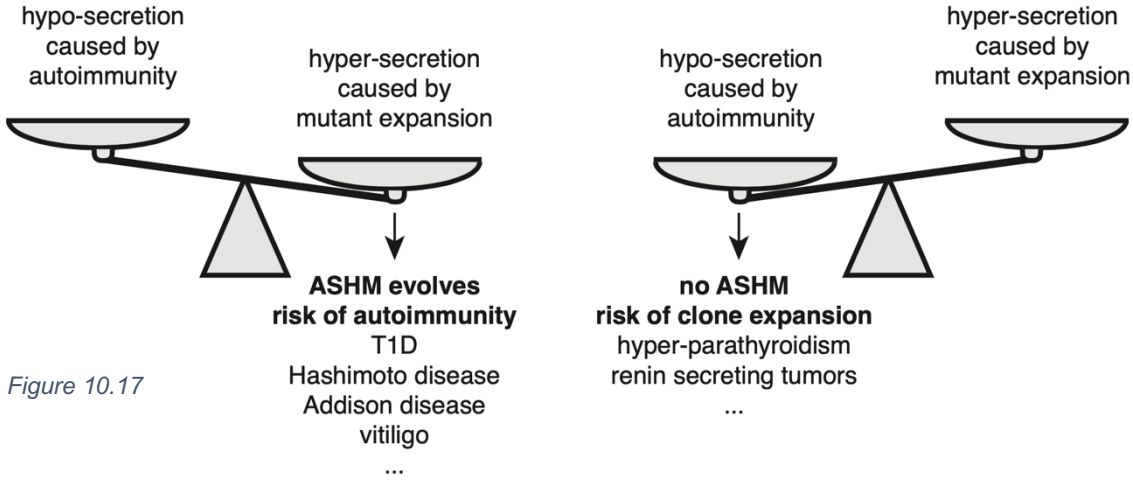



*Figure 10.17*

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 overactive 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.

Perhaps the simplest explanation for which organ gets which disease stems from the number of mutations in the organ. The smaller the organ, the less cell divisions are needed to make it, and the fewer cell divisions occur over life (assuming most glands have a similar turnover time). The fewer the mutations, the less the need for ASHM. The cutoff seems to be at a mass of about 1g, which is about 10^9 cells. Above 1g are endocrine organs with autoimmune diseases: beta cells (1g), adrenal (10g),

thyroid (10g). Below 1g are glands with mutant expansion and very rare autoimmunity: pituitary cells (0.1g), parathyroid (0.3g), renin secreting cells (0.1g).

At above 10-30g, the disease spectrum shifts again, with less autoimmunity and more cancer (prostate 30g, pancreas 100g, skin several Kg). This is because there are so many cell divisions, that mutations would become too frequent. The required levels of ASHM would be too high to avoid autoimmune disease. Organs thus change strategy to stem-cell-based production, in which a single stem-cell division is amplified to make thousands of cells by transient amplifying cells. This reduces the number of mutations that remain in the stem cells of the tissue. But stem cells are more prone to cancer, being cells with high proliferation potential. In the transition zone of 10-30g one sees both cancer and autoimmunity (thyroid, prostate) (Fig. 10.18)

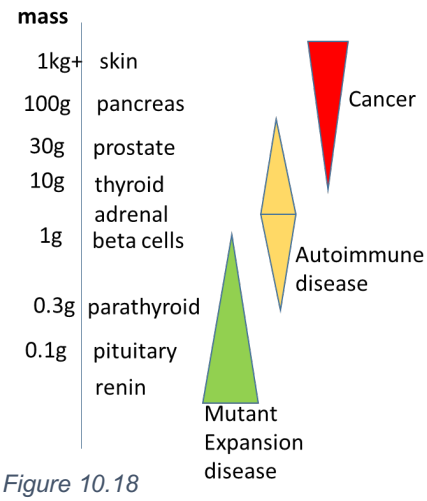



*Figure 10.18*

I like the prospect of such 'rules' for diseases, pointing towards a 'Mendeleev table' of diseases (see the Systems Medicine course 2020, lecture 12). Missing blocks in the table can point to 'diseases that might have been' (such as autoimmune disease of alpha cells), and to explain them based on first principles. We will expand on this theme in the last lecture of the course.

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