Science & Society

Attacking the system

Next-generation auto-immune therapies target pathways rather than symptoms

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Auto-immune diseases are a major health problem in both developed and developing countries: They cause as many deaths as the leading infectious diseases and exact an even greater toll on patients’ quality of life given their chronic nature (Box 1). Reliable data for all auto-immune diseases are hard to collect, but a 2011 study by the American Autoimmune Related Diseases Association (AARDA) reported that the total annual cost of just seven leading auto-immune diseases (Crohn’s disease, ulcerative colitis, systemic lupus erythematosus (SLE), multiple sclerosis (MS), rheumatoid arthritis (RA), psoriasis, and scleroderma) was somewhere between US$1.8 billion and US$70.6 billion in the USA alone (http://www.diabetesed.net/page/_files/autoimmune-diseases.pdf). The AARDA report also drew attention to the indirect societal toll with one example being sufferers from RA in the USA, who experienced a decline in average earnings from US$18,409 to US$13,900 per year, and the number of jobs they were able to perform dropped from 11.5 to 2.6 million. It was also found that approximately 50 percent of RA patients were unable to work at all within ten years after disease onset.

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The prevalence and impact of auto-immune diseases have risen during the past decades: The AARDA estimates that 50 million people in the USA alone suffer from an auto-immune disease (http://www.aarda.org/autoimmune-information/autoimmune-statistics/), while an earlier report from the US National Institutes of Health estimated that 23.5 million people are affected. The difference in the numbers is owing to the increasing number of auto-immune diseases recognized by medical science: more than 80 diseases now, compared to the 24 or so that were used as the basis for the NIH estimate, according to the AARDA website (same reference). There is also strong evidence that the incidence of at least some major auto-immune diseases is increasing, especially in developed nations: For example, a number of studies have found that type 1 diabetes has been on the rise for a century. What makes the impact of auto-immune diseases particularly damaging is that curative treatments have mostly proved elusive. Auto-immune diseases can rarely if ever be cured; instead, their progression can be controlled and the symptoms alleviated, although there is some potential to achieve remission for long periods with low levels of symptoms.

The major challenge for efficient therapy is that auto-immune diseases are complex and usually involve numerous genetic and environmental factors. There is no pathogen to attack and no clear-cut immunological or genetic factors, proteins, or metabolic or regulatory pathways that can be targeted with drugs. To date, treatments have therefore relied on broad-spectrum drugs that target inflammatory systems, but with mixed results that vary significantly between diseases.

One of the few real success stories is the treatment of RA, the root cause of which is not yet fully understood. It has been known for some time, however, that one characteristic of RA is upregulation of TNF (tumor necrosis factor)-dependent signaling, which regulates the activity of various immune cells. This knowledge led to the identification of anti-TNF drugs that alleviate the symptoms of RA [1]. One of the most successful drugs, infliximab, was actually first approved for Crohn’s disease, another auto-immune condition, in 1998. Infliximab is a monoclonal antibody against TNF-alpha, which prevents the cytokine from binding to its target receptor. Anti-TNF drugs in general have proved unexpectedly successful against RA, according to Tim Vyse, Professor of Molecular Medicine specializing in Lupus disease at King’s College in London, UK: “Rheumatoid arthritis was one of the early beneficiaries of anti-inflammatory drugs in the sense that anti-TNF had an incredible effect and got the game going,” he said. But he pointed out that this success has turned out to be a mixed blessing, as it created unrealistic expectations that drugs could have a similar impact on other auto-immune diseases.

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strong,” Vyse explained. “It was as much luck as judgment that TNF worked. People still can’t answer the question of why anti-TNF is so effective.” Part of the puzzle is that the immune system has redundant pathways that can take over if one part is knocked out, but this does not seem to happen in many cases of RA. “It’s a bit surprising that targeting one molecule has such a big effect,” Vyse said.

A lack of knowledge about how a drug works increases the risk of serious unforeseen side effects, however. According to Chris Cotsapas, Assistant Professor of Neurology and Genetics at the Yale School of Medicine, who focuses on MS: “If you treat rheumatoid arthritis patients with no history of MS […] with anti-TNF, the rheumatoid arthritis recedes, but they then tend to develop a neurological deficit […] If you stick them in an MRI (Magnetic Resonance Imaging) machine, you can see clearly that they have developed MS. You don’t see it until the treatment has been administered, so it is not a
Although only a minority of RA patients on anti-TNF develop MS, it highlights the shortcomings of the prevailing treatments for many auto-immune diseases, despite individual successes against the target condition. “For autoimmune diseases, most therapies chase the proximal consequence of pathology, the immune response, and knock it down, but they don’t address the underlying deficit,” Cotsapas explained. “The reason you care about that is that if you hit a walnut with a hammer, you rarely have a whole nut left.” Yet Cotsapas is optimistic that the current generation of broad-spectrum immune suppressants, such as steroids, will eventually be substituted with more specific treatments that can be tailored to a particular condition. Indeed, recent research has
shown that most auto-immune diseases share many genetic loci [2].

There is still a lot of work to do mapping these loci to specific transcription pathways and to different conditions. A key point is that each pair of auto-immune diseases share a different set of common loci, but each disease also has other loci that are shared with other conditions. "[B]ecause the genetics are shared it looks like some of the pathways are shared," Cotsapas said. "So given the molecular insight we can gain from the genetics, one question for us is: can we use it to develop new drugs and decide which patients should receive those drugs?"

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The insight that auto-immune diseases have genetic loci in common explains why a given drug can sometimes be used to treat more than one disease. Infliximab is now prescribed for sufferers of several auto-immune diseases including ulcerative colitis as well as RA and Crohn’s disease (http://www.drugs.com/news/ida-expands-remicade-indication-ulcerative-colitis-1943.html). It may also explain some of the side effects, including the effect of causing one auto-immune disease while treating another: “If you block some part of the immune system, for example with TNF receptor antagonism, there might be some other compensatory mechanisms, especially in some people, that might release susceptibility to some auto immune diseases,” Vyse explained. “My understanding is that that’s quite uncommon though.”

Improved knowledge of the pathways involved should help physicians to reduce the risk of side effects and better tailor drug regimes to individual patients. The goal is not to personalize treatments to the patient’s specific genetics, but more to the specific pathology of the disease. “The game is twofold in terms of how far genetics can be useful for therapy development,” Cotsapas said. “One, can we figure out which patient should receive which therapy. […] So instead of having this one-size-fits-all, if this patient looks like this, we should try therapy X first. The genetics here is telling us there are multiple pathways associated with increased risk, and if we can understand what those pathways are, we can understand what the risk factors for that disease are and see if the patient has that deficit.”

I might also make research into drugs for auto-immune diseases more viable for pharmaceutical companies if they can be used for multiple diseases. “The economics of auto-immune drug development can become quite challenging,” Cotsapas commented. “If a drug targets 1 in 1,000 people and you then slice that population into quarters or fifths, that becomes a small market share. If, however, that therapy is useful for 25% rheumatoid arthritis patients and 10% of MS patients and 35% of Crohn’s patients, then it becomes economically more viable.”

Among recently approved drugs that target multiple auto-immune diseases is Tecfidera, based on the ester dimethyl fumarate and approved for the treatment of MS in the EU in 2013. It has been heralded as a breakthrough because it can be taken orally, and was earlier approved in Germany for the treatment of psoriasis, an apparently unrelated disease that affects the skin rather than the central nervous system [3]. It is also an example of a drug approved on the basis of its efficacy in clinical trials, rather than because its makers understand precisely how it works. “Its exact mechanism of action is still unknown, but oxidative stress may be involved,” commented Bonnie Dittel, Senior Investigator at the Wisconsin Blood Research Institute in the USA and head of a research team focusing on regulation of the auto-immune response.

There are also examples where the development of auto-immune drugs has been halted or delayed for economic reasons, despite promising results in early clinical trials. This was the case for rontalizumab, a monoclonal antibody developed by Roche that targets interferon type 1, one of a group of signaling cytokines that alert neighboring cells to virus infection and instigate various immune responses. Rontalizumab successfully completed phase II trials for treatment of SLE, which attacks multiple organs, and achieved clinical proof of concept. Yet Roche announced in October 2013 that they will not proceed with phase III trials because the compound does not meet economic criteria.

This decision came despite a growing understanding that interferon could be a promising target for the therapeutic treatment of a range of auto-immune diseases, not just Lupus. “I think in Lupus the next thing that will be quite big will be inhibition in the interferon system,” Vyse said. “I think that’s going to work in a subset of patients and inhibition of interferon will be relevant for a number of other diseases as well. That pathway is dis-regulated in a number of different auto-immune diseases.”

The finding that the same drug can work against multiple diseases suggests that the whole approach to developing and approving therapies for specific targets should be revised, Cotsapas explained. “Right now, for very good reasons, we don’t use therapies developed for one disease on another disease, because doctors prescribe based on symptoms and if a medicine is approved for use in rheumatoid arthritis, there is no reason that a neurologist treating an MS patient will prescribe it. It doesn’t make sense. But it may make perfect sense if it’s hitting the same pathway partially underlying both diseases and a given patient has a deficit in that pathway,” he said.

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However, discovering single drugs that effectively treat a wide range of auto-immune diseases will not mean that all such diseases become treatable. A clear example is type 1 diabetes, the symptoms of which occur only after the immune system has already destroyed most insulin-producing cells. “Since type 1 diabetes is largely diagnosed after beta cell destruction has reached a critical point, it cannot be treated with immune modifiers at that stage,” Dittel
explained. Until cell-based therapies become available to regrow these beta cells, there is no point in modifying immune responses to treat diabetes, and insulin remains the only viable option. Even for auto-immune diseases that do share common underlying pathways, a single drug to treat both may not be possible, as they can require quite different therapeutic approaches. “In MS, if you can prevent or diminish the T cell response, the disease will be tempered,” Dittel said. “Then RA has a large inflammatory component that is driven in part by TNF-α, a major pro-inflammatory molecule that can be targeted quite successfully.”

Overall, a better understanding of the underlying mechanisms, pathways, and molecules involved in auto-immune diseases should lead to the better use of existing drugs and the development of new therapies to modify the action of specific target pathways. On the research side, such knowledge will help to unify the understanding of auto-immune diseases, while on the clinical side, it will give physicians more options to treat patients based on their individual molecular deficiencies. The ultimate goal, however, remains the discovery of real cures for auto-immune diseases, not just therapies for managing their progress or symptoms.

References