The evolutionary origins of autoimmune diseases

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Standfirst

Most autoimmune diseases are caused by the interplay between common genetic risk variants and environmental factors. Many of these variants evolved under strong selection pressures, likely due to lifestyle-specific environmental pathogens, the consequences of which shape the distribution of present-day disease risk and point to novel therapeutic interventions.

Genetic basis of autoimmune diseases

Our understanding of the aetiology of autoimmune diseases has increased substantially over the past 20 years as large genome-wide association studies (GWAS) have characterised their underlying genetic architecture. The picture which emerges is that autoimmune diseases are influenced by common genetic variants (population frequency >5%), the majority of which lie within or near immune genes[1]. However, it is the interaction of these variants with environmental factors, rather than genetics alone, which drives the majority of disease risk.

Recent studies have shown that many genetic risk variants are shared between different autoimmune diseases—suggesting a shared evolutionary history—and that many also confer protection against various infectious diseases. The relatively high frequency of risk variants in the present implies that they may have been subject to positive selection in the past due to their protective benefit against infections. The hypothesis that autoimmune diseases are the byproduct of past selection against environmental pathogens (i.e.,

“antagonistic pleiotropy”) has been framed as a trade-off between protection against infection and risk of autoimmunity. Classic examples are genetic variants in the HLA region, which are under pathogen-driven selection[2] but are also associated with autoimmune diseases[1]. Most empirical studies have taken the form of observing an overlap between genes influencing autoimmune disease and susceptibility to pathogenic infection, with few studies showing statistical evidence for selection of these variants until recently[3–5]. With the availability of extensive ancient DNA data and more powerful statistical methods, the gap between theory and findings has begun to close, revealing the evolutionary origins of autoimmune diseases.

Advances from Ancient DNA

Recently, the sequencing of thousands of ancient human genomes has provided unprecedented insight into the genetics of past populations. Using these data, and advances in understanding European demographic history, researchers have been able to study the evolution of genetic risk variants underlying autoimmune diseases, linking natural selection to specific time periods and subsistence lifestyles.

For example, Kerner et al.[5] investigated signals of selection in ancient European genomes and found that most genetic adaptation occurred after the start of the Bronze Age (~4,500 BP) and was enriched for genes related to host-pathogen interactions. They showed that autoimmune disease risk variants are highly enriched for pleiotropic associations with infectious diseases, and that these pleiotropic variants showed stronger evidence of selection than randomly matched controls. When considering risk variants in aggregate, they identified a general trend, over the last 10,000 years, of reduced risk for infectious diseases and increased risk for autoimmune diseases. It should be emphasised, however, that any inferred differences in genetic risk between ancient and modern populations does not necessarily imply differences in disease prevalence, as environmental factors play a critical role in mediating disease development.

In contrast to these broad conclusions, Barrie et al.[3] decomposed allele frequency trajectories by genetic ancestry and found that genetic risk for multiple sclerosis (MS) rose steeply in the Bronze Age, and was brought into Europe by the Steppe migrations from central Asia, ~5,000 years ago. This study showed that risk variants for MS were subject to positive polygenic selection between 5,000 and 2,000 years ago, likely in response to pathogen pressure. The same study also showed that risk variants for rheumatoid arthritis (RA) were subject to negative polygenic selection over the last 15,000 years, and were present at the highest frequencies in hunter-gatherer populations before the arrival of agriculture. The contrast between MS and RA points to radically opposing evolutionary histories, despite their genetic correlation. These results suggest that the pastoralist lifestyle of the Steppe populations, and the increase in population density during the Bronze Age, may have exposed people to a wider range and increased intensity of zoonotic pathogens, which triggered positive selection for MS risk variants due to pleiotropy. This interpretation is supported by evidence from the recovery of ancient pathogens, which shows that the introduction of pastoralist lifestyles was associated with a sudden increase in the prevalence of zoonotic pathogens[6].

Consequences and Implications

Major changes in diet and lifestyle are not limited to past populations, and it appears that our modern sanitary lifestyle, with its increased hygiene and vaccination, may be interacting with previously beneficial genetic variants to drive the increased prevalence of MS over the last 50 years[7]. This is increasingly an area of research for understanding MS aetiology, risk prediction, and disease management. The link between changing lifestyle and disease risk fits into the view of MS as a 'lifestyle disease'[7], and emphasises the need to study pathogen exposure[8]. In the case of RA, the genetic risk variants show a steady decline beginning in the Mesolithic, before more rapidly decreasing in the Bronze Age, where lifestyle and environmental changes may have triggered a systemic RA-associated inflammatory state, which increases the risk of infection[9], potentially resulting in negative selection.

The evidence that autoimmune disease risk has been shaped by pathogen-driven evolution may partly explain the distribution of disease prevalence in the present. For example, Steppe pastoralist ancestry is highest in Northern Europe[4], where MS prevalence is also highest; the reasons for which have been debated for decades[10].

It may also offer clues for potential treatments. Autoimmune diseases are notoriously difficult to treat, and many of the most efficacious drugs are associated with serious side effects. The majority of these drugs target the immune system by neutralising or deleting individual cytokines or cells. The evolutionary history of autoimmune disease implies that we are fighting an uphill battle against an immune system which evolved over thousands of years to counter a combination of pathogenic challenges which no longer exist. Future treatments should therefore aim to re-calibrate the immune system, rather than disrupt it, so that it continues to protect against infection while also dampening autoimmune responses[1]. Experiments aimed at attenuating the overactive immune response in MS patients using helminths have had modest success with the swine parasite *Trichuris suis*[11]. However, the Steppe populations did not keep or consume domesticated pigs, so the evolution of their immune response took place without this parasite. Future studies might therefore benefit from using parasites found in beef or dairy products instead.

Demystifying autoimmunity may improve patients' perspectives on a seemingly obscure process. Understanding why genetic risk persists in our DNA provides a paradigm shift in our view of disease, moving from an emphasis on abnormal function to past adaptation and the gulf between modern and ancient environments. We hope this will reduce misconceptions, and reframe genetic risk as the consequence of a complex and fascinating history of adaptation.

While it is well established that many genetic variants which increase the risk of autoimmunity also mediate the risk of infectious diseases, it now appears that autoimmune risk is not associated with a single pathogen but with a multitude, despite the lack of GWAS data for many important pathogens. We can now also describe these as 'lifestyle' diseases, which reflect both their evolutionary histories—inextricably linked to human subsistence and cultural practices—and their modern aetiology, in which the sanitary environment has created an immune absence of requirement. This absence may now disrupt the fine balance between pro- and anti-inflammatory pathways which were fine-tuned in our evolutionary past. Autoimmune diseases are also increasing among non-European populations, and

future work should expand to include more diverse ancestries. However, such research is limited by sparser sampling of ancient genomes and by a lack of large-scale biomedical databases in many regions. This is an exciting time for research into autoimmune diseases, as scientists reveal their origins and causes, in steps that lead us towards better treatments for all patients, irrespective of ancestry.

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