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Unresolved issues in theories of autoimmune disease using myocarditis as a framework

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HIGHLIGHTS

- Clinical and experimental evidence support some aspects of all theories.
- Critical comparative studies differentiating between theories and models needed.
- Theories monocausal but animal models suggest multi-factorial cause of disease.
- Theories do not adequately explain adjuvant, innate immunity or sex differences.
- New synthetic theory needed integrating anomalies, innate and adaptive immunity.

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ABSTRACT

Many theories of autoimmune disease have been proposed since the discovery that the immune system can attack the body. These theories include the hidden or cryptic antigen theory, modified antigen theory, T cell bypass, T cell–B cell mismatch, epitope spread or drift, the bystander effect, molecular mimicry, anti-idiotype theory, antigenic complementarity, and dual-affinity T cell receptors. We critically review these theories and relevant mathematical models as they apply to autoimmune myocarditis. All theories share the common assumption that autoimmune diseases are triggered by environmental factors such as infections or chemical exposure. Most, but not all, theories and mathematical models are unifactorial assuming single-agent causation of disease. Experimental and clinical evidence and mathematical models exist to support some aspects of most theories, but evidence/models that support one theory almost invariably supports other theories as well. More importantly, every theory (and every model) lacks the ability to account for some key autoimmune disease phenomena such as the fundamental roles of innate immunity, sex differences in disease susceptibility, the necessity for adjuvants in experimental animal models, and the often paradoxical effect of exposure timing and dose on disease induction. We argue that a more comprehensive and integrated theory of autoimmunity associated with new mathematical models is needed and suggest specific experimental and clinical tests for each major theory that might help to clarify how they relate to clinical disease and reveal how theories are related.

1. Introduction

In this review we have four primary goals. One is to test the adequacy of autoimmune theories that were largely derived in animal models to describe clinical disease (Table 1). Secondly, we examine the mathematical models that have been developed for each major theory of autoimmunity. Third, we argue that there is a need for more integration across theories, across mathematical models, and between theories and mathematical models, particularly in light of our more recent understanding of the importance of innate immunity in the development of autoimmune disease. And our final goal is to highlight problems with individual theories and mathematical models that may lead to the development of novel or hybrid theories of greater explanatory and predictive power. In an ideal world, a good theory of autoimmunity combined with insightful modeling should lead to new and better approaches to effective translational research.

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Table 1
Theories on causes of autoimmune disease.

Theory	Description	References
Hidden/cryptic antigen	Tissue damage releases hidden antigens	Liao et al. (1995) and Rigante et al. (2014)
Epitope spread	Multiple epitopes against self needed before autoimmune disease develops	Lehmann et al. (1992), Powell and Black (2001) and Vanderlugt and Miller (2002)
Anti-idiotype	Cellular receptor targets induce crossreactive autoAbs	Plotz (1983) and Weremeichik et al. (1991)
Molecular mimicry	Accidental crossreactivity	Damian (1962, 1964), Lane and Koprowski (1982), Fujinami et al. (1983, 2006), Fujinami and Oldstone (1985), Oldstone (1987) and Cusick et al. (2012)
Bystander or adjuvant effect	Microbial or cytokine activation of pre-existing autoreactive immune cells	Tough et al. (1996, 1997), Theil et al. (2001), Von Herrath et al. (2003), Fujinami et al. (2006) and McCoy et al. (2006)
Dual TCR	Non-specific activation of 2nd TCR	Padovan et al. (1995) and Cusick et al. (2012)
Antigenic complementarity	Multiple infections by microbes that share antigenic complementarity/cross-reactivity	Westall and Root Bernstein (1983, 1986), Pendergraft et al. (2004, 2005), Preston et al. (2005), McGuire and Holmes (2005), Root-Bernstein (2007) and Preston and Falk (2011)
Co- infection (or co-exposure)	Releases self tissue and activates immune response, may involve crossreactivity or antigenic complementarity	

In order to achieve our goals in a relatively short review article such as this one we have imposed three constraints on our content. The first is to limit our discussion of autoimmune theories to myocarditis. Myocarditis is clinically and experimentally well-characterized, and most of the major theories of autoimmunity have been tested making it well suited to our purpose. The second constraint is to limit our discussion to data that represent critical tests of assumptions that underpin specific theories or that can differentiate between theories. We will not, therefore, make any attempt at completeness, nor does this seem necessary in light of the many previous reviews on the topic. The third constraint is to focus these critical tests of theories to points that have potential clinical relevance or future treatment implications for myocarditis patients. Because all of the theories that are used to direct research on myocarditis and to explain the resulting data are also used to understand other autoimmune diseases, we are reasonably confident that the general conclusions that we reach in this review will be applicable to a much wider range of experimental and clinical autoimmune diseases.

It is important to note from the onset that for most theories described here there is a significant body of literature substantiating its case and in some instances mathematical models to explore its mechanisms. However, data "proving" each theory are open to different interpretations according to at least two, and often more, theories of autoimmunity and their mathematical models. Although it would be convenient to have a "crucial experiment" that clearly "proves" one theory or model correct and all the rest wrong, such is not the case. Theories are, in reality, built on *systems* of experimental studies and models assume the validity of the theories they mathematize. The value of a theory is based on three fundamental functions: one is to connect the most data in the most meaningful way; the second, to do so with the fewest assumptions; and the third, to predict connections (and therefore testable phenomena) that have yet to be observed. Good mathematical models facilitate these three functions. Thus, the value of a theory (and its mathematical and animal models) is not found in whether there are data that supports it, but rather how much data have accumulated for which it *cannot* account and how many predictions it makes that *cannot* be validated. Because these are the most important aspects of theory evaluation, we have focused our review on what each theory has *not* accomplished and the data and predictions each makes that *differentiate* it from other theories. In this sense, our review is not about what we know regarding autoimmunity, but rather about the problematic aspects that reveal what we do not know.

2. Myocarditis

Before discussing theories, a brief summary of clinical and experimental models of myocarditis is needed. Clinically, myocarditis is defined as inflammation of the myocardium and is a relatively rare autoimmune disease. Myocarditis is also frequently associated with inflammation of the pericardium, a single cell layer on the outside of the heart, and termed perimyocarditis or myopericarditis (Imazio and Cooper, 2013). No formal epidemiology studies exist on the incidence of myocarditis, but based on autopsy records myocarditis occurs in approximately 10% of cases of sudden death (Fabre and Sheppard, 2006). However, it is thought that myocarditis is likely to occur asymptomatically in a larger percentage of individuals (Imazio and Cooper, 2013). This is at least partly because so many different environmental agents, and particularly infections, are known to be able to cause myocarditis like viruses, bacteria, parasites, and drugs (Elamm et al., 2012; Kindermann et al., 2012). Myocarditis is a leading cause of sudden death in individuals under age 40 (Gupta et al., 2008) and may lead to dilated cardiomyopathy (DCM) and chronic heart failure predominantly in men (women with myocarditis are far more likely to recover without progressing to DCM) (McNamara et al., 2011, Elamm et al., 2012).

Myocarditis can be induced experimentally in mice using infections such as coxsackievirus B3 (CVB3), murine cytomegalovirus (MCMV), encephalomyocarditis virus (EMCV), reovirus, influenza virus, parvovirus, and the parasite *Trypanosuma cruzi* (modeling Chagas disease) or adjuvants (i.e., complete Freund's adjuvant/CFA supplemented with inactivated *Mycobacterium tuberculosis* and/or pertussis toxin) with self-peptide (usually cardiac myosin) (Fairweather et al., 1998; Myers et al., 2013; Esper et al., 2014), reviewed in (Pankuweit and Klingel, 2013). Myocarditis induced by adjuvant and self peptide is termed experimental autoimmune myocarditis (EAM). Interestingly, the time-course of disease progression from myocarditis to DCM is similar between animal models and human disease. Regardless of the agent used to induce myocarditis, the primary infiltrate during the acute stage of disease in patients and mice are macrophages (about 80% of infiltrate) followed by T and B cells (around 10–15% of the infiltrate) (Afanasyeva et al., 2004; Frisancho-Kiss et al., 2007; Fairweather et al., 2014). Autoimmune diseases have historically been considered as T and B cell-mediated diseases, but more recently the importance of innate cells like macrophages is being understood. For example, T cells have been considered to be the primary cells mediating damage in the classic autoimmune disease model

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