Journal of Immunological Methods 374 (2011) 62–69

Contents lists available at ScienceDirect

Journal of Immunological Methods

journal homepage: www.elsevier.com/locate/jim

Research paper

Applications for T-cell epitope queries and tools in the Immune Epitope Database and Analysis Resource

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ARTICLE INFO

Article history:
Received 8 September 2010
Received in revised form 23 October 2010
Accepted 27 October 2010
Available online 31 October 2010

Keywords:
Epitope conservation
Epitope predictions
Vaccine design
Major Histocompatibility Complex

ABSTRACT

The Immune Epitope Database and Analysis Resource (IEDB, http://www.iedb.org) hosts a continuously growing set of immune epitope data curated from the literature, as well as data submitted directly by experimental scientists. In addition, the IEDB hosts a collection of prediction tools for both MHC class I and II restricted T-cell epitopes that are regularly updated. In this review, we provide an overview of T-cell epitope data and prediction tools provided by the IEDB. We then illustrate effective use of these resources to support experimental studies. We focus on two applications, namely identification of conserved epitopes in novel strains of a previously studied pathogen, and prediction of novel T-cell epitopes to facilitate vaccine design. We address common questions and concerns faced by users, and identify patterns of usage that have proven successful.

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1. Introduction

The goal of the IEDB (Peters et al., 2005; Peters and Sette, 2007) is to catalog and organize information related to T- and B-cell epitopes, as well as to provide tools to predict novel epitopes and to analyze known epitopes to gain new information about them. The IEDB website has been updated continuously based on user feedback, resulting in fundamentally revised versions of both the database itself (Vita et al., 2010) and the tools hosted in the associated Analysis Resource (Zhang et al., 2008). The continued use of the database and tools has broadened our understanding of what applications are possible and refined the methodology to achieve optimal results.

While a similar suite of data and tools exists for B-cell/antibody epitopes, they are outside of the scope for the present article. Moreover, details of curation process used to capture data from the literature (Vita et al., 2008), development of a formal ontology to represent the immune epitope data (Sathiamurthy et al., 2005), all available prediction and analysis tools (Zhang et al., 2008), and recent updates to the database structure (Vita et al., 2010) are described elsewhere. We here present a summary of the currently available resources in the IEDB that are related to T-cell epitopes.

Multiple applications can benefit from identifying T-cell epitopes, including the design of prophylactic vaccines (Kaech et al., 2002; Sette and Fikes, 2003; Purcell et al., 2007), therapeutics (Bousquet et al., 1998; Banchereau and Palucka, 2005), diagnostics (Brock et al., 2004; Pai et al., 2008), reagents for research (Altman et al., 1996), and de-immunization of biological drugs (Bryson et al., 2010). Designing vaccines against infectious agents is the most frequent application that can benefit from knowing T-cell epitopes. Basically, for a vaccine to induce the creation of a memory T-cell population capable of recognizing a pathogen, the vaccine has to contain T-cell epitopes from that pathogen. This does not mean that the vaccine itself has to be comprised of individual epitopes, but minimally that antigens that harbor the epitopes are being included. In the case of therapeutics (sometimes also called therapeutic vaccines), the goal is to modulate an existing immune response that either needs to be enhanced (cancer, chronic infection), or reduced (autoimmune diseases, allergy). Again, designing such a therapeutic requires knowing the epitope targets of the T-cell responses that are intended to be modulated. For

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doi:10.1016/j.jim.2010.10.010

diagnostics, the goal is to identify if a patient has been in contact with certain antigens in order to help identify a patient's disease status. The use of epitopes as diagnostics has the potential to distinguish infections with related pathogens, which can be difficult when relying on whole organism or antigen preparations, which can often be cross-recognized. Finally, a major application of T-cell epitopes is their direct use as reagents for basic research, as they allow tracking specific T-cell populations, notably in the form of MHC tetramers.

As more protein based drugs are developed, minimizing immunogenicity of these drugs becomes another important application of T-cell epitope identification. The term 'de-immunization' has been coined to refer to a set of technologies that reduce immunogenicity by removing T-cell epitopes from protein therapeutics (Jones et al., 2009). The procedure entails first identifying epitopes and their anchor residues for HLA binding, applying point mutations to these anchor residues to neutral ones such that mutations do not interfere with folding and function of proteins, and finally carrying out validations to confirm absence of immunogenicity of the mutated proteins (Scott and De Groot, 2010). The general T-cell epitope identification tools in the IEDB can be applied to this problem, but currently no dedicated tools exist in the IEDB to e.g. suggest what mutations in a protein drug are recommended.

Following the overview of resources in the IEDB, we present examples of applications how the IEDB can be used to 1) discover conserved epitopes in a novel antigen, and 2) predict novel epitopes to facilitate vaccine design. Overall, this article provides examples on how the IEDB data and tools can be used effectively for practical experimental applications, and addresses commonly encountered issues.

2. Overview of T-cell epitope related resources available in the IEDB

2.1. Data contained in the IEDB

The IEDB provides a catalog of experimentally characterized T-cell epitopes, as well as data on Major Histocompatibility Complex (MHC) binding and MHC ligand elution experiments. These three types of experimental data differ in what they convey: While MHC binding data shows a molecular association between a ligand (typically a peptide) and an MHC molecule, MHC ligand elution data shows that the eluted ligand is not only capable of binding an MHC molecule, but can also be created by the cellular antigen processing machinery. T-cell epitope mapping experiments, on the other hand, test the ability to engage a T-cell receptor (TCR), which requires binding to an MHC molecule and activation of the TCR. The IEDB represents the molecular structures tested for MHC binding, MHC ligand elution or T-cell recognition, and the details of the experimental contexts in which these molecules were tested. Only peptides that test positive in a T-cell recognition assays are truly 'T-cell epitopes', while those that are only shown to be positive in a binding assay should be referred to as 'MHC binders' and those that can be eluted from MHC on the cells surface are 'naturally processed ligands'. Epitopes recognized in humans, nonhuman primates, rodents, pigs, cats and all other tested host species are included in the IEDB. Moreover, both positive and negative experimental results are captured. Lastly, the scope of the database to date includes data relating to epitope derived from all infectious diseases, including NIAID Category A, B and C priority pathogens (http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/research/CatA.html), NIAID Emerging and Reemerging infectious diseases (http://www3.niaid.nih.gov/topics/emerging/), allergens, and autoantigens involved in autoimmune disorders. In particular, HIV epitopes are explicitly excluded, which can instead be found in the Los Alamos HIV Molecular Immunology Database (http://www.hiv.lanl.gov) (Korber et al., 2006).

Since the IEDB was initiated 4 years ago, the data from 158,067 T-cell, 198,877 MHC binding, and 2007 MHC ligand elution assays have been collected through either manual curation or direct submissions. Curated data from the literature covers 99% of all publicly available journal articles on peptidic epitopes mapped in infectious agents (excluding HIV) and 97.7% of those mapped in allergens. In addition, the curation of epitopes related to autoimmunity is expected to be completed by the end of 2010. In terms of direct submissions, 194,862 assays were submitted by investigators to the IEDB that would otherwise be unavailable to the public. Table 1 provides an overview of the journal articles available in each of the main categories of peptidic epitopes included in the IEDB and their level of completion.

2.2. Query interfaces

The query interface of the IEDB has been completely redesigned in early 2009 for the IEDB 2.0 release (Vita et al., 2010). For instance, more frequently used query features are prominently displayed in the left panel of the home page (Fig. 1). The query interface is divided into epitope structure (to query by e.g. peptide sequence), epitope source (to query by the antigen or organism in which an epitope is contained) and immunological contexts (to query by the type of assay, host organism of the response, or MHC restriction). The user can for example search for any epitope contained in Influenza A viruses that is recognized in a T-cell assay by human effector cells and restricted by MHC class II molecule. The results of this query are presented in Fig. 2. For users with the need to perform more detailed queries, an advanced query mode is provided through the 'Search' menu item, allowing one to search any field in the database. In addition, epitope entries can be 'browsed' using features such as MHC alleles or

Table 1
Main curation categories of peptidic entries in the IEDB.

Main Category	Total number journal articles	% Processed
Infectious diseases	8616	99
Allergens	741	97.7
Autoimmune	3924	84.1
Transplants/Alloantigens	631	20.4

For each category, a broad PubMed query was carried out to retrieve all journal articles of potential relevance. These article abstracts were then scanned using a combination of automated and manual text classification to filter out false positives, resulting in the numbers shown in the second column. Any epitopes from these articles were then manually curated into the IEDB. The percentage completion of the manual curation process in each category to date is shown in the last column.

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