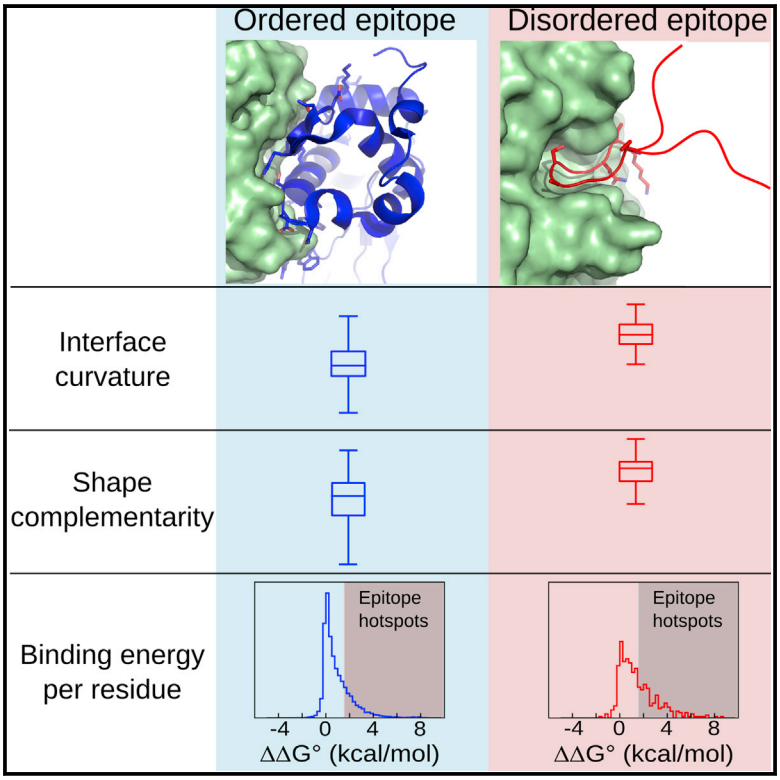
Article

Structure

Antibody Recognition of Disordered Antigens

Graphical Abstract



Highlights

- Disordered antigens are bona fide targets of antibody recognition
- Disordered epitopes are smaller, but more efficient, than ordered epitopes
- Recognition of disordered epitopes is more sensitive to epitope sequence variation
- Distribution of hotspots in the disordered antigen-antibody interface is asymmetric

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In Brief

MacRaild et al. examine the molecular basis for the antibody recognition of disordered antigens, finding that disordered proteins are frequent targets of high-affinity antibodies. Structural details of these interactions are revealed, shedding light on the interplay between conformational disorder and the specificity of molecular recognition.

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Antibody Recognition of Disordered Antigens

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SUMMARY

Disordered proteins are important antigens in a range of infectious diseases. Little is known, however, about the molecular details of recognition of disordered antigens by their cognate antibodies. Using a large dataset of protein antigens, we show that disordered epitopes are as likely to be recognized by antibodies as ordered epitopes. Moreover, the affinity with which antigens are recognized is, unexpectedly, only weakly dependent on the degree of disorder within the epitope. Structurally defined complexes of ordered and disordered protein antigens with their cognate antibodies reveal that disordered epitopes are smaller than their ordered counterparts, but are more efficient in their interactions with antibody. Our results demonstrate that disordered antigens are bona fide targets of antibody recognition, and that recognition of disordered epitopes is particularly sensitive to epitope variation, a finding with implications for the effects of disorder on the specificity of molecular recognition more generally.

INTRODUCTION

There is an increasing recognition that many proteins naturally lack a defined folded state, and that their function depends instead on conformational disorder (Dunker et al., 2002; Wright and Dyson, 2015). These intrinsically disordered proteins are widespread in nature and are abundant in a range of pathogenic organisms. Several parasite species have an unusually high proportion of disordered proteins (Feng et al., 2006), and although the extent of disorder in viral proteomes is highly variable, some are predicted to be extensively disordered (Xue et al., 2014). Nonetheless, the implications of protein disorder for immune recognition by B cells and antibodies have received remarkably little attention.

On the one hand, it has been suggested that intrinsically disordered proteins will elicit weak immune responses or even be completely non-immunogenic (Dunker et al., 2002). This argument is based in part on the fact that disordered proteins often adopt relatively well-defined conformations when bound to partner proteins or to antibodies, and that this is achieved by a process of coupled folding and binding, which places both kinetic and thermodynamic constraints on the interaction (Uversky, 2013). As a result, the interactions of disordered proteins are often of relatively low affinity, despite maintaining high specificity. These properties are ideally suited to mediators of signals that must be switched on or off rapidly, and, accordingly, disorder is particularly common in proteins involved in signal transduction (Wright and Dyson, 2015). They are quite distinct, however, from the properties of typical antibody-antigen interactions, which are selected for high affinity. Consistent with the argument that disordered proteins may be poor immunogens, it has been observed that functionally important sites on protein antigens are often highly flexible, or are surrounded by flexible loops (Colman, 1997; Kwong et al., 2002; MacRaild et al., 2011); this flexibility is proposed to serve as a means of immune evasion, with "conformational masking" being mediated by the entropic cost of inducing order in the otherwise flexible antigen (Kwong et al., 2002).

In sharp contrast, however, disordered antigens can be immunodominant. In some instances these antigens, despite their immunodominance, fail to contribute to immune protection, and thus are believed to function as a "smokescreen", diverting the immune system from targets with greater protective potential (Kemp et al., 1987). Nonetheless, numerous B-cell epitopes have been characterized in disordered proteins, and many of these appear to contribute to functional immune responses and therefore represent potential vaccine candidates (Adda et al., 2012; Foquet et al., 2014; Foucault et al., 2010; Olugbile et al., 2009; Raj et al., 2014; Yagi et al., 2014). For example, the protective effects of the most advanced malaria vaccine, RTS,S, appear to be mediated by antibodies to the disordered repeats of the circumsporozoite protein (Dyson et al., 1990; Foquet et al., 2014).

To explore the implications of disorder for antibody recognition, we have examined the immune epitope database (IEDB) (Vita et al., 2015) for the presence of antigens that are predicted to be disordered. We find that disordered antigens are no less likely than ordered antigens to be recognized by antibodies, and that the affinity of the antibody-antigen interaction is only weakly dependent on epitope disorder. Using a dataset of structurally defined antibody-antigen complexes, we reveal structural features that contribute to the unexpectedly high affinity of the interactions between disordered antigens and their cognate antibodies.

RESULTS

Disordered Proteins Are Common Targets of Antibody Responses

Although there is increasing awareness of the importance of disordered antigens in the immune response to a number of

