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Critical assessment of approaches for molecular docking to elucidate associations of HLA alleles with adverse drug reactions

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ABSTRACT

Adverse drug reactions have been linked with genetic polymorphisms in HLA genes in numerous different studies. HLA proteins have an essential role in the presentation of self and non-self peptides, as part of the adaptive immune response. Amongst the associated drugs-allele combinations, anti-HIV drug Abacavir has been shown to be associated with the HLA-B*57:01 allele, and anti-epilepsy drug Carbamazepine with B*15:02, in both cases likely following the altered peptide repertoire model of interaction. Under this model, the drug binds directly to the antigen presentation region, causing different self peptides to be presented, which trigger an unwanted immune response. There is growing interest in searching for evidence supporting this model for other ADRs using bioinformatics techniques. In this study, in silico docking was used to assess the utility and reliability of well-known docking programs when addressing these challenging HLA-drug situations. The overall aim was to address the uncertainty of docking programs giving different results by completing a detailed comparative study of docking software, grounded in the MHC-ligand experimental structural data – for Abacavir and to a lesser extent Carbamazepine - in order to assess their performance. Four docking programs: SwissDock, ROSIE, AutoDock Vina and AutoDockFR, were used to investigate if each software could accurately dock the Abacavir back into the crystal structure for the protein arising from the known risk allele, and if they were able to distinguish between the HLA-associated and non-HLA-associated (control) alleles. The impact of using homology models on the docking performance and how using different parameters, such as including receptor flexibility, affected the docking performance were also investigated to simulate the approach where a crystal structure for a given HLA allele may be unavailable. The programs that were best able to predict the binding position of Abacavir were then used to recreate the docking seen for Carbamazepine with B*15:02 and controls alleles.

It was found that the programs investigated were sometimes able to correctly predict the binding mode of Abacavir with B*57:01 but not always. Each of the software packages that were assessed could predict the binding of Abacavir and Carbamazepine within the correct sub-pocket and, with the exception of ROSIE, was able to correctly distinguish between risk and control alleles. We found that docking to homology models could produce poorer quality predictions, especially when sequence differences impact the architecture of predicted binding pockets. Caution must therefore be used as inaccurate structures may lead to erroneous docking predictions. Incorporating receptor flexibility was found to negatively affect the docking performance for the examples investigated. Taken together, our findings help characterise the potential but also the limitations of computational prediction of drug-HLA interactions. These docking techniques should therefore always be used with care and alongside other methods of investigation, in order to be able to draw strong conclusions from the given results.

1. Introduction

An adverse drug reaction (ADR) is a harmful or unpleasant reaction, resulting from the use of medicinal products. Type A reactions are those that are dose-related. Idiosyncratic drug reactions (IDRs) or Type B hypersensitivity reactions are dose-independent, occurring in some but not all people (Edwards and Aronson, 2000). The incidence of ADRs has increased globally from 2.2 million in 1994 to 10 million in 2014 (Vazquez-Alvarez et al., 2017). This is therefore a very important issue which needs to be addressed.

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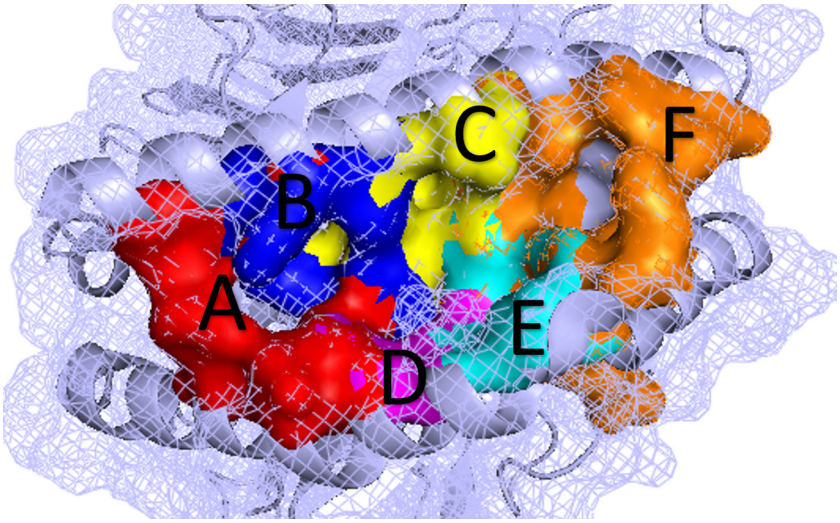

Fig. 1. Organisation of the subsites along the HLA peptide binding groove. The peptide-binding groove of the HLA molecule is separated into 6 different pockets (A–F) (Saper et al., 1991; Sidney et al., 2008), as shown here. Image created using PyMOL (Schrodinger, 2015).

These ADRs have been linked with specific Human Leukocyte Antigens (HLA) in numerous studies, whereby individuals carrying particular alleles of HLA genes are at higher risk of developing adverse reactions to particular drugs (Carr et al., 2013; Tangamornsuksan et al., 2015; Zhou et al., 2015). HLA gene products play a key role in the adaptive immune response, presenting peptides (self and non-self) to a T cell receptor to elicit a response when needed. The HLA system is highly variable, both in individuals and in populations. Individuals carry multiple HLA genes with similar functions: A, B, C in class I, or DRA, DRB, DQA, DQB and others in class II. In general, Class I gene products are responsible for presentation of peptides from pathogens internal to cells, such as viruses. Class II gene products present peptides from extracellular pathogens.

The role of HLA in ADRs has been hypothesised in three main ways. The *Hapten* model predicts that the drug binds covalently to a self protein, and is processed via HLA molecules to the presented peptide; this drug-protein combination then being recognised as being non-self and initiating an immune response. The *Pharmacological Interaction (PI)* model predicts that the drug binds non-covalently, directly to the immune receptors; mainly T-cell receptors or HLA. The *Altered Peptide Repertoire* model states that the drug interacts with the HLA molecule directly and non-covalently, leading to a different self-peptide set being presented, which is recognised as foreign, and thus eliciting the immune reaction (Yun et al., 2016). Illing et al. showed that the Abacavir modifies the anchor residue for the binding peptide in the F-pocket, altering the binding specificity for peptides in B*57:01 but not B*57:03 (Illing et al., 2012).

ADRs are associated with different HLA alleles for numerous different drugs. The 'HLA and Adverse Drug Reactions' database on the Allele Frequency Net Database website (Gonzalez-Galarza et al., 2015; Ghattaoraya et al., 2016) allows users to search for studies showing associations between different HLA alleles and ADRs. The current, most strongly associated ADR is that of Abacavir (an anti-retroviral drug) with HLA-B*57:01. If certain alleles have been significantly associated with ADRs, patients can be screened prior to being given the drug to predict if an ADR is likely to occur. Mallal et al. showed how screening for HLA-B*57:01 alleles can reduce the risk of hypersensitivity reactions in patients receiving Abacavir (Mallal et al., 2008). While there is still some disagreement which of the models best explains how they interact with drugs to cause ADRs, Illing *at al.* and Ostrov *et al.* have demonstrated the Altered Peptide Repertoire model with high confidence for Abacavir, including a crystal structure of Abacavir bound to the antigen presenting region of HLA-B*57:01, as well as proteomics evidence for different peptides being presented than in the unbound case. As a result, many researchers investigating ADRs now work under the assumption that this hypothesis explains a high proportion of HLA ADRs observed, although much debate continues. There is therefore considerable and growing interest in searching for evidence supporting this mode for other ADRs using modelling and bioinformatics techniques, for example using in silico molecular docking (Illing et al., 2012; Carr et al., 2017; Van Den Driessche and Fourches, 2017; Wei et al., 2012; Luo et al., 2015).

Molecular docking is used to predict the preferred orientation of a molecule when bound to another in a stable complex. Most docking programs assume the target to be rigid and allow ligand flexibility (Pagadala et al., 2017). Protein-ligand docking can be used to aid understanding of biological processes and drug design (Lengauer and Rarey, 1996; Gaba et al., 2010). Docking gives a prediction of the structure of the ligand-receptor complex using computational methods by first sampling the conformations of the ligand in the active site and then ranking these conformations using a scoring function as a proxy for the free energy of interaction (Meng et al., 2011).

Molecular docking is being used increasingly commonly for investigating HLA-mediated ADRs (Illing et al., 2012; Carr et al., 2017; Van Den Driessche and Fourches, 2017; Luo et al., 2015; Goldstein et al., 2014; Teh et al., 2016; Hirayama, 2017; Schotland et al., 2016; Isogai et al., 2013; Yang et al., 2015). The HLA structure presents unusual challenges for molecular docking protocols. HLAs bind peptides in a long hydrophobic cleft formed between the α-helices and β-sheet platform. This cleft is much larger than the naturally evolved binding sites that proteins have for small organic molecules. The polymorphic residues located along this cleft determine the size and stereochemistry of the subsites (Zeng et al., 1997). The peptide binding groove contains six subsites (Fig. 1). The specificity of peptide binding is determined in part by the interactions between anchor residues on the peptide side chains and two or more of these subsites (Johansen et al., 1997). Therefore care must be taken when using docking methods to investigate these complex cases. The purpose of this exercise is to compare multiple docking programs to assess their performance on the challenging HLA-ADR cases.

Four different freely available and commonly used programs were used for docking the compounds with the target alleles – SwissDock, ROSIE, AutoDock Vina and AutoDockFR, as follows.

The SwissDock (Grosdidier et al., 2011a) server is an online tool based on the EADock DSS engine using a multiobjective scoring function designed around the CHARMM22 force field and FACTS solvation