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The HLA library for drug screening in preventing severe drug hypersensitivity

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Background

The clinical and economic impact of severe drug hypersensitivity is huge for both healthcare and pharmaceutical industry; however, no method for predicting culprit candidate t drugs under clinical development exists currently. As genetic variants in human-leukocyte antigens (HLA) have been linked to inter-individual differences in the risk of drug hypersensitivity, we ascertained whether HLA library can serve as a drug screening tool for their potential to cause severe drug hypersensitivity.

Method

We cloned and generated stable cell lines expressing one common HLA allele, and then purified each HLA protein genetically linked to particular hypersensitivity, immobilized on a protein chip and analyzed the interaction between HLA and drugs by surface plasmon resonance (SPR) analysis.

Results

With HLA library coating on the chip, the direct interaction between specific HLA protein complexes and culprit drugs were detected by SPR analysis. For example, HLA-B*1502 protein interacted with aromatic anti-epileptic drugs, such as carbamazepine (CBZ), CBZ analogs (10,11-eposide CBZ, oxcarbazepine, licabazepine and eslicarbazepine), phenytoin (PHT), and lamotrigine (LTG), but not structure-unrelated compounds, such as gabapentin (GBP), levetiracetam (LEV), and topiramate (TPN); In addition to HLA-B*1502, other HLA-B75 members could also present CBZ, whereas HLA-B62 and HLA-B72 members could not, consistent with pharmacogenetic data. Moreover, HLA-B*5801 binds to allopurinol and oxypurinol, but not febuxostat. Similar, HLA-B*5701 could interact with the nucleoside reverse transcriptase inhibitor, abacavir, but not the non-nucleoside reverse transcriptase inhibitor, nevirapine.

Conclusion

These data suggested the possibility of using HLA library which contains different HLA molecules for its ability to bind drug as a screen tool to screen drugs for their potential to cause severe drug hypersensitivity.

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