Abstract of Presentation

Note: This paper should be typed in "Times New Roman" of 12pt.

Presentation Title(Should be no more than 20 words):

Exploring genetic basis of GvHD by whole-genome association studies using a cohort from the Japan Marrow Donation Program (JMDP)

Abstract :

Allogeneic stem cell transplantation (allo-SCT) is one of the most effective therapeutic options for blood cell cancers. While its major therapeutic benefits are obtained from allo-immune reactions against leukemic cells, or GVL, the same kind of allo-reactions could be also directed to normal host tissues, giving rise to a severe complication, know as GvHD. In HLA-matched transplantation, the development of both reactions absolutely depends on the presence of one or more mismatched minor histocompatibility antigens (mHags) and could be further modified by other genetic as well as environmental factors, including for example, cytokine polymorphisms and GvHD prophylaxis. Thus, in view of better preventing GvHD and specifically targeting allo-immunity to the tumor component, it is critical to understand what mHAgs are responsible for the development of GVHD or GVL and what genetic factors can influence the overall reactions. To address these questions, we conducted whole genome association studies by genotyping more than 500,000 SNPs in donors and recipients of 1598 unrelated transplants from Japan Marrow Donation Program (JMDP). All transplants were matched for HLA-A, B, C, DRB1 and DQB1, while 1033 (63%) transplants were mismatched for HLA-DPB1. 656 (41.7%) and 245 (14.9%) of transplants had developed >grade II and >gradeIII of acute GvHD (aGvHD), respectively. Statistical thresholds for genome-wide-P value of 0.05 were determined empirically by doing 1,000 permutations for each analysis. In the analysis of mismatched genotypes, SNPs around the HLA-DPB1 locus showed a strong association with the development of >grade II aGvHD with the maximum P-value of 1.81×10^{-9} at rs6937034, and thus, successfully captured the association of DPB1 allele mismatch as directly defined by HLA typing (HR = 1.91, P= 2.88×10^{-13}). To facilitate target mHags for aGvHD, we performed subgroup analysis, where analysis was confined to those transplants sharing particular HLA types based on the fact that recognition of mHags is restricted to particular HLA contexts (HLA restriction). Six loci was identified as candidate mHag loci, including rs17473423 on chr12 associated with an A*2402/B*5201/C*1201/DRB1*1501/DQB1*0601 allele shared in ~40% of unrelated transplants in Japanese (>grade III aGvHD with maximum P=3.99×10^{-13}), rs9657655 on chr9 associated with another common allele in Japanese, A*3303/B*4403/C*1403 (>grade III aGvHD with maximum P=8.56×10^{-10}), and other four loci associated with DQB1*0501, C*0102, B*5201, and C*1202. Two SNPs in patients were also found to be associated with aGvHD, rs5998746 on chr22 (P=3.41×10^{-8}) and rs11873016 on chr18 (P=1.26×10^{-8}), although no donor SNPs showed significant associations). Current study provided a unique opportunity, in that combination of two different genotypes, not merely genotypes of single individuals, that is associated with particular disease phenotypes, is explored by whole genome association scans. Although further replication studies and biological confirmation are required, our results suggest that whole genome association studies of allo-SCT could provide a novel clue to our understanding of genetic basis of allo-SCT.