

Modeling disease in human ESCs using an efficient BAC-based homologous recombination system.

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Public Summary:

Scientific Abstract:

Although mouse models have been valuable for studying human disease, the cellular and physiological differences between mouse and human have made it increasingly important to develop more relevant human disease models for mechanistic studies and drug discovery. Human embryonic stem cells (hESCs), which can undergo unlimited self-renewal and retain the potential to differentiate into all cell types, present a possible solution. To improve the efficiency of genetic manipulation of hESCs, we have developed bacterial artificial chromosome (BAC) based approach that enables high efficiency homologous recombination. By sequentially disrupting both alleles of ATM or p53 with BAC targeting vectors, we have established ATM(-/-) and p53(-/-) hESCs as models for two major human genetic instability syndromes and used the generated cells to reveal the importance of p53 in maintaining genome stability of hESCs. Our findings suggest that it will be feasible to develop genetically modified hESCs as relevant human disease models.

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