Abstract

Changes of gene expression profile are one of the most important biological responses in living cells after ionizing radiation (IR) exposure. Although some studies have shown that genes up-regulated by IR may play important roles in DNA damage repair, the relationship between the regulation of gene expression by IR, particularly genes not known for their roles in double-strand break (DSB) repair, and its impact on cytogenetic responses has not been well studied. The purpose of this study is to identify new roles of IR inducible genes in regulating DSB repair and cell cycle progression. In this study, the expression of 25 genes selected on the basis of their transcriptional changes in response to IR was individually knocked down by small interfering RNA in human fibroblast cells. Frequency of micronuclei (MN) formation and chromosome aberrations were measured to determine efficiency of cytogenetic repair, especially DSB repair. In response to IR, the formation of MN was significantly increased by suppressed expression of five genes: Ku70 (DSB repair pathway), XPA (nucleotide excision repair pathway), RPA1 (mismatch repair pathway), RAD17 and RBBP8 (cell cycle control). Knocked-down expression of four genes (MRE11A, RAD51 in the DSB pathway, SESN1, and SUMO1) significantly inhibited cell cycle progression, possibly because of severe impairment of DNA damage repair. Moreover, decreased XPA, p21, or MLH1 expression resulted in both significantly enhanced cell cycle progression and increased yields of chromosome aberrations, indicating that these gene products modulate both cell cycle control and DNA damage repair. Nine of these eleven genes, whose knock-down expression affected cytogenetic repair, were up-regulated in cells exposed to gamma radiation, suggesting that genes transcriptionally modulated by IR were critical to regulate IR-induced biological consequences. Furthermore, eight non-DBS repair genes showed involvement in regulating DSB repair, indicating that successful DSB repair requires both DSB repair mechanisms and non-DSB repair systems. These results reveal that many genes play previously unrecognized roles in multiple DNA repair responses, all of which are required for successful repair of IR-induced damage.