Hematopoietic stem cells (HSC) constitute a rare population within the bone marrow (BM) which actively maintains continuous production of all mature blood cell-lineages throughout life. They are finely regulated to respond rapidly and specifically to modifications of the number of circulating cells or to environmental modifications such as radiation exposure. Although a marked sensibility to radiation exposure of these cells has been reported, little is known about the underlying mechanisms. To understand at the molecular level the cell-dependent IR response, phenotypical and transcriptional changes occurring in stem cells were monitored following exposure to total body irradiation at 2Gy, 3Gy, 6Gy, in a kinetic study from 1 hour up to 60 days. Different stem cell populations were isolated using combinations of surface molecules such as Lin-/low Sca+ C-Kit+ (LSK) with or without CD150+ and CD135+. Our results show that cells with this phenotype were completely eradicated 48h after radiation exposure. Microarray analysis showed that as early as 1 hour after radiation exposure stem cells elicit a specific damage response mostly triggered by the modulation of apoptotic genes. Many genes identified were never described before as playing a role in the IR response. Moreover, QT clustering of expression profiles and subsequent promoter analysis of co-clustered genes reveal several novel P53 co-regulated genes. The induction of these genes after radiation exposure was impaired in mutant mice deficient for P53. Two months after 3 Gy or 6 Gy TBI, the BM cellularity was back to normal but the percentage of LSK cells was reduced and the proportion of LSK subsets expressing CD150+ and CD135+ was modified in a dose-dependent manner. Moreover, HSC presented a major defect in their long-term reconstitution potential that aroused from a blockage in their differentiation potential. This blockage can be partially abrogated by the administration of thrombopoietin. Novel actors in this signalling pathway were identified and will be presented. These results demonstrate that irradiation, on the one hand, kill a vast majority of cycling cells in the BM by the early onset of genetic network of apoptotic genes, and on the other hand affect quiescent HSC in a cell-autonomous but reversible manner. Altogether our approach help producing a more complete knowledge of the molecular mechanisms of the stem cell radiation response by unraveling molecular networks and finding novel and specific molecules involved in this process. This information might facilitate the derivation of clinically useful targets for patient benefit.