

can thus conclude that translocations in our model are mainly due to alternative NHEJ.

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S-5. MDM2 ubiquitin-ligase down-regulate energy metabolism of cancer cells

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MDM2 is an E3 ubiquitin ligase that is controlled by p53, one of the most important tumor suppressors. At the same time, MDM2 targets p53 for ubiquitin-dependent degradation. This mechanism, which protects normal cells from excessive p53-induced death, is frequently deregulated in different types of tumors. MDM2 also has p53-independent oncogenic functions. Besides p53, MDM2 ubiquitinylates a number of proteins, including the catalytic subunit of

telomerase (hTERT), transcription factors Snail and Slug, *etc.* Thus, MDM2 possesses both tumor promoting and tumor suppressing functions, depending on a particular cellular context. To uncover additional targets of MDM2, we carried out a proteomic study in which GST-MDM2 was used as a bait to pull-down interacting proteins, which were then identified by mass-spectrometry (LC-MS/MS). Whole cell extracts derived from U2OS (human osteosarcoma) cells, MCF7 (breast carcinoma, luminal subtype) were used as a source of proteins that potentially bind MDM2. According to the data obtained, we consistently observed a significant number of various metabolic enzymes among the proteins interacting with MDM2. Importantly, they are the key enzymes of glycolysis, and are frequently deregulated in different cancers. We have verified interactions of MDM2 with several enzymes identified and investigated the influence of MDM2 on their expression, ubiquitination and stability. Moreover, we have shown that MDM2 affects the metabolic state of cancer cells, as well as their susceptibility to several pharmacological inhibitors of corresponding metabolic pathways. Taken together, these data revealed a novel role for MDM2 ubiquitin ligase in the regulation of cancer-related metabolic pathways. The common set of metabolic alterations is considered now as one of the “hallmarks of cancer” and the corresponding enzymes are considered as promising targets for anticancer therapeutics. These notions emphasize the importance of MDM2 for cancer metabolism and warrants further investigations.

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