1.1 Abstract

Prohibitin is a ubiquitously expressed protein, highly conserved throughout evolution. Although originally identified by its ability to inhibit G_1/S progression in human fibroblasts, which was later ascribed to its 3'UTR, its role as a tumor suppressor is still debated.

In the present study the function of prohibitin 1 in the maintenance of cell homeostasis was investigated by generating cancer cell lines in which prohibitin expression could be down-regulated *via* doxycycline induced shRNA expression. It was now shown for the first time that prohibitin protein is necessary for the proliferation of cancer cells. Loss of prohibitin expression by shRNA-mediated mRNA knockdown reduces the rate of division remarkably, without affecting the cell cycle progression. Most interestingly, reduction in prohibitin expression led to the complete loss of anchorage-independent growth of certain cancer cells. Moreover, these cancer cells showed reduced adhesion to the extracellular matrix, which suggests that metastasis could be hampered in these cells. Taken together, these observations point to a crucial role of prohibitin in cancer cell propagation and survival, making it an ideal target for new therapeutic approaches.

Besides playing a role in cancer propagation, prohibitin 1 was found to be a protein that stabilizes mitochondrial proteins when it is in a complex with its homologue prohibitin 2. Loss of the complex stability by the reduced expression of one of the two prohibitin proteins resulted in an increase in mitochondrial fragmentation. OPA1, a mitochondrial fusion protein that is expressed as five isoforms, showed a decrease in the expression of its fusion competent isoforms. The resulting increase in mitochondrial fragmentation was in dependence of a strong reduction in prohibitin protein expression. The protease involved in OPA1 processing is m-AAA, and it is this protease that is presumably overactive in prohibitin knockdown cell.

Keywords: prohibitin, proliferation, mitochondria, OPA1, RNAi