Aberrantly upregulated Drp1 induces mitochondrial fission and promotes colorectal cancer cell migration

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Metastasis is the major cause of cancer death. One of the major challenges in the management of cancer is to identify cancer cells with high metastatic potential, and to confine the cancer cells to their current location for destruction once detected. Understanding the molecular mechanism that allows cancer cells to acquire migratory abilities can lead to development of novel therapies. Mitochondria exist as dynamic networks that often change size and distribution, and these dynamics are maintained by two opposing processes: fission and fusion, regulated by Drp1 and mitofusin (Mfn) proteins, respectively. The present study was to investigate the role and mechanism underlying dysregulation of mitochondrial dynamics (unbalanced fission or fusion) in colorectal cancer (CRC), the 3rd leading cause of cancer-related deaths in the United States.

We performed immunohistochemical (IHC) analysis of Drp1 protein expression in commercial microarrays of 266 human CRC specimens and adjacent normal tissues. Average Drp1 staining intensities in carcinoma were increased as compared with normal or adjacent normal tissues (2.34±0.05 vs 1.12±0.08, P<0.001). Drp1 protein expression was further increased in lymph node metastases as compared to carcinoma (2.96±0.13 vs 2.34±0.05, #P<0.01). These data suggest that upregulation of Drp1 mitochondrial fission protein is proportional to the degree of metastasis of these CRCs. We then characterized mitochondrial dynamics in different CRC cell lines. Mitochondria are tubular network-like structures in non-metastatic SW480 cells whereas in metastatic HCT-116 and LoVo cells, mitochondria are short tubules and spheres. Transwell migration assay showed that HCT-116 and LoVo cells have 20-50-fold higher migratory abilities than SW480 cells. Western blot showed that Drp1 was markedly increased in HCT-116 and LoVo cells as compared to SW480 cells. Silence of endogenous Drp1 expression leads mitochondrial elongation and decreases migratory abilities of HCT-116 cells in vitro by over 70% whereas overexpression of recombinant Drp1 induces mitochondrial fragment and promotes SW480 cell migration in vitro. Together, our study may provide a novel strategy to prevent metastasis via target Drp1-dependent mitochondrial fission in CRC patients.

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