Metabolism of saturated fatty acids accelerate Src-mediated prostate tumor progression

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Epidemiological studies suggest that a high fat diet or certain saturated fats are associated with advanced stages and/or mortality of prostate cancer. However, the molecular basis of this association is unknown. We demonstrate that Src kinase modulates prostate tumor growth under a diet high in saturated fatty acids. Knockdown of Src kinase prevented high fat diet-induced tumor growth, whereas a high fat diet significantly accelerated prostate tumorigenesis mediated by overexpression of Src kinase. We present evidence that dietary saturated fatty acids accelerate Src-mediated tumorigenesis by two complementary mechanisms that result in increased Src kinase signaling in detergent resistant membranes. The mechanisms include altering ceramide compositions and elevated myristoylation of Src kinase. The combination of these dual effects accelerated Src-dependent MAPK pathway signaling and prostate tumorigenesis. Targeting myristoylation of Src kinase, which is required for its association at the cellular membrane, inhibited high fat diet accelerated Src-mediated tumorigenesis. Our findings provide a molecular basis for the association of a high fat diet with prostate tumor progression.

Biography

The association between the risk of prostate cancer development and progression and a high fat diet is controversial. We provide evidence that Src kinase, a frequently up-regulated oncogene in prostate cancer mediates high fat diet accelerated tumor progression. We demonstrate a mechanistic understanding of how dietary saturated fatty acids influence Src-mediated prostate cancer progression through alteration of plasma membrane compositions and protein acylation. This study suggests that diet choice can be used as a strategy in modulating tumor progression of cancer patients and provides therapeutic approaches for inhibiting Src-induced cancer progression. For prostate cancer survivors, a diet low in saturated fat may be beneficial in reducing the risk of Src-mediated aggressive prostate cancer.

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