VIEW POINTS
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The Src/PI3K/Akt Signal Pathway May Play a Key Role in Decreased Drug Efficacy in Obesity-Associated Cancer

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Obesity not only results in increased incidence but also leads to poor prognosis of many cancers. The increased cancer incidence in obesity is accounted for by the activation of cellular signal pathways which are carcinogenic such as Src/PI3K/Akt pathway [Chen, 2008; Huang and Chen, 2009b]. However, the mechanism for the poor prognosis in obesity-associated cancer is still unclear. It is an urgent issue required to be solved so that the treatment of obesity-associated cancer can be improved. A possible explanation is that the poor prognosis in obesity-associated cancer is caused by decreased drug efficacy due to the activation of multiple cellular signal pathways. Among these pathways the Src/PI3K/Akt may play a critical role. It is well demonstrated that the Src/PI3K/Akt pathway is activated by multiple cancer risk factors in obesity, while the activation of the pathway has also been shown to associate with decreased drug efficacy. Thus, it will be interesting to further demonstrate the critical role of the pathway in decreased drug efficacy caused by obesity and confirm that the activation of the pathway has lead to poor prognosis in obesity-associated cancer.

EVIDENCE FOR THE POOR PROGNOSIS OF OBESITY-ASSOCIATED CANCER

There are many evidences that obesity can cause poor prognosis of many cancers such as ovarian cancer, leukemia, papillary thyroid cancer, and colon cancer [Dignam et al., 2006; Uddin et al., 2010]. Epidemic studies showed that severe obesity (BMI $>35\,kg/m^2$) caused increased mortality and recurrence of colon cancer [Dignam et al., 2006; Jacobs et al., 2007]. However, it has not been studied if this is related with PI3K and drug efficacy. Obesity has also been shown to lead to poor prognosis in ovarian cancer. Uddin et al. [2009] showed that there is correlation between the poor prognosis of ovarian cancer and the activation of leptin pathway. The increased expression of leptin receptor caused the activation PI3K/Akt which plays a key role in the poor prognosis. However, if it is associated with decreased drug efficacy is not studied. In leukemia, obesity is demonstrated to increase and drug resistance leading to poor prognosis [Behan et al., 2009]. In vitro experiment showed that adipocytes increased drug resistance in the treatment of leukemia. It is not known if it is via PI3K/Akt pathway.

ACTIVATION OF THE SRC/PI3K/AKT SIGNAL PATHWAY IN OBESITY

The Src/PI3K/Akt pathway is highly activated by multiple cancer risk factors which are elevated in obesity [Jaffe and Schwartz, 2008; Huang and Chen, 2009b]. These factors include increased blood levels of insulin, IGF-1, leptin, TNF-alpha, and IL-6. These factors have been demonstrated to activate Src/PI3K/Akt to promote carcinogenesis [Jaffe and Schwartz, 2008; Roberts et al., 2009; Huang and Chen, 2009b]. In addition, decreased blood level of adiponectin in obesity also contributes to the action of the pathway as adiponectin can block insulin and leptin [Fujisawa et al., 2008; Huang and Chen, 2009a]. Recently, IL23/17 has also been shown to be activated in obesity which in turn activates the Src/PI3K/Akt pathway [Hsieh et al., 2002; Sumarac-Dumanovic et al., 2009].

THE ROLE OF THE SRC/PI3K/AKT PATHWAY IN DECREASED DRUG EFFICACY

Src has been demonstrated to be responsible for inherent and acquired oxaliplatin resistance in colon cancer and the inhibition of Src by dasatinib has been shown to synergize the effect of oxaliplatin [Kopetz et al., 2009]. In human renal cancer cells, the activation of the PI3K/Akt has been demonstrated to increase the cancer cells resistant to oxaliplatin [Kim et al., 2008b]. Evidence also showed that the activation of the PI3K/Akt pathway increases resistance to cisplatin in ovarian cancer cell line [Lee et al., 2005]. The down-stream of the Src/PI3K/Akt pathways Bcl2, Bad, and Pim have also been associated with decreased drug efficacy caused by isolated adipocytes from obesity [Behan et al., 2009]. However, to fully understand the mechanism of decreased drug efficacy in

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obesity, it may be necessary to test the change of the Src/PI3K/Akt pathway caused by adipocytes.

THERAPEUTIC IMPLICATIONS

Due to the important role of the Src/PI3K/Akt in the decreased drug efficacy in obesity-associated cancer, the inhibition of the signal pathway may have clinical implication. The use of the inhibitors of the pathway may overcome the decreased drug efficacy. It could have synergistic effect with chemotherapy drugs. It has been demonstrated in cholangiocarcinoma cells, the inhibition of PI3K increased oxaliplatin cytotoxicity [Leelawat et al., 2009]. In colon cancer, inhibition of PI3K has also been shown to increase the cytotoxicity of low dose of BBR3610 [Mitchell et al., 2007]. Inhibition of the down-stream protein of the Src/PI3K/Akt pathway bcl2 by sanguinarine caused apoptosis and sensitize the TRIAL-mediated apoptosis in breast cancer cells [Kim et al., 2008a].

CONCLUSIONS

In conclusion, a possible explanation for poor prognosis of obesity-associated cancer is activation of the Src/PI3K/Akt by multiple cancer risk factors like insulin, IGF-1, leptin, IL-6, IL-17, IL-23, TNF-alpha, which in turn reduces chemotherapy efficacy. Inhibition of the Src/PI3K/Akt pathway should have therapeutic implications to improve the treatment of obesity-associated colon cancer and warrant further study.

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