Abstract

Obesity is one of the most important public health problems across the globe. It is characterized by increased accumulation of fat in the body. Due to increasing affluence of people and booming economy, the number of overweight and obese people is likely to increase in India as well as all over the world. Many epidemiological studies have shown a possible link between obesity and risk of cancers as documented by International Agency for Research on Cancer (IARC). More than 20% of all cancers are attributed to obesity and overweight. In addition, obesity is associated with poor prognosis and outcome of cancer therapy. Obesity-associated factors are purported to promote growth, survival, proliferation and invasiveness of cancer cells. However, the mechanistic link between obesity and cancers is poorly understood. Melanoma is the deadliest form of skin cancer. Since it lies in the close proximity of subcutaneous layer of skin, we used melanoma as a relevant model to unravel obesity-cancer connection.

In the first part, we studied the impact of controlling obesity (by pharmacological or dietary intervention) on melanoma progression in diet-induced obese (HFD) C57BL/6J and NOD/SCID mice, and the molecular events involved. We found that melanoma progression was significantly reduced in HFD mice treated with orlistat or in those shifted from high fat diet to normal diet. The diminished tumor progression was associated with reduction in body weight/fat mass, and normalization in obesity-associated parameters. At molecular level, it was found that reduction in tumor progression in HFD mice was associated with reduced levels of activated Akt, FASN and Cav-1 in tumors upon employing weight control interventions. These findings suggest that controlling adiposity could reduce the obesity-induced rapid progression of melanoma, and possibly in other cancer types.

In the second part, we intended to study the role of obesity on the outcome of melanoma chemotherapy in C57BL/6J mice. To understand the impact of controlling obesity on the outcome of dacarbazine (DTIC) therapy in melanoma, we employed weight control interventions in conjunction with DTIC
therapy. We observed that diet-induced obesity impaired the response of melanoma to DTIC therapy. The impaired response to DTIC was associated with increased levels of FASN, Cav-1 and P-glycoprotein (P-gp) in tumors. Obesity caused the reduction in the accessibility of DTIC to tumors. The impaired response to DTIC was significantly improved upon using weight control interventions in HFD mice. These findings were also confirmed by performing suitable in vitro studies. Therefore, it is of clinical relevance that obesity management is critical for chemotherapeutic outcome of obesity-promoted malignancies. These findings suggest that there is a need of reconsideration of dosing pattern complemented with interventions that reduce adiposity in the better management of such cancers.

In the third and last part, we studied the role of important adipokines leptin and resistin in melanoma growth. Both of these are the major adipokines elevated in obesity. We found in vitro that both these adipokines enhanced proliferation of A375 melanoma cells. Both leptin and resistin treatment not only caused activation of Akt but also enhanced the protein levels of FASN and Cav-1 respectively by their stabilization in A375 cells. Further, we observed that these leptin and resistin caused impaired response of melanoma cells to DTIC in vitro via upregulation of heat shock protein 90 (Hsp90) and P-gp. The role of leptin in impairing the response to DTIC was also confirmed through in vivo studies in ob/ob and db/db mice. These findings unraveled the role of these adipokines (leptin and resistin) in melanoma progression, and more importantly in the outcome of DTIC therapy.

Overall, the present study is a cumulative effort towards mechanistic understanding how obesity and obesity-associated factors contribute to increased melanoma progression, and worsen the outcome of chemotherapy though modulation of key molecules and signaling pathways. As an offshoot of this work, the study provides a link between controlling obesity and melanoma progression through involvement of obesity-associated factors. Therefore, translational strategic means of controlling adiposity may render obesity-promoted tumor progression in check, improve chemotherapeutic outcome, and prolong the survival of obese cancer patients.