SESSION 4

Prospects of Surrogate Endpoints and Biomarkers in Cancer Prevention

S11. IGF-Related Signalling and Cancer Development

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Insulin-like growth factors and insulin initiate signal transduction in pathways such as PI3K → AKT → mTOR → s6K and also MAPK that are key components of the networks that control cell survival and proliferation. The first prospective population study linking IGF-I circulating levels to subsequent cancer risk was reported in 1998 [1], and stimulated a great deal of followup laboratory and population research, much of which has been recently reviewed [2]. We will present examples of results obtained in the last few months.

IGF-I levels and risk: Large meta-analyses have in general confirmed the association of higher IGF-I levels with increased risk of common epithelial cancers, particularly for prostate and colon cancer. An update [3] of our original study that involved only 152 cases and 152 controls [1] involves 762 cases and 762 controls, and largely confirms the original trend, although with the larger sample size, we now have evidence that the higher levels are not associated with risk for 'all' prostate cancer, but rather are associated specifically with increased risk of more aggressive prostate cancer. These data suggest that individuals with higher IGF-I levels may have increased rates of 'neoplastic progression' rather than (or in addition to) alterations in early steps of carcinogenesis. Many groups are now exploring the genetic basis for the inter-individual variation in IGF-I levels that influence cancer risk, and several SNPs, some known to be functional [4], are indeed associated with both circulating levels and with risk [5].

Insulin receptors and metabolic influences on cancer risk and prognosis: There is increasing evidence from several independent studies that obesity and insulin resistance syndromes are associated with modest increase in cancer risk, but significantly decreased time to progression and increased mortality. We have been able to obtain some of these data by examining metabolic factors associated with poor outcome in adjuvant therapy trials. Several candidate molecular mechanisms are under investigation, but the simplest involves direct stimulation by insulin of insulin and/or hybrid insulin-IGF-I receptors on neoplastic cells. Several groups are addressing an important gap in knowledge concerning the role of insulin receptors on normal and transformed epithelial cells of breast, colon, and prostate; insulin receptor signal transduction in these cell types may have different consequences than in classic insulin sensitive tissues such as liver, fat, and muscle. Leptin is another candidate hormone than may influence cancer behaviour. Preliminary laboratory results show that genetic or dietary manipulation of mice can influence the mitogenicity of murine serum for human neoplastic cells in vitro, suggesting that metabolic "host" prognostic factors (as distinct from better described "tumor" factors such as PTEN deletion or HER2 amplification) influence outcome. Some of these factors may be pharmacologically modifiable.

Targeting pathways downstream of the IGF-I and insulin receptors: Following preclinical evidence for attenuation of neoplastic behaviour by targeting the IGF-I receptor, several drug development programs were initiated, and there are now IGF-IR blocking drug candidates from Pfizer, Imclone, and many others entering phase I clinical trials, as well as several promising small molecule tyrosine kinase inhibitors in advanced preclinical development. We have shown that metformin, known to reduce insulin levels systemically by reducing hepatic glucose output, also activates the LKB1/AMPK cellular energy sensor in neoplastic epithelial cells, simulating cellular energy deprivation and acting via blockade of mtor and other mechanisms to reduce protein synthesis and proliferation. Drugs of this class may have roles in enhancing adjuvant therapy or prevention strategies, particularly for subjects with markers of insulin resistance.

References

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