Saturday 24 September 2011

Opening Session (Sat, 24 Sep, 09:00−11:00)

1 INVITED

Metabolism and Cancer

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Cancer cells must fulfill the three basic metabolic requirements for rapid cell growth: production of useable energy stores as ATP, production of precursors for biosynthesis of macromolecules, and maintenance of an optimal redox balance in the cell. These requirements are often met through mutations in oncogenic signaling pathways that result in dramatic changes to cellular metabolism. These adaptations also synergize with the tumour microenvironment to select for cancer cells with the ability to proliferate under the harsh conditions frequently found in solid tumours, such as hypoxia and limited nutrients. Cells with this ability are said to have undergone “metabolic transformation”, and the metabolic changes that potentiate this growth constitute a characteristic profile.

Rapid cell growth produces high levels of reactive oxygen species (ROS) that can damage the cell. Cells can neutralize such oxidative stress by using NADPH to maintain the activity of antioxidant molecules such as reduced glutathione and thioredoxin. NADPH is thus not only a crucial cofactor for many biosynthetic reactions but also an essential component of intracellular defense against oxidation. The main pathways of NADPH generation are: (1) the pentose phosphate pathway, which is an alternate pathway of glucose utilization that produces ribose sugars; (2) malic enzyme, which converts malate acid to pyruvate; and (3) isocitrate dehydrogenase (IDH), which converts isocitrate to α-ketoglutarate (α-KG).

Recently, specific driver mutations were identified in the IDH gene that alter the activity of its gene product. Instead of catalyzing the conversion of isocitrate into α-KG with the concomitant production of NADPH, the mutant enzyme produces 2-hydroxyglutarate (2-HG) and NADP. Not only is a major metabolic source of NADPH compromised, but 2-HG has been identified as an oncometabolite linked to tumorigenesis. Current studies are focused on determining precisely how these effects of IDH mutation affect cellular metabolism and promote tumorigenic transformation. Increased knowledge of the nature of the metabolic changes that occur in tumour cells will enable the design of anticancer therapeutics that can target these pathways and block aggressive cell growth.

2 INVITED

Personalised Medicine is the Future

Abstract not received

3 INVITED

Challenges to Implementation of Personalised Cancer Therapy

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While personalized cancer therapy through implementation of molecular marker driven targeted therapy holds great promise, there are multiple hurdles, technical, theoretical and cultural, to be overcome before personalized cancer therapy becomes the standard of care. Indeed, while remarkable responses to targeted therapy have been reported, only a subpopulation of patients responds and responses are all too frequently short term with the rapid emergence of resistant clones. More critically, there appear to be cases where targeted therapies make tumours grow faster and in some cases resistant clones appear more aggressive than the primary clone. Further the cost of assessing molecular markers such as sequencing and the cost of targeted therapies that benefit only a few patients constitutes an incredible burden on already strained health care resources. Thus we are far from understanding the challenges and overcoming the pitfalls to the implementation of personalized cancer therapy.

Next generation sequencing (NGS) approaches are held forward as the next great step forward in implementing personalized cancer therapy. Indeed, it is possible to sequence a human genome for under 10,000 dollars and the costs continue to drop rapidly. However, NGS is currently fraught with major problems. As currently implemented, it remains challenging to attain an accurate idea of the mutations, copy number and rearrangements in the patient genome and in particular to determine which changes are relevant. The accuracy of NGS in patient tumours, where there is contamination with normal tissues and likely multiple important subclones, is driven by the depth of sequencing. The cost of 10,000 dollars for a human genome is presupposed on a depth of sequencing of 30−60 fold. Unfortunately at this depth of sequencing, achieving a true positive rate of 60% results in a false positive rate approaching 60%. Both of these are unacceptable for patient management. Further the 10,000 dollars does not include the costs of bioinformatics analysis or data storage and handling. Indeed, it has been estimated that even the eventual 1,000 dollar genome will cost 100,000 dollars to manage and interpret.

We now know that the majority of the aberrations seen in the human genome of a cancer patient are likely to be non-informative. First most of the aberrations present are likely to be “passengers”; a consequence of genomic instability or aberrations in DNA repair, rather than “drivers” where they determine the behavior of the tumour. Further the vast majority of the “drivers” present are not actionable in that they are not druggable or we do not know which drug to use. Further, we now know that even different aberrations in a single gene may have markedly different consequences or the same aberration in two different diseases could indicate markedly different sensitivity to drugs. The current lack of a useful functional genomics platform to link aberrations in a specific patient to the optimal therapeutic intervention is currently the most major limitation to implementation of personalized cancer therapy. As an example, we have yet to find a useful actionable event in patient tumours through NGS.

We now treat a number of cancers based on underlying genetic aberrations. However, we usually base this treatment on tumour material that does not reflect the disease that is currently threatening the patient. For example, the genomic aberrations in a primary tumour may not reflect those in a metastasis or those in a recurrence that happens many years later. Further, each tumour likely contains many important subclones. If we fail to characterize all of the subclones, we may manage only a subset of the tumour and indeed by eliminating the dominant clone could allow a more aggressive subclone to grow out. We already have data that patient with differences between primary and metastases in terms of biomarkers fare far worse than patients without differences. Does this require a biopsy of all metastases and recurrences and a characterization of the genome. This would massively increase the cost as well as be associated with the morbidity associated with repeat biopsies. The goal of replacing biopsies with molecular imaging or characterization of circulating tumour cells or DNA remains a dream; an important dream but a dream nevertheless.

In lieu of an ability to treat individual patients based on the changes in the genomes, we are currently moving towards stratified therapy, treating groups of patients based on similarities in their tumours. This is also fraught with challenges. Indeed, ductal breast cancer, the most common cancer in women is now a set of orphan diseases with at least eight different therapeutically relevant groups. It is now difficult to mount and complete clinical trials based on the underlying genetic aberrations. The ultimate goal of truly individualized cancer therapy is an anathema to the current trial design and regulatory processes.

Finally, resistance to targeted therapies arises all too rapidly in almost all cases. This could be due to errors in molecular analysis, incorrect hypotheses originally, the tumour heterogeneity described above or the induction of regulatory loops that bypass the effects of the drugs. This has led to the concept that we will need to develop rational combinatorial therapies. This however is fraught with its own challenges of increased costs, increased toxicity and difficulty in getting multiple companies to cooperate in clinical trials. The orphan disease problem described above also contributes.

Thus while there is incredible excitement about the potential implementation of personalized cancer therapy, it is easy to contend that the spectacular press and excitement is massively overblown. The number of successes, and in most cases these are only found in small subpopulations of patient and are transient, are far outnumbered by spectacular failures. The attendant cost of implementing personalized cancer therapy has added a massive burden to health care costs at a very minor improvement in outcomes for a small population of patients. We are far from overcoming the hurdles associated with the implementation of personalized cancer therapy.

Oncology Nursing Opening and Award Session (Sat, 24 Sep, 11:00−11:30)

4 EONS Distinguished Merit Award

The Impact of a Maternal Cancer Diagnosis on School-age Children

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Whilst the patient/client is always the central focus of cancer care it is important to consider the impact of a cancer diagnosis and treatment on the family members, especially young children, whose developmental and social capacity are evolving. Cancer is a major healthcare issue and the experience of living with a mother’s diagnosis and treatment of breast cancer affects many children in Europe. However, a limited amount of research exists on children’s experiences in the context of maternal breast cancer. Well and sick children are of particular interest to me and therefore I undertook my PhD in this area entitled ‘School-age children’s experiences