groups. CONCLUSIONS: Radiotherapy results in a modest improvement in survival, without reducing the quality of life or cognition, in elderly patients with glioblastoma.

25 INVITED

Short radiotherapy versus long radiotherapy – should temozolomide be added?

R. Rampling. *UK*

Abstract not received.

Symposium (Mon, 24 Sep, 14:45−16:45)
Stem cells in solid tumours

26 INVITED

Glioma stem cells: from biology to clinics

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Cancer stem cells are the rare population of undifferentiated tumorigenic cells responsible for tumor initiation, maintenance and spreading. Such population should represent the preferential target of effective therapies aimed at eradicating the tumor. The development of technologies that allow the unlimited in vitro expansion of cancer stem cells is a powerful tool for basic and translational research aimed at studying the pathogenic events that drive cancer initiation and progression, while providing crucial information for the development of new antineoplastic compounds. Moreover, the analysis of biological parameters concerning cancer stem cells could be a valuable approach to determine the prognostic value in the clinical setting.
Glioma stem cells have been identified as a subset of CD133+ cells present in the tumor. These cells are resistant to conventional chemotherapeutic drugs and radiotherapy. Moreover, they show a considerable ability to migrate and infiltrate the normal tissues surrounding the tumor. These feautures most likely account for the poor clinical outcome of glioma patients. Thus, the study of glioma stem cells in the clinical setting is a key step to improve the prognostic and therapeutic procedures. We designed a prospective study to determine whether it is possible to identify subgroups of glioblastomas with different intrinsic and prognostic features based on cancer stem cell biology features. We observed that the evaluation of glioma stem cell frequency into the tumor mass, their in vitro growth potential and the expression levels of CD133 together with those of the proliferative marker Ki67 are able to clearly identify the patients at higher risk of disease progression and death.
Thus, although the identification of cancer stem cells from solid tumors is very recent, this research area appears extremely promising and able to foster novel prognostic and therapeutic applications in experimental and clinical oncology.

27 INVITED

ALDH1 is a marker of normal and cancer breast stem cells and a predictor of poor clinical outcome

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Application of stem cell biology to breast cancer research has been limited by the lack of simple assays for identification and isolation of normal and malignant stem cells. We show that stem/progenitor cells in normal breast epithelium and breast tumors have increased aldehyde dehydrogenase activity. Furthermore, immunostaining using ALDH1 antibody identifies normal and malignant stem/ progenitor cells in situ. In a series of 577 breast carcinomas on tissue microarrays, expression of ALDH1 was an independent predictor of poor prognosis. These findings provide support for the “cancer stem cell hypothesis” and offer an important new tool for the study of normal and malignant breast stem cells. Moreover, In situ detection of the cancer stem cell population using ALDH1 would be an important step in developing new diagnostic and prognostic methods for breast cancer.

28 INVITED

Wnt/beta catenin signaling in intestinal and mammary cancer stemness

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Breast and colon cancers are generally thought to arise from normal epithelial cells through a stepwise accumulation of genetic alterations in oncogenes and tumor suppressor genes. However, this genetic model does not take into account other essential characteristics of human cancers, namely their vast intratumor cellular heterogeneity and the role played by a minority of cells, the cancer stem cells (CSCs), in determining invasion into surrounding tissues and distant organ sites. The Wnt/β-catenin signal transduction pathway is known to play a central role in self-renewal and differentiation during embryonic development and in the maintenance of many stem cell niches in adulthood. To study how different dosages of Wnt signaling activation may trigger multi-organ tumorigenesis, we have generated several hypomorphic alleles of the Apc tumor suppressor gene by gene targeting. Notably, while both in man and mouse Apc mutations result in intestinal cancer, we have generated specific allelic variants associated with tumor susceptibility in organs other than the GI tract, namely in the mammary gland, skin and liver. Notably, in cancers resulting from Apc mutations intracellular β-catenin accumulation, the earmark of canonical Wnt signaling activation, is found to be heterogeneous within the tumor mass. Here, I will present experimental data indicating that intracellular β-catenin accumulation earmarks cancer stem cells capable of self-renewal and differentiation. The results also indicate that the specific Wnt signaling dosages encoded by different Apc mutations differentially affects homeostasis of adult stem cell compartments and triggers tumor initiation, progression, and metastasis in a organ-specific fashion.

29 INVITED

Prostate cancer stem cells: new therapeutic targets?

N.J. Maitland, A.T. Collins. *YCR Cancer Research Unit University of York, Department of Biology, York, United Kingdom*

Background: Prostate cancer is characterised by not only its heterogeneity of appearance, which can compromise diagnosis of the course of the disease, but also by its heterogeneity of response to most conventional therapies. This heterogeneity is also apparent in the genetic constitution of the tumours where, unlike many of the more common tumours, there remains an inconsistency in the types of genetic lesions and phenotypes observed. Such heterogeneity is characteristic of a stem cell mechanism of cancer differentiation, in contrast to a stochastic mechanism, where all cells are clonal, rapidly dividing, and have a common appearance. At present most therapies for prostate cancers are based on a stochastic mechanism and, as a result, it is probably not surprising that tumour recurrence from a therapy resistant fraction occurs so frequently.
Materials and Methods: We have sought to examine the cancer stem cell hypothesis by fractionation and primary culture of human prostate tumours. Short term cultures in non-differentiating conditions have allowed us to purify sufficient material to carry out microarray expression analysis (using the Affymetrix platform) on the different cell populations present within various grade of human prostate cancers, and non-malignant control cultures derived as described by Collins et al, 2005 Cancer Res. 65: 10946.
Results: The cultured “cancer stem cells” have a unique phenotype which marks them apart from both their non-malignant equivalents (cultured from benign prostatic tissues) and also from their more differentiated, but still basal, amplifying progeny. There is also an association with patient outcome, as the Gleason 4 pattern tumours are distinguishable from Gleason pattern 3 (and below) based on the stem cell phenotype. Clinical outcome has been clearly associated to the relative prevalence of Gleason pattern 4 histology. The phenotype most closely associated with prostate cancers, androgen receptor-expressing and PSA/PAP secretion, is not present within the stem cell population. However, both in vitro and in vivo, stem cells can be manipulated to generate three dimensional structures and also tumours in an orthotopic xenograft which will regenerate the androgen sensitive phenotype.
Conclusions: Detailed knowledge of the phenotype of the cancer stem cells should allow us to design stem cell-specific therapies. These therapies are likely to be carried out in parallel or immediately after the destruction of the mass of tumour cells which surround, and interact with, the cancer stem cell. The availability of both cultures and of a robust in vivo model using cells from individual patients should allow us to design the optimum therapies in the future. Ultimately, it is only the destruction of the cancer stem cells and a resultant abrogation of tumour recurrence which will provide the proof of the cancer stem cell hypothesis for prostate cancer. Deletion of prostate cancer stem cells offers a real hope for curative rather than palliative long term therapy.