different from primary tumors, but harbor frequently altered chromosomal regions. The data emphasize the need to directly analyze the target cells of adjuvant therapies and indicate that the development of a novel pathology for minimal systemic cancer may overcome the limitations inevitably linked to conventional diagnostic studies of the primary tumor.

44 INVITED

Invasive growth: a MET-driven genetic programme for cancer and stem cells

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Invasive growth is a genetic program in which cell proliferation combines with cell-cell dissociation, migration and protection from apoptosis. It occurs under physiological conditions –during development of epithelial organs, angiogenesis, wound healing- and in cancer progression towards malignancy. Recent evidence suggests that, in post-natal life, invasive growth is a program for stem and progenitor cells. This program is triggered by MET, a proto-oncogene whose expression is regulated by self-renewal signals and by unfavourable microninvironment conditions, such as hypoxia, which typically occurs during tissue regeneration and tumour growth. MET encodes a tyrosine kinase receptor that, upon activation by its ligand HGF (a protein closely related to blood coagulation factors), induces cell motility and displacement toward more favourable tissue environments. Interestingly, MET activation turns on hemostasis genes, promoting a thrombohemorragic phenotype in the mouse, which resembles the Trousseau's syndrome observed in cancer patients. Hemostasis activation ends up in peritumoral fibrin deposition. Fibrin acts as a quick-setting extracellular matrix that promotes angiogenesis and offers anchorage for cancer cell migration and intravasation. The MET oncogene thus provides a functional mechanistic link between tumor hypoxia, hemostasis activation and invasive growth.

45 INVITED

Inhibition of hypoxia-induced lysyl oxidase prevents metastasis

A. Giaccia, J.T. Erler. *Stanford University Medical Center, Center for Clinical Science researchRoom 1250, Stanford, USA*

Cancer progression involves the spread of tumor cells through the body. Understanding this process (metastasis) is invaluable, particularly in metastatic breast cancer which is currently incurable. Tumors contain areas of low oxygen (hypoxia) because cells grow and divide faster than blood vessels can provide oxygen. Cells that exist in these areas are highly aggressive and prone to metastasis, although the reasons for this are unknown. All solid tumors contain areas of low oxygen tension (hypoxia). Hypoxic cells are highly aggressive and metastatic, though the underlying processes remain unclear. We report that lysyl oxidase (LOX), an enzyme essential for the formation of the extracellular matrix, is increased by hypoxia. Inhibition of LOX expression/activity prevents in vitro invasion of human breast and cervical cancer cells and in vivo metastasis. Orthotopically grown breast cancer tumors demonstrates co-localized protein expression of LOX and hypoxia. Estrogen receptor negative breast cancer patients with high LOX expressing tumors, have poor distant recurrence-free metastasis and overall survival. These findings indicate LOX increases the metastatic potential of hypoxic human breast cancer cells, and that inhibition of LOX prevents development of metastases, and thus provides a novel therapeutic target.

46 INVITED

The role of tumour-associated macrophages in tumour angiogenesis and metastasis: regulation by hypoxia and angiopoietin-2

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Monocytes are recruited into tumors from the circulation, differentiate into tumor-associated macrophages (TAMs) and promote tumour angiogenesis and metastasis. Our recent data has shown that exposure to two signals in the tumour microenvironment; hypoxia (low oxygen) and the cytokine, angiopoietin-2 (Ang-2), helps to activate this aggressive pro-tumour phenotype in TAMs. These cells accumulate in hypoxic areas in tumours where they are exposed to tumor hypoxia and undergo marked phenotypic changes. These include the upregulation of a number of hypoxia-inducible transcription factors like HIFs 1 and 2, which in turn activate the expression of a wide array of genes encoding mitogenic, pro-angiogenic and pro-metastatic cytokines and enzymes. As hypoxia is a hallmark feature of malignant tumors and hypoxic tumor cells are relatively resistant to radio- and chemotherapy, these areas have become a target for novel forms of anticancer therapy. We therefore developed a form of hypoxia-targeted gene therapy in which macrophages are armed with therapeutic genes or viruses that are activated by hypoxia-responsive promoter elements. This restricts transgene expression/viral replication to hypoxic tumour areas, where the gene product/virus is then released and acts on neighboring hypoxic tumour cells or proliferating blood vessels. In this way, the responses of macrophages to tumour hypoxia can be exploited to deliver potent anti-tumor agents to these poorly vascularized, and thus largely inaccessible, areas of tumours. Ang-2 is upregulated by blood vessels and tumour cells in many forms of tumour. It binds to the Tie2 receptor on endothelial cells and regulates vessel stabilization and angiogenesis. Recently, Tie-2+ monocytes have been shown to be recruited to experimental and human tumours where they promote tumour angiogenesis. Here we show that Ang-2 is a chemoattractant for Tie-2+ monocytes in vitro which suggests that it may help to recruit such cells into tumours. Ang-2 is upregulated by hypoxic tumour cells and macrophages upregulate Tie-2 in hypoxia. Exposure to the combined effects of Ang-2 and hypoxia suppressed the release of the pro-apoptotic cytokine, TNFalpha, and the powerful anti-angiogenic cytokine, IL-12 by macrophages. Conclusion: our data indicate that Ang-2 is capable of recruiting Tie-2+ monocytes to tumours where, together with hypoxia, it modulates their release of cytokines centrally involved in angiogenesis and metastasis.

Symposium (Mon, 24 Sep, 14:45−16:45)
Biology-driven treatment selection in head & neck cancer

47 INVITED

Molecular classification of head and neck squamous cell carcinomas using patterns of gene expression

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Despite great progress in our understanding of the mechanisms that lead to cancer, there are currently no validated biomarkers of that reliably predict metastasis or survival, or whether a patient will benefit from radiation therapy. Even for targeted therapies, it is unlikely that all patients who will experience clinical benefits can be identified by a single gene analysis because of the complexity of the tumor phenotype. Technologies such as genomics and proteomics probing a large number of genes and proteins allow determining complex molecular profiles or signatures of tumors that are useful for predicting survival and treatment response. Our data suggesting that genomic and proteomic profiling can predict clinical outcome and response to therapy will be presented at the meeting. The comprehensive molecular profiles will facilitate the understanding of the tumor biology, drug mechanism and may aid proper patient selection in clinical trials; and ultimately, will improve the overall care for our cancer patients.

48 INVITED

New understanding of hypoxia-driven pathways and their potential for targeting with radiotherapy

B.G. Wouters. *Maastricht University, Radiation Oncology (Maastro), Maastricht, The Netherlands*

The majority of head and neck tumors have been demonstrated to contain areas that are poorly oxygenated. These hypoxic areas lead to treatment resistance and are implicated in promoting malignancy through changes in metabolism, angiogenesis and metastasis. Oxygen sensing pathways strongly influence both cell behavior and cell survival during hypoxia through their ability to alter gene expression, and have thus received attention as novel targets for therapy. Most research to date has focused on the HIF family of transcription factors and their target genes that are activated during moderate hypoxic conditions. We and others have identified additional oxygen-sensing pathways that affect gene expression and hypoxia tolerance by regulating mRNA translation. Hypoxia results in inhibition of mRNA translation through at least two independent mechanisms both of which provide new opportunities for biomarkers and/or therapy targets. Each of these newly discovered oxygen-sensing pathways have unique activation parameters and are likely relevant for different oxygenation patterns in tumors. I will discuss recent insight into the mechanistic basis behind the oxygen sensitivity of these pathways, their effects on hypoxia tolerance and gene expression, and their potential as new prognositic and therapeutic targets alone or in combination with radiotherapy.