has long been recognized, progress in identifying susceptibility genes has been slow. To identify genetic factors that modify disease risk, we conducted a genome-wide association study of lung cancer. The initial phase constituted an analysis of 317,139 SNPs in 1,989 lung cancer cases and 2,625 controls from 6 central European countries. We identified a locus in chromosome region 15q25 that was strongly associated with lung cancer ($p=9x10^{-10}$). This locus was replicated in 5 separate lung cancer studies comprising an additional 2,518 lung cancer cases and 4,752 controls ($p=5x10^{-20}$ overall), and it was found to account for 14% of lung cancer cases (Hung et al, Nature 2008). The association region contains several genes, including three that encode nicotinic acetylcholine receptor subunits (CHRNA5, CHRNA3, and CHRNB4). This effect has been identified in two other studies (Thorgeirsson et al, Nature 2008; Amos et al, Nat Gen 2008). The interpretations and implications of these results will be discussed.

Finally, we have since extended our genome-wide study of lung cancer by including two further studies comprising an additional 750 cases and 800 controls. We subsequently replicated the top 31 independent findings in a further 4 studies comprising 3339 lung cancer cases and 6064 controls (total 5911 cases and 9416 controls). After pooling the genome-wide and replication phase results, two additional variants were strongly associated with lung cancer, suggesting new susceptibility loci.

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YOUNG CANCER RESEARCHER'S WORKSHOPS

Introduction to pharmaceutical research and development

07 July 2008 13:45 - 14:35

AWARD LECTURE

Anthony Dipple Carcinogenesis Award

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Mechanisms of malignant progression

R.A. Weinberg[1]
[1]*Whitehead Institute for Biomedical Research, Department of Biology, Cambridge, USA*

While a coherent picture has begun to emerge about the biological and molecular mechanisms that create primary tumors, the processes that lead subsequently to invasion and metastasis have, until recently, been relatively obscure. However, over the past five years, research of diverse sorts has begun to generate the conceptual outlines that explain how high-grade malignancies arise. These discussions invariably are motivated by a widely accepted depiction of how metastatic dissemination occurs – the sequence termed the "invasion-metastasis cascade" (1). Thus, primary tumor cells invade locally, enter into the circulation (intravasation), are transported through the circulation, are lodged in microvessels in distant tissues, invade the parenchyma of such tissue (extravasation), form micrometastatic deposits, some of which eventually grow into macroscopic metastases, the last process being termed colonization.

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SYMPOSIUM

Cancer cells metabolism

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Hypoxia, Autophagy and Tumour Metabolism

J. Pouyssegur[1], J. Chiche[1], R. Garcia-Medina[1], G. Bellot[1], F. Dayan[1], D. Roux[1], N. Mazure[1]
[1]*Institute of Developmental Biology and Cancer - CNRS UMR6543, University of Nice Centre A. Lacassagne, Nice, France*

During embryonic development or in the context of tumor expansion, growing cells rapidly outstrip the supply of nutrients. Although cells sense and respond to variations in concentrations of all nutrients, oxygen sensing has emerged as a central control mechanism of vasculogenesis and energy metabolism. At the heart of this regulatory system is the Hypoxia-Inducible Factor, HIF, which interestingly controls, among other gene products, the expression of VEGF-A and Angiopoïetin-2 (Ang-2), two key angiogenic factors. This finding has therefore placed the hypoxia-signaling pathway at the forefront of nutritional control. HIF can induce a vast array of gene products controlling glycolysis, intracellular pH (pHi), angiogenesis, cell migration and invasion, and so has become recognized as a strong promoter of tumor growth. This pro-oncogenic feature is only one facet of the dual action of HIF. Besides being a 'guardian' of oxygen homeostasis, HIF is capable of inducing pro-apoptotic genes leading to autophagy and cell death, which can be features of hypoxic tissues and tumors. In the context of this meeting, we will highlight some of the HIF-induced markers that participate in tumor resistance to nutrient-depleted and acidic microenvironment. First we will show that the two HIF-induced 'BH3-only'-proteins (BNIP3, BNIP3L), in contrast to the current believe, do not trigger cell death but tumor cell survival by inducing autophagy. Second we will show how tumor cells by expressing two HIF-dependent membrane-bound carbonic anhydrases, CAIX and CAXII, acidify the extracellular milieu, and ensure a more alkaline pHi favoring migration and survival to the acidic tumor microenvironment. Finally we will show that additional HIF-regulated targets controlling intracellular pH (MCT1, MCT4, NHE1) could be exploited to enforce tumor regression by collapsing ATP levels.

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Targeting glycolytic enzymes and mitochondria as novel cancer therapy

V. Fantin[1]
[1]*Merck Research Laboratories, Department of Cancer Biology & Therapeutics, Boston, USA*

Alterations in metabolism are a common feature of tumor cells. Among them, elevated rates of glucose-to-lactate conversion in the presence of oxygen, known as aerobic glycolysis, was noted by Otto Warburg in the 20s'. Although, the role of the glycolytic shift in the early stages of tumorigenesis is still unknown, it is becoming increasingly clear that this metabolic pathway is essential for tumor maintenance. Along those lines, our results indicate that LDH-A ablation severely impairs tumorigenicity of malignant cells in vitro and in vivo. Another hallmark of cancer cells is their increased resistance to apoptosis induction. Alterations in many apoptosis regulators at the level of mitochondria confer emerging neoplastic cells with a selective growth advantage, and contribute to resistance to radiation and chemotherapy of tumor cells. Mitochondria play a central role in the process of cell death. Our data further supports the notion that strategies aimed at directly triggering mitochondrial membrane permeabilization including delocalized lipophilic cations or targeted mitochondriotoxic peptides, may help to overcome resistance to standard cancer therapy. Furthermore, distinct metabolic and mitochondrial features of cancer cells may provide opportunities for the development of novel therapies and rational drug combinations for the treatment of cancer.

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Causes and consequences of Increased glucose metabolism in metastatic cancers

R. Gillies[1]
[1]*Arizona Health Sciences Center, Department of Radiology, Tucson AZ, USA*

Metastatic cancers invariably exhibit increased trapping of 18-fluoro deoxyglucose. This occurs even in well-oxygenated tumors, and thus is likely a manifestation of the "Warburg Effect" described more than 70 years ago. Modern molecular techniques have identified numerous pathways that can be associated with the Warburg Effect, including HIF-1/2 (alpha), c-myc, pAkt, p53/TIGAR, PDH kinase, etc. We have analyzed these data using Evolutionary Game Theory and have concluded that the glycolytic phenotype is selected during carcinogenesis because it confers a survival and selective advantage, and that this occurs without respect for the molecular mechanisms underlying the phenotype. We further propose that the selective advantage of glucose hypermetabolism in metastatic cancers occurs because it produces acid, and that this facilitates colonization and expansion of micrometastases into malignant disease. This has been tested in a mouse models of breast cancer and we have observed that neutralization of tumor acid leads to a significant reduction in the incidence of spontaneous metastases.