response. Recently we identified a novel ATM-mediated pathway that leads to transient, global chromatin relaxation. We found ATM's effector in this pathway to be the KAP-1 protein (TRIM28), which is phosphorylated by ATM at DSB sites and then rapidly conveys the chromatin relaxation signal across the nucleus. However, optimal processing and repair of DSBs require chromatin reorganization at damaged sites as well. Chromatin reorganization associated with DNA transactions such as transcription is intimately coupled to alterations in post-translational modifications (PTMs) of the histone proteins. We found that monoubiquitination of histone H2B (mUbH2B) – a modification previously associated with transcription-coupled nucleosome dynamics – is induced by DSBs and is essential for timely DSB repair. This pathway is dependent on ATM and the responsible ubiquitin E3 ligase – a tight complex of the RING finger proteins RNF20 and RNF40, both ATM targets. Damage-induced mUbH2B is specifically required for the stable accumulation of repair proteins at DSB sites. These pathways demonstrate once again the multi-pronged approach of ATM to the systems it regulates, one that allows tight but fine-tuned control.

Monday 28 June 2010 14:35–16:35

Symposium
Inflammation and cancer

345 Improving cancer immunotherapy by preventing chemokine nitration

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Background: The tumour microenvironment is not suitable for T lymphocyte functions, and indeed a number of reports indicate that tumour-infiltrating lymphocytes (TILs) have defects in both signal transduction compartment and killing effector systems.
At the tumour site, the reactions of nitric oxide (NO) with oxygen (O_2) or oxygen-related reactive intermediates yield numerous reactive nitrogen and oxygen species (RNOS). One of the most studied reaction implicates NO and superoxide anions and the generation of peroxynitrite ($ONOO^-$), a potent oxidant with pleiotroic activities. In the past, we and others provided data showing that intratumoural RNOS, produced by either myeloid cells or by the very same tumour cells, are involved in tumour-induced immunosuppression. In addition to being dysfunctional, TILs are also unable to reach the core of the tumour mass, and they concentrate at the border of the neoplastic lesions. We speculated that RNOS might affect chemokine biology and contribute to keep TILs distant from the tumour.
Materials and Methods: Chemokine nitration was analyzed by Mass Spectrometry and immunohistochemistry in human prostate and colon cancer as well as in several murine tumours.
For adoptive cell therapy, mice bearing the EG7-OVA tumour were treated or not with our compound (AT38) before receiving OT-I CTLs.
Results: We found that the chemoattractants CXCL12, CCL21 and CCL2 lose their ability to recruit T lymphocytes when exposed to peroxynitrite. However, the modified chemokine CCL2 retains its capacity of recruiting myeloid cells to the tumour site, suggesting that chemokine post-translational modification might represent a way to selectively modify the tumour microenvironment and favor immune dysfunction.
Based on our findings, drugs controlling the *in situ* production of RNOS might be useful to aid immunotherapeutic approaches for the treatment of cancer, by creating a favorable tumour environment for lymphocyte recruitment and activation. We have developed and screened novel small molecules aimed at interfering with multiple, interconnected metabolic pathways leading to RNOS generation within tumour microenvironment. One of these new compounds (AT38) was used to verify *in vivo* the hypothesis that peroxynitrites may restrain T cell access to the tumour.
We found that *in vivo* inhibition of intratumoural RNOS production results in massive TIL infiltration and has a strong impact on the outcome of adoptive T cell therapy.
Conclusions: These data indicate that chemokines are post-translationally modified by RNOS in the tumour microenvironment and identify novel targets for regulating the composition of tumour infiltrate and sustain properly the antitumour immune response.

346 From inflammation and regeneration to hepatocarcinogenesis

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Hepatocellular carcinoma (HCC) is the third leading cause of cancer mortality worldwide and is considered to be the outcome of chronic liver inflammation. Currently, the main treatment for HCC is surgical resection. However, survival rates are suboptimal partially because of tumour recurrence in the remaining liver. Our aim was to understand the molecular mechanisms linking liver regeneration under chronic inflammation to hepatic tumourigenesis. Mdr2-KO mice, a model of inflammation-associated cancer, underwent partial hepatectomy (PHx), which led to enhanced hepatocarcinogenesis. Moreover, liver regeneration in these mice was severely attenuated. We demonstrate the activation of the DNA damage-response machinery and increased genomic instability during early liver inflammatory stages resulting in hepatocyte apoptosis, cell-cycle arrest, and senescence and suggest their involvement in tumour growth acceleration subsequent to PHx. We propose that under the regenerative proliferative stress induced by liver resection, the genomic unstable hepatocytes generated during chronic inflammation escape senescence and apoptosis and reenter the cell cycle, triggering the enhanced tumourigenesis. Thus, we clarify the immediate and long-term contributions of the DNA damage response to HCC development and recurrence.

347 The inflammatory tumour microenvironment: tumour-protective or tumour promoting?

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Whereas it has become generally accepted that chronic activation of innate immune cells contributes to cancer development and/or progression, the role of the adaptive immune system during tumourigenesis is still a matter of debate. Both tumour-protective and tumour-promoting properties of the adaptive immune system have been described in clinical and experimental settings. The overall goal of our research is to address the role and underlying pathways of the adaptive and innate immune system during sporadic breast cancer progression and metastasis formation. We utilize a mouse tumour model that faithfully recapitulates human invasive and metastatic lobular carcinoma, e.g. a conditional mouse breast cancer model based on mammary epithelium-specific deletion of p53 and E-cadherin. Like human breast cancers, mammary carcinomas arising in this mouse model are characterized by abundant presence of innate immune cells, including degranulating mast cells and macrophages, T and B lymphocytes, antibody depositions and increased levels of pro-inflammatory mediators. By genetic elimination and pharmacological inhibition of specific subsets of the adaptive and innate immune system, we are currently investigating their functional significance in a tumour-stage specific manner. Genetic elimination of the adaptive immune system in this mouse model did not alter latency and outgrowth of primary breast cancers, indicating that immunosurveillance does not play a role during sporadic breast cancer development. Importantly, absence of the adaptive immune system resulted in almost complete abrogation of spontaneous metastasis formation. We are currently assessing the underlying mechanisms by which the adaptive immune system promotes metastasis formation of sporadic breast cancer. Ultimately, the outcome of these studies may shift therapeutic focus from a cancer cell intrinsic point of view towards a more combined cancer cell intrinsic and extrinsic point of view.
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348 Control of tumour progression and metastasis by inflammatory signals

No abstract received.

Monday 28 June 2010 17:30–18:20

Dentist O. Aase and E. Granqvist Memorial Lecture

349 Targeted therapy – novel anti-HER2 strategies in the therapy of breast cancer

No abstract received.

Monday 28 June 2010 09:45–17:30

Poster Session
Cell and Tumour Biology

350 Role of c-Fos/AP-1 in the progression to squamous cell carcinomas

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Background: The proto-oncogene *c-fos* is a component of the AP-1 transcription factor complex, which is involved in the regulation of cell proliferation, differentiation and transformation. AP-1 is the effector downstream of many signal transduction pathways and *c-fos* particularly plays important roles in bone, skin and muscle tumourigenesis *in vivo*. However,