EJC SUPPLEMENTS 8, NO. 5 (2010) 5–81

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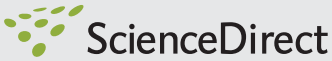

Sunday 27 June 2010

Sunday 27 June 2010 07:15–08:00

After Sunrise: Meet the Expert

14 Lung cancer progression

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Like other solid tumours, lung adenocarcinoma progresses through multiple stages including tumour initiation, expansion in the lung, and metastasis of the primary tumour to distant organs. Dissection of this process requires quantitative and tractable models that recapitulate the human disease at the genetic and histological level. We have employed autochthonous mouse models of lung adenocarcinoma that recapitulate tumour initiation, progression and metastasis in the human disease both genetically, and pathologically. We have established oncogenic *Kras* as the initiating event in lung adenoma and amplification of the oncogenic signaling is associated with progression to adenocarcinoma. The p53 tumour suppressor limits tumour progression in this model. Restoration of the *Trp53* locus has pinpointed the adenoma-adenocarcinoma transition as the stage in which p53 function is critical for tumour suppression. Expression of oncogenic *Kras* in the absence of p53 leads to the development of distant metastases after long latency. This suggests that unknown cooperating genetic events are required for metastatic spread and we are utilizing multiple tools to identify these changes. Use of lentiviral vectors that drive stable GFP expression in tumours allows for identification and purification of tumour cells. Additionally, identification of the lentiviral integration site in each tumour allows the clonal relationship between metastases and the primary tumours to be unequivocally established. Gene expression and DNA copy number analyses of metastasis-derived cell lines and primary lung tumours have uncovered a metastasis associated gene expression signature and recurrent genomic alterations. Integration of these datasets, other genome-wide analyses and human tumour data are providing insights into the molecular mechanism and biology of lung cancer progression and metastasis.

15 Cancer stem cells: current controversies

R. Bjerkvig[1]. [1]*NorLux Neuro-Oncology Laboratory CRP-Santé Luxembourg and Department of Biomedicine University of Bergen Norway, Translational Cancer Research, Bergen, Norway*

The molecular events that lead to the cancer-initiating cell involve critical mutations in genes regulating normal cell growth and differentiation. Cancer stem cells, or cancer initiating cells have been described in several cancers including acute myeloid leukemia, breast, bone and brain cancers. These cells have been shown to be critical in tumour development and should harbour the mutations needed to initiate a tumour. The host microenvironment has been shown to play an important role in tumour progression and there is an increasing body of evidence suggesting that the surrounding stroma not only support tumour growth and invasion, but also has a direct role in tumourigenesis. The origin of the cancer stem cells is not clear. It is also not clear if the cancer stem like cells represent a distinct sub-population within tumours or if they represent highly adaptive tumour cells that can acquire stem cell like properties. Recent evidence from our laboratory, using human xengraft models, indicates that there are cells within tumours that display stem cell like properties. These cells show a high adaptability when exposed to different microenvironments and may display different phenotypes based on the environmental context (niche) where they reside. Thus, they are difficult to identify based on a set of fixed phenotypic markers. Our results suggest that the stem like cells residing in such niches use aneorobic metabolism and will therefore better adapt to hypoxic environments. Major challenges will be to characterize these highly adaptive cells and to determine how they differ from normal stem cells. By the identification of such differences, novel targets leading to the development of new therapeutic strategies can be identified.

Sunday 27 June 2010 08:00–08:50

Educational Lecture
Immunotherapy

16 Induction of objective clinical responses by immunotherapy with synthetic long peptides in patients with high grade HPV16-induced premalignant vulva lesions

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Therapeutic vaccination with a synthetic long peptide (SLP®) vaccine mediated the eradication of established human papilloma virus type 16 (HPV16)-positive tumours in mice and controlled wart growth and latent virus infection in rabbits persistently infected with cottontail rabbit papilloma virus. Subsequent phase I/II studies with an HPV16 SLP® vaccine, consisting of 13 long peptides covering the HPV16 E6 and E7 antigens, in patients with advanced HPV16-positive cervical cancer, revealed that this vaccine was safe and highly immunogenic. The purpose of the current study was to test the clinical efficacy of this HPV16 SLP® vaccine in HPV16-induced high grade vulvar intraepithelial neoplasia (VIN3), a premalignant epithelial disorder, spontaneous regression of which occurs in less than 2% of patients and in which recurrence after standard treatment is high.

In a phase 2 trial, 20 women with VIN3 were vaccinated three times sc in the limbs with a mix of the HPV16 E6 and E7 synthetic long peptides formulated in Montanide ISA-51. The endpoints were objective clinical responses, defined as reduction of at least 50% in lesion size (partial response) or complete regressions, and HPV16-specific T-cell responses, determined before and after vaccination.

The vaccine was safe, as no side effects exceeding CTC grade 2 were observed. At 3 and 12 months after the last vaccination an objective response was observed in 12/20 (60%) and 15/19 (79%) patients respectively. Nine of them showed a complete and durable regression of the lesions at 12 months and at 24 months. The strength of the vaccine-induced HPV16-specific T-cell response was significantly higher in the group of patients with a complete regression of their lesions as compared to non-responders.

This study shows that in women with VIN3 objective clinical responses can be achieved by therapeutic vaccination with synthetic long peptides that is able to induce effective HVP16-specific T-cell responses.

Reference(s)

[1] Kenter GG, Welters MJ, Valentijn AR, Lowik MJ, Berends-van der Meer DM, Vloon AP, Essahsah F, Fathers LM, Drijfhout JW, Offringa R, Wafelman AR, Oostendorp J, Fleuren GJ, Burg van der SH, Melief CJ. Vaccination against Human Papillomavirus 16 oncoproteins for vulvar intraepithelial neoplasia. N Engl J Med. 2009 Nov 5; 361(19): 1838–47.

[2] Melief CJ, van der Burg SH. Immunotherapy of established (pre)malignant disease by synthetic long peptide vaccines. Nat Rev Cancer 2008 May; 8(5): 351–60.

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1359-6349/ $ – see front matter