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BM-derived cells that foster tumor growth and their manipulation

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Myeloid-lineage cells that infiltrate tumors are more likely to promote tumor growth than to they are to mount effective anti-tumor responses. We studied the contribution of bone marrow-derived cells to transplanted and endogenous tumor models, and evaluated the recruitment and functional importance of hematopoietic cells and endothelial progenitors in the process of tumor angiogenesis. By using transcriptionally targeted lentiviral vectors and conditional cell elimination strategies, we demonstrated that bone marrow-derived myeloid cells, but not endothelial progenitors, play important roles during tumor vascularization. In particular, we showed that tumor angiogenesis and growth are dependent on a small subset of circulating and tumor-homing monocytes, which express the angiopoietin receptor Tie2 (Tie2-expressing monocytes, TEMs). Both mouse and human TEMs belong to the "resident monocyte" subset, a monocyte population that does not participate in inflammatory responses. We will present data that highlight the molecular and functional features of TEMs, and their relationship with other myeloid cell subsets previously implicated in tumor growth, such as tumor-associated macrophages (TAMs) and the so-called "myeloid-derived suppressor cells".

Given their tumor-specificity, we speculated that TEMs could be used as gene delivery vehicles for the selective transport of gene therapy to tumors. By transplanting hematopoietic stem cells transduced by lentiviral vectors with TEM-restricted expression, we targeted interferon-alpha (IFN-α) delivery to tumors and achieved substantial anti-tumor activity in mouse tumor models, including orthotopic, spontaneous and metastatic tumor models. In a spontaneous breast carcinoma model (MMTV-PyMT), we achieved significant inhibition of the mammary tumor burden in early (incipient tumors) and late (established tumors) intervention trials. The treated tumors were massively infiltrated by T cells and activated macrophages, suggesting the occurrence of an immune cell-mediated anti-tumor response. Remarkably, prevention trials achieved near-complete suppression of metastatic outgrowth in the lungs. Importantly, TEM-mediated IFN-α delivery did not impair hematopoiesis or wound healing detectably in the mice. Conversely, expression of IFN-α broadly in hematopoietic cells or in the plasma were highly toxic and, paradoxically, poorly effective. These results illustrate the therapeutic potential of gene- and cell-based IFN-α delivery, and should allow developing IFN-based treatments that more effectively treat cancer.

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SYMPOSIUM

Molecular pathology

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Gene expression profiling of breast cancer

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Breast cancer is presently classified based on tumor diameter, histologic type and grade, lymph node status and estrogen receptor, progesterone receptor and HER2 status. A more refined classification should be possible based on genetic alterations and gene expression profiles.

We have previously defined a gene expression profile of 70 genes that is predictive for a short interval to distant metastases (<5 yrs) in lymph node negative (LN0) patients. We have subsequently validated the prognostic value of this 70 gene profile in a cohort of 295 stage I and II breast cancer patients younger than 53 years of age.

To test whether gene expression profiling can be used in clinical practice, we have performed a study in 16 hospitals in the Netherlands. For 427 lymph node negative breast cancer patients, the 70 gene prognosis profile was assessed; 50% of the tumors were shown to have a good prognosis profile.

To identify gene expression profiles associated with response to chemotherapy, we are conducting neoadjuvant chemotherapy studies. Gene expression profiles are generated from core needle biopsies obtained before treatment and correlated with the response of the primary tumor to the chemotherapy administered. To date, no gene expression profile predicting the response of primary breast carcinomas has been identified, but we are currently expanding the series of patients in this neoadjuvant chemotherapy study.

We conclude that gene expression profiling is a method that will lead to improved classification of breast cancer by incorporating novel diagnostic tests that can be reliably implicated in clinical practice.

1. van de Vijver M, He Y, Van 't Veer L, et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 2002, 347:1999-2009.
2. Hannemann J, Oosterkamp HM, Bosch CAJ, et al. Changes in gene expression associated with response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol 2006 23: 3331-3342.

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Breast cancer phenotype and genetic alterations: how are they connected?

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Breast cancer is a heterogeneous disease, encompassing a number of histological entities with distinct biological features, pathological characteristics, and most importantly, clinical behaviour. In recent years, expression profiling analysis has demonstrated that breast cancers can be systematically classified into reproducible molecular subgroups according to their expression profile. Although still heterogeneous, these subgroups have been shown to be of prognostic significance. Several studies have suggested that this phenotypic variation may be explained by their cell of origin. However, there is increasing evidence in support of the concept that molecular subtypes and special histological types of breast cancer are characterised by distinct genetic aberrations, which may explain their phenotypic diversity and clinical behaviour. Firstly, our group and others have demonstrated that sporadic basal-like breast carcinomas, although known not to harbour BRCA1 somatic mutations, not only phenocopy tumours arising in BRCA1 germline mutation carriers, but also have remarkably similar genetic profiles. Secondly, tubular, cribriform, low grade invasive ductal and invasive lobular cancers have been shown to have a luminal phenotype, to evolve from the same precursors and to harbour remarkably similar genetic aberrations (i.e. gains of 1q and deletions of 16q). The main difference between lobular carcinomas and other tumours pertaining to this low grade luminal group has been shown to be the target gene of 16q deletions; whilst in lobular cancers it is the CDH1 gene that encodes E-cadherin, in other tumours pertaining to this molecular subgroup, the target gene is yet to be identified. Further evidence for this concept stems from the reported increased risk of lobular breast cancer in patients with CDH1 gene mutations and from K14cre;$Cdh1^{F/F}$;$Trp53^{F/F}$ engineered mice, which consistently develop tumours with histological features of lobular breast cancer. Finally, we demonstrate that other special types of breast cancer, such as pleomorphic lobular carcinomas and micropapillary carcinomas, are characterised by a constellation of genetic changes that differentiate them from oestrogen receptor and histological grade matched invasive ductal carcinomas. Taken together, the above findings support the concept that to some extent the phenotypic characteristics of breast cancers are underpinned by specific patterns of genetic aberrations.

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The genetic future of pathology: of pancreatic cancer and other malignancies

No abstract received

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Tumor metastasis: mechanistic insights and clinical challenges

No abstract received

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PLENARY LECTURE

Inflammation and cancer

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Inflammation and cancer

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There is amply epidemiological and mechanistic evidence that inflammation and inflammatory processes, such as these that lead to activation of NF-κB, play critical role in early tumor promotion and the growth and progression of primary tumors. Little information, however, exists regarding