The cryptic path of tumor-microenvironment interactions in prostate cancer

Rendicontazione

Informazioni relative al progetto

STOPCa

ID dell'accordo di sovvenzione: 748836

Sito web del progetto

DOI
10.3030/748836

Progetto chiuso

Data della firma CE
14 Luglio 2017

Data di avvio
1 Ottobre 2017

Data di completamento
20 Gennaio 2020

Finanziato da
EXCELLENT SCIENCE - Marie Skłodowska-Curie Actions

Costo totale
€ 175 419,60

Contributo UE
€ 175 419,60

Coordinato da
UNIVERSITAET BERN
Switzerland

Periodic Reporting for period 1 - STOPCa (The cryptic path of tumor-microenvironment interactions in prostate cancer)

Periodo di rendicontazione: 2017-10-01 al 2019-09-30

Sintesi del contesto e degli obiettivi generali del progetto

Prostate cancer (PCa) is the most frequent cancer in men and the second leading cause of cancer-associated death in men. Metastasis to other organs is the main cause of cancer-related mortality. PCa frequently metastasizes to the bone, with no curative treatments being currently available. Widespread screening of prostate specific antigen (PSA) is often associated with overdiagnosis and overtreatment of low-risk PCa, associated with high socioeconomic impact, while there is a lack of diagnostic tools to identify patients in high risk of metastasis. Understanding the mechanisms of tumor progression to metastatic stage is necessary for the design of therapeutic and prognostic schemes. An important component of tumor growth is the supportive stroma/microenvironment: the extracellular matrix (ECM) and the non-tumoral stroma cells. However, it is unclear whether the stroma is modulated by the tumor cells or by intrinsic abnormal alterations. The preferential metastasis to the bone, also suggests that optimal conditions for the PCa cell growth exist in that microenvironment and may facilitate this process. The bi-directional influence of tumor and stroma, along with tumor heterogeneity multiplies the degree of complexity, thus in STOPCa we sought to elucidate the tumor-stroma interactions which is critical for the proper design of diagnostic tools/ putative therapies.
Action objectives
We hypothesized that bone metastatic, stroma-specific molecular signature may be conserved in tumor models even in diffenent (non bone) microenvironments. The main objective of the STOPCa was to determine whether the stroma of metastatic PCa contains a specific (pre)metastatic gene expression signature which may be detectable in primary PCa either prior to or during metastasis and act as prognosis factor.
Aim 1. To identify the molecular transcriptome of tumor and tumor-stroma cells in patient-derived xenograft models
Aim 2. To uncover the mechanisms of tumor-stroma interactions and their prognostic value
Conclusions
Our data show that metastatic PCa PDXs, that differ in androgen sensitivity, trigger a differential stroma response suggesting that stroma is influenced by tumor cues. Selected stromal markers commonly found in bone metastatic sites were induced in the microenvironment of the host organism in metastatic xenografts, although implanted in a non-bone site, indicating a “transcriptional memory” mechanism inherited by tumor cells and inducing a stromal premetastatic signature with high potential prognostic/ diagnostic value.
1. Conservation of bone metastasis stromal signature genes in other PDXs from BM, maintained in non-bone microenvironment. 2. Proof of modulation of stromal cells by tumor cells, which is specific to the tumor properties. 3. Molecular identification of transcriptome of androgen-dependent and androgen independent stroma. 4. Identification of key stromal proteins involved in the crosstalk with tumor cells with prognostic value assessed in clinical PCa cases

Lavoro eseguito dall’inizio del progetto fino alla fine del periodo coperto dalla relazione e principali risultati finora ottenuti

In STOPCa, we identified tumor and stroma profiles using unique disease models of PCa bone metastasis, from two patient-derived xenograft (PDX) models of differential aggressiveness; androgen dependent (BM18) versus androgen independent (LAPC9).

-Characterisation of tumor growth kinetic of BM18 and LAPC9 PDXs established in intact or androgen deprived (castration) immunodeficient mice, showed androgen dependent tumor growth of BM18, and in contrast androgen independent tumor growth of LAPC9, indicating the differential aggressiveness of the two models.
-Molecular characterisation of BM18 and LAPC9 PDXs at the gene expression level. To identify the human-specific and mouse-specific transcriptome we employed next-generation sequencing (RNASeq) and analysed the whole transcriptome of BM18 and LAPC9 tumors, following castration and androgen replacement. Computational analysis allowed separation of species- specific transcriptome on the same sample, after using human/mouse reference genome sequences.
- We assessed the expression of stromal genes, specifically found in PCa bone metastatic stroma signature (OB-BMST), as reported in previous studies with PCa cell line models. Interestingly, all seven genes which activated in OB-BMST signature, were also active in the stroma of both PDXs.
-We identified novel relevant stroma expression alterations that occur due to changes in tumor cells, by subjecting the BM18 and LAPC9 PDXs to androgen deprivation (castration) and androgen replacement.
-We demonstrated that human (tumor) and mouse (stroma) transcriptomes follow androgen dependent transcriptomic changes in the BM18 groups (Intact vs castrated vs replaced) and even in the aggressive, androgen independent LAPC9 tumors. We curated the list of topmost activated genes in the aggressive LAPC9, indicated candidate stromal and tumor genes of potential interesting tumor-stroma interactions.
-We optimised maintainance of stromal and tumor cells in vitro in order to functionally assess the role of key genes by interfering with their activation.
-Molecular characterisation of BM18 and LAPC9 PDXs by proteomic functional analysis, validated the expression of key stromal genes as identified in the RNASeq. and their corresponding interaction partners in tumor cells.
-Evaluation of prognostic value of identified candidate genes in clinical PCa cases with clinical progression (recurrence/metastasis) and survival follow-up information.

Exploitations and Dissemination
The results of STOPCa were and will be disseminated on different national and international conferences by posters and oral presentations. The proposed project work was presented at the “Modelling fibrosis and cancer” talk by Dr.S.Karkampouna at the Bio Cell, Development & Biomedicine (CDB) Seminar Series hosted by the University of East Agglia. (https://twitter.com/biouea/status/933984832304111616). STOPCa project “Tumor-microenvironment interactions in prostate cancer” will be presented (poster presentation) by Dr.S. Karkampouna at the 10th International Conference “Microtechnologies in Medicine and Biology” under session “Tissue Engineering Applications” (MMB 2020, https://mmb2020.org/) in Bern, Switzerland. Two research publications summarising the results of this project are currently under preparation.

Progressi oltre lo stato dell'arte e potenziale impatto previsto (incluso l'impatto socioeconomico e le implicazioni sociali più ampie del progetto fino ad ora)

In STOPCa, we elucidated tumor and stroma-specific gene expression of metastatic PCa PDXs, with a focus on aggressive, androgen independent phenotype. We demonstrated that PCa stroma has a conserved signature indicative of the metastatic site. Unique stromal gene expression found in different tumors suggest that tumor cells directly modulate their microenvironment in a tumor-specific manner. We identified tumor-stroma interactions and evaluated their prognostic value in tissue microarrays of 210 primary PCa cases with follow-up information. Such finding may provide prognostic tools for improved patient stratification follow-up after initial PCa diagnosis and preventive surveillance for metastasis risk. The asymptomatic early stages of the disease, the overdiagnosis based on PSA measurement, the overtreatment/ treatment resistance acquisition and the lack of prognostic tools, consequently result in substantial health care costs and unavoidable morbidity, thus highlighting the importance of identifying disease progression biomarkers for lethal PCa.

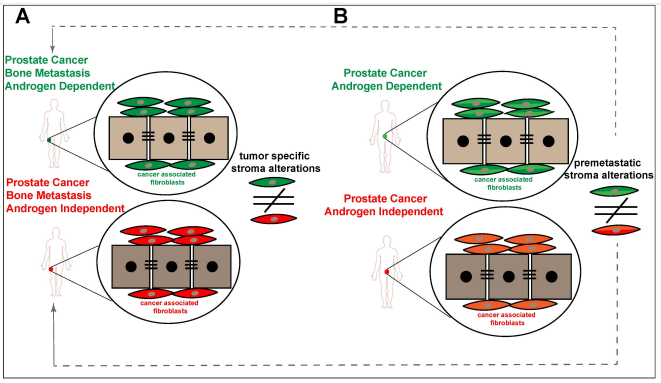

Figure 1. A. Bone metastasis from prostate cancer tumors of differential aggressiveness induce differential microenvironment (stroma) alterations. **B.** Bone Metastasis Stroma signature is preserved in non-bone implantation sites in xenografts, suggesting that prior to metastasis, stroma of primary tumors is orchestrated by the tumor, in order to acquire a pre-metastatic signature resembling the metastasis site of the most favorable growth conditions.

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Ultimo aggiornamento: 10 Febbraio 2022

Permalink: https://cordis.europa.eu/project/id/748836/reporting/it