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INVOLVEMENT OF N-, E-CADHERIN AND BETA-CATENIN IN PROGRESSION OF INTRACRANIAL MENINGIOMA

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The majority of intracranial meningiomas are benign primary tumors. However, 20% are classified as atypical (grade II) and anaplastic (grade III) showing aggressive character and higher probability of recurrence. We believe that such an invasive character of meningioma subtypes could be explained due to the epithelial-mesenchymal transition (EMT) and the activation of canonical Wnt signaling pathway. The malfunctioning of Wnt signaling has been found in many human tumors and many key molecules of Wnt pathway are also involved in EMT. EMT is a biological process necessary for tumor invasion, during which cells undergo molecular changes, become motile and metastasize. During EMT, cells show the so called "cadherin switch" which is characterized by loss of expression of E-cadherin - protein marker of epithelial cells, and by increased expression of N-cadherin followed by the acquisition of mesenchymal phenotype. Therefore, the aim of this study was to investigate if main actors of EMT and canonical Wnt signaling pathway are affected in progression of intracranial meningiomas and to identify potential markers for the control of cellular mobility. In order to do so, we analyzed protein expression and localization of N-cadherin, E-cadherin and beta-catenin in 50 samples of human meningioma with different grades of malignancy. Expression and localization of proteins was investigated using DAB-labeled immunohistochemistry (EnVisionTM, Dako REALTM) and specific monoclonal antibodies for N-cadherin, E-cadherin and beta-catenin on paraffin-embedded meningioma sections. Image analysis (ImageJ – NIH, NCI, Bethesda MD, USA) was also used. For the purpose of identifying the subcellular localization and levels of expression, 200 cells of tumor hot spots were selected and counted. Also, we tested if the expression of E-cadherin protein was influenced by genetic alternations of its CDH1 gene. This was studied by polymerase chain reaction (PCR)/ loss of heterozygosity (LOH) or microsatellite instability (MSI) analyses using microsatellite marker D16S3025. Our results demonstrated that the majority of meningioma samples (70%) showed moderate expression levels of N-cadherin. Beta-catenin was upregulated and transferred to the nucleus in 71.2% of meningiomas which is indicative of the pathway activation. The results on CDH1 genetic changes showed that 9% of meningiomas harbored LOH, 13% showed MSI and 4% of them showed both LOH and MSI. In patients who demonstrated CDH1 genetic changes moderate expression levels of E-cadherin protein were observed. The higher percent of observed MSI could be explained by our previous study (Pećina-Šlaus et al., Tumour Biol. 2017; 39(7):1010428317705791.) where we showed constant presence of MSI and alterations of mismatch repair genes MLH1 and MSH2 in our collection of meningioma patients. After additional future analyses our findings could be useful as potential biomarkers of cellular mobility of invasive intracranial meningiomas.

BIOGRAPHY

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EVIDENCE FOR A MOLECULAR SIGNATURE OF METASTATIC POTENTIAL OF AN ORAL SQUAMOUS CELL CARCINOMA CELL LINE

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Recent evidences show that there is a link between cancer stem cells (CSC) and the process of epithelial-mesenchymal transition (EMT). The purpose of the present study was to *in vitro* evaluate the combination of the biological properties related to CSC and EMT phenotypes with the invasive and metastatic behavior of the corresponding primary and metastatic oral squamous cell carcinoma (OSCC) cell line SCC-9. To accomplish this parental (SCC-9 ZsGreen) and metastatic (SCC-9 ZsGreen LN-1) OSCC cell lines, obtained after *in vivo* tumorigenesis assays, were initially characterized regarding the ability of migration and invasion by *in vitro* scratch and 3D invasion assays, respectively. Further, qRT-PCR was conducted to verify the differential expression levels of CSC (CD44, BMI-1, ALDH-1 and p75NTR) and EMT (SNAIL1, TWIST1, AXL, vimentin, E-cadherin and N-cadherin) markers in both tumor cell lines, using human palate epithelial cells (HPEC) as control. The study provides evidence of a CSC subpopulation within the metastatic cell line undergoing EMT to acquire greater migratory and invasion capacities, depending on the simultaneous overexpression of CD44, AXL, vimentin and N-cadherin, associated with loss of E-cadherin. This can be considered as a "molecular signature" of CSCs undergoing EMT (EMT-CSC) in OSCC, with potential to be used clinically in the classification of tumors with higher or lower metastatic potential, as well as to support new therapeutic strategies against this neoplasm.

BIOGRAPHY

C O Rodini has completed her PhD at the age of 30 years from University of São Paulo, Brazil. She is an Assistant Professor of Biological Sciences at Bauru School of Dentistry, University of São Paulo, since 2010. She has 36 publications that have been cited over 200 times, and her publication H-index is 11. She has been responsible for two ongoing grants funded by the Brazilian government (FAPESP). She is the head of the research group "Cancer Stem Cells in Head and Neck Cancer", studying the role of cancer stem cells and tumor microenvironment in the process of invasion and metastasis of oral squamous cell carcinoma.

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DECIPHERING THE ROLE OF A2B5 IN GLIOBLASTOMAS

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Patterns of ganglioside expression are characteristic of a particular cell type, tissue or tumour. This reflects their functional roles and their involvement in biological functions such as adhesion, cell-cell interaction and proliferation. In glioblastoma (GBM), not much has been explored. Our interest ingliomagenesis led us to focus on A2B5, a monoclonal antibody specific of polysialogangliosides and to a lesser extend of polysialoproteins. Our previous results suggested that A2B5+ cells isolated from human GBM had properties of GBM cancer stem like cells (CSLC) (1, 2, 3). To go further, it is now essential to establish the relationship between gliomagenesis and A2B5 immunoreactivity. A2B5 IgM specifically recognizes trisialogangliosides from the c-series (mainly GT3 and its acetylated form, but also GQ1c and GP1c) at the membrane. As little is known about glycosyltransferases involved in ganglioside biosynthesis, in a first step we focused on the ST8 alpha-N-acetyl-neuraminide α-2,8-sialyltransferase 3 enzyme (ST8sia3), reported to add a third sialic acid on GD3 by an α2-8 liaison to produce GT3. We developed GBM cell lines with various levels of A2B5 reactivity by overexpressing/suppressing ST8sia3 enzyme and tested for stem cell properties. To achieve this goal, we introduced the ST8sia3 coding sequence into U87-MG and U251-MG GBM cell lines which are not considered as GBM CSLC but are highly proliferative and aggressive *in vivo*. Thus the overexpression of ST8sia3 resulted in a huge increase of A2B5 immunoreactivity and ST8sia3 and A2B5 were detected in the same cells by flow cytometry and immunofluorescence. The increase of A2B5 immunoreactivity induced deep changes in cell behavior. As compared to control cells, the overexpression of ST8sia3 (thus increase of A2B5) triggered cellular migration and proliferation but no difference in their clonogenic potential was measured. Moreover, the survival of mice orthotopically injected with ST8sia3+-overexpressing U87-MG cells was slightly reduced when compared to mice injected with U87-MG control cell line. At this stage, these results showed that A2B5 expression is positively correlated with a more aggressive cellular behavior.

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ACTIVATION OF DOPAMINE RECEPTOR 2 INCREASES TUMORGENECITY AND ALTERS METABOLISM IN GLIOBLASTOMA IN SUB-TYPE DEPENDENT MANNER

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Of all cancers, glioblastoma (GBM) remains one of the least treatable. Evidence indicates cellular plasticity—GBM cells' ability to adopt various expression profiles and functional attributes—is a key factor in this aggressive phenotype. This process includes the ability of differentiated GBM cells to attain a glioma-intiating cell (GIC) phenotype, characterized by heightened therapy-resistance and elevated self-renewal capacity. A variety of factors in the microenvironment have been shown to influence this process, including hypoxia, acidity, and therapeutic stress. Therefore, a better understanding of the mechanisms governing this conversion is needed. Developmental neurobiology suggests that dopamine, a monoamine neurotransmitter, may represent one such factor. Dopamine signaling influences differentiation of brain progenitor cells, highly similar to GICs. We set out to investigate how dopamine influences cellular plasticity in GBM. First, we analyzed epigenetic regulation of the five dopamine receptors (DRDs) in patient derived xenograft (PDX) cells. We found that therapy induces increased acetylation of H3K27 in the DRD2 promoter. Western blots and FACS confirmed increased DRD2 protein. Next, we performed neurosphere assays in the presence of a specific DRD2 agonist. Agonist treated classical PDX cells increased in sphere-forming capacity, while proneural PDX showed no change. Blocking DRD2 attenuated neurosphere-formation. To determine what pathways drive this DRD2 activated plasticity, we performed bioinformatics analysis of human GBM samples. DRD2 expression correlated positively with hypoxia inducible factor (HIF) signaling. Agonist treatment of PDX cells induced HIF protein, despite normoxic conditions. Microarray analysis of HIF genes confirmed subtype-dependent alterations in gene expression following DRD2 activation. Finally, we examined how these gene expression changes influence metabolism, a key functional output of HIF signaling. Seahorse analysis revealed classical GBM cells augment glycolytic rate following DRD2 activation, while proneural GBM cells decrease their consumption of glucose. In summary, these data highlight the contribution of CNS-specific molecules to cellular plasticity of GBM cells and provide evidence for functional differences in genetically defined tumor subpopulations.

BIOGRAPHY

Seamus Caragher earned his B.S. in Neurobiology, summa cum laude and Phi Beta Kappa, from Georgetown University in 2016. He then worked in the laboratory of Atique Ahmed, PhD at the Lurie Cancer Center of Northwestern University, focusing on cellular plasticity and the influence of the brain microenvironment in glioblastoma. He is currently pursuing an MSc in Cancer Sciences at the University of Glasgow as a British Marshall Scholar.

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June 11-13, 2018 | Dublin, Ireland

DISCRIMINATION OF GLIOBLASTOMA CANCER STEM LIKE CELLS BY UHF-DIELECTROPHORESIS CROSSOVER FREQUENCY

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CSCs appear as major biological and therapeutic targets, in particular for GBM. Heterogeneity of tumor cell population, leads to optimize characterization and sorting methods. It is actually based on the target of a set of biological markers, which are efficiently used to validate the stemness lineament. Besides the biological properties, physical characteristics of CSCs are expected to be a potential way to discriminate and sort CSC populations. These data summarize first's results glioblastoma cell lines' characterization; measuring their crossover frequencies by dielectrophoresis (DEP) technics in the UHF frequency range (above 50 MHz). LN18 line cell was cultured following different conditions, in order to achieve an enrichment of cancer stem cells (CSCs). Based on DEP electrokinetic method, CSCs were discriminated the from the differentiated cells. In this study, microfluidic lab-on-chip systems implemented on Bipolar-Complementary Oxide Semiconductor (BiCMOS) technology is used allowing single cell handling and analysis. Based on measurements of their own intracellular specificities, the enriched CSCs population, cultured in dedicated define medium, have shown clear differences of DEP crossover frequency signatures compared to differentiated cells cultured in normal medium. That demonstrates the concept and validates the technique efficiency for CSC discrimination in glioblastoma.

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A NEW LABEL FREE APPROACH FOR CSC DETECTION ON GLIOBLASTOMA MODEL *IN VITRO*

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Cancer stem cells (CSCs) were a critical point in cancer making them a central target of the different area of interest for new diagnosis, therapeutic and theranostic approaches. The postulate of poor number of CSCs in cell culture and the lack of real specific markers to well recognize these cells conduct to establish new methods to isolate and characterize them. Invent label free technique described in this study is able to provide a great number of CSCs and finally deserve a CSCs signature and neutralize them. This process is based on combine devices forming. Several culture conditions allows an enrichment in CSCs. This enrichment was enhanced using SdFFF cell sorting method. This method was coupled to a biosensor to measure a specific electromagnetic (EM) signatures corresponding to each condition obtained. A unique EM signature was also obtained for CSCs opening the way to study these critical cells in glioblastoma and more largely in cancer.

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CIRCULATING EPITHELIOID CELLS AND PERSONALIZED MEDICINE: THE GOOD, THE BAD AND THE UGLY AND MANY OTHERS

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When tissues are damaged, such as during inflammation or cancer, epithelial cells circulates in the blood at low frequencies. Circulating epithelioid cells (CECs) represent a non-invasive way to access to information on distant damaged tissue sites. Recent technologies now allow the detection of CECs with a very high sensitivity. However, not all CECs are informative. In the case of cancer, only a minority of these CECs is at risk to give rise to metastases, and is thus the actual population to identify. We develop new models for Personalized Oncology. We search for markers related to tumor evolution and drug resistance in CECs, and more specifically in true Circulating tumor cells (CTCs) from breast and colorectal tumors. Using histological (count, morphology) and phenotypical (multi-color staining) analyses, we identified several types of CECs in the blood of cancer patients: normal epithelial cells (most certainly collateral damage), epithelioid cells of unknown significance, isolated tumor cells at different degree of epithelial-to-mesenchymal transition (EMT) stages, and tumor micro-emboli. We established the multidrug resistance phenotype and stemness status of these cells. The data were correlated to patients' clinical information and response to treatment. Our results show that specific subsets of CTCs, rather than the unselected population, should be considered and characterized, if one wants to use CTCs as a window for patient's tumor heterogeneity and/or evolution. This makes more complex a situation already difficult due to limited number of available cells, but which should be workable now in the single-cell era.

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POLYPLOID GIANT CANCER CELLS MAY REPRESENT A SOMATIC EQUIVELANT OF BLASTOMERE

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It is now generally accepted that all mature somatic cells retain the capability to be reprogrammed (or dedifferentiated) to pluripotent state. However, it remains unclear how the endogenous developmental pathway is activated for such a reprogramming. We have recently shown that chemotherapy drug paclitaxel (PTX) can induce cancer cells undergo senescence and lead the formation of a big monster cells, refer as polyploid giant cancer cells (PGCCs). PGCCs bypass the spindle checkpoint and replicate the DNA without cell division. PGCCs show time- and space-dependent activation of expression of reprogramming factors OCT4, NANOG, and SOX2; lack expression of Xist; and are capable of de-differentiation. The parental cancer cells are reprogrammed via formation of PGCCs which can give a birth of diploid resistance cancer cells via budding. This division mode recapitulates that of blastomere-to-morula stage embryo and facilitates the dedifferentiation toward the blastomere stage embryonic stem cells. PGCCs use an evolutionarily conserved embryonic program used to reprogram zygote to new embryonic state for for disease relapse and thus represent a somatic equivalent of blastomere. Here, we provide a model on how PGCCs divide and how they achieve the dedifferention, named the blastomere model for cancer and disease relapse. This new conceptual paradigm, which integrates different tumors along bidirectional developmental hierarchy, should facilitate our understanding of cancer origin and to guide our efforts for therapeutic intervention.

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June 11-13, 2018 | Dublin, Ireland

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INCREASING TELOMERASE IN HUMAN CANCER STEM CELLS BY NOVEL COMPOUNDS ENHANCED THE SENSITIVITY OF THE CELLS TO CERTAIN ANTI-CANCER AGENTS

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Telomerase, a ribonucleoprotein is responsible for the re-elongation of telomeres and is not or is slightly expressed in somatic cells but it is highly expressed in most of the tumor cells. Telomerase expression is regulated by various factors and recently it was suggested that some mRNA splice variants for human telomerase catalytic subunit (hTERT) regulate the activity of telomerase. The expression of telomerase in cancer stem cells was previously reported but the regulation of its expression and activity in cancer stem cells was not thoroughly investigated. Here we show that the hTERT dominant negative splice variant beta is highly expressed in both the adherent and the mammospheres (cancer stem cells) of human breast cancer cell line (MCF7). We found that telomerase activity in cancer stem cells is also regulated by the relative expressions of the full length and the betta splice variants of TERT. We synthesized novel compounds (AGS) that activate telomerase expression in various human and animal cells as well as, *in vivo*, in animal models. Treating cancer stem cells with these compounds increased the expression of the full length TERT relatively to the beta splice variant. Pretreatment of cancer stem cells with the telomerase increasing compound increase the sensitivity of these cells to anti- cancer agents in general and specifically to topoisomerase inhibitors. The results of this study suggest a novel approach, based on telomerase activation, for increasing the sensitivity of cancer stem cells to chemotherapeutic agents.

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EGFR SORTING IN LUNG CANCER: "SMELLS LIKE A SORTILIN SPIRIT"

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The aim of the present project is to obtain a better understanding of EGFR deactivation in lung cancer. To accomplish this we investigated the role of sortilin in EGFR regulation following EGF-induced EGFR internalization. The study also provides evidence that sortilin expression represents a favorable prognostic marker in lung adenocarcinoma patients.

Tyrosine kinase receptors such as the epidermal growth factor receptor (EGFR) transduce information from the microenvironment into the cell and activate homeostatic signaling pathways. Internalization and degradation of EGFR after ligand binding limits the intensity of proliferative signaling, thereby helping to maintain cell integrity. In cancer cells, deregulation of EGFR trafficking has a variety of effects on tumor progression. Here we report that sortilin is a key regulator of EGFR internalization. Loss of sortilin in tumor cells promoted cell proliferation by sustaining EGFR signaling at the cell surface, ultimately accelerating tumor growth. In lung cancer patients, sortilin expression decreased with increased pathologic grade, and expression of sortilin was strongly correlated with survival, especially in patients with high EGFR expression. Sortilin is therefore a regulator of EGFR intracellular trafficking that promotes receptor internalization and limits signaling, which in turn impacts tumor growth.

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June 11-13, 2018 | Dublin, Ireland

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miR-148A INHIBITS COLON CANCER STEM CELL PROPERTIES BY TARGETING PREGNANE X- RECEPTOR SIGNALING

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Therapeutic failure seen in patients with colorectal cancer (CRC) frequently involves post-treatment tumor recurrence, due to the enhanced resistance of cancer stem cells (CSCs). Recently, we reported that the nuclear receptor Pregnane X- Receptor (PXR, NR1I2) behaves as a key driver of CSC-mediated tumor recurrence where it drives the expression of a large network of genes involved in self-renewal and chemoresistance (Planque C et al. Oncotarget, 2016). In order to determine the molecular mechanisms that define PXR enrichment in CSCs, we investigated the role of miR-148a on PXR expression and CSC phenotype. The miR-148a has been reported to post-transcriptionally regulate PXR in human liver (Takagi S et al. J Biol Chem, 2008) and has been proposed as a predictive biomarker in patients with advanced CRC (Takahashi M et al. PLoS One 2012).The present study demonstrated that miR-148a is down-regulated in CSC-enriched colonospheres and ALDHbright cells or after cytotoxic treatments. We also observed a negative correlation between miR-148a-3P and PXR and PXR target genes expression in these conditions. Moreover, transient transfection of miR-148a-3P mimics in CRC cell lines and in patient-derived CRC cells decreased PXR and PXR target genes expression (ALDH1A1, ABCG2, FGF19) and PXR-induced promotion of the CSC phenotype (proportion of ALDHbright cells, sphere forming potential and self-renewal following serial spheroid passaging). Finally, we observed that miR-148a-3P overexpression impairs chemotherapy-induced enrichment of ALDHbright cells after Firi treatment. In conclusion, we propose that the deficiency of miRNA-148a-3P is associated with the preferential expression of PXR in colon CSCs. In addition, our findings highlight miR-148a as a promising therapeutic agent that may reduce cancer relapse by selectively sensitizing CSC to chemotherapy via PXR signaling inhibition.

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ELUCIDATING THE UNDERLYING MECHANISM OF CSC ENRICHMENT BY PLATINUM TREATMENT IN EPITHELIAL OVARIAN CANCER CELLS: A STORY JUST BEGINS TO UNFOLD

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High grade serous epithelial ovarian cancer (HGSOC) is notoriously known for high recurrence and mortality due to acquirement of chemoresistance. Both chemonaive and platinum sensitive relapse cases of HGSOC patients are treated with cisplatin/carboplatin with or without other drugs as a standard therapy regime for last two decades. Unfortunately, both cases eventually develop platinum resistance and succumb to the disease. Whether and how repetitive exposure of platinum drugs in cancer cells creates enriched drug resistant cancer stem cells like fate has not been explored in detail. To decipher this molecular mechanism, we looked into IGF1R-PIK3CA-AKT signalling pathway alteration during acquirement of platinum resistance in indigenously developed chemoresistant cellular models. Increased CSC-marker expression, side population, spheroid formation were observed during the course of resistance acquirement. Interestingly, CSC like SP cells which are in early phase of resistance development demonstrated faster tumorigenic potential than CSC like SP cells isolated from late resistant phases (Singh et al, Scientific Reports, 2016). This late resistant cells contain maximal percentage of CSCs and other characteristics of stem cells. Using a DNA-protein pull down assay, we identified NF- B as a prime transcriptional regulator of PIK3CA-Akt signalling in these late cisplatin resistant cells and their corresponding SP cells after cisplatin treatment. Along with PIK3CA, NF-κB also escalated TNFα expression specifically in SP fraction upon cisplatin treatment. Our data conclusively showed that this CSC-specific NF-κB-TNFα-PIK3CA bi-modal loop, on one hand, maintains persistent activation of NF-κB through TNFα- NF-κB autocrine loop, while NF-κB-PIK3CA loop nurtures CSC population under cisplatin treatment. Overall, activation of PI3K/AKT and NF-κB signaling in resistant cells favours survival and enrichment of CSCs by acquiring anti-apoptotic, quiescent state (Thakur and Ray, J. of Exp. Clin. Cancer Res., 2017). In order to explore a mode to inhibit enrichment of CSC with progression of resistance, we developed chemoresistant cellular model treated with platinum-taxol along with Metformin, a known anti-diabetic drug. Intriguingly, concurrent treatment of metformin with platinum-taxol significantly reduced the CSC like side population (32% vs. 10%) and the resistance properties (92% to 70%) of these cells. Further studies are ongoing to understand the alleviating effect of Metformin on platinum resistance with a special emphasis on NF-B-TNFα-PIK3CA bi-modal loop present in platinum resistant ovarian cancer cells.

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QUIESCENT EPITHELIAL STEM CELLS EVADE IMMUNE SURVEILLANCE

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There is a long-standing interest in understanding the immunogenicity of adult stem cells due to their role in tissue homeostasis, regeneration and oncogenesis. Notably, their self-renewing capacity means they are long-lived, and can accumulate mutations over time, which would result in neo-antigens. These neoantigens could make stem cells potential targets of T cells. However, whether they are subject to immune surveillance is unknown. Here, we utilized a novel technology to study immune responses against virtually any cell type, along with specific stem cell mouse models, to interrogate the immunogenicity of adult stem cells in their niche *in vivo*. We found that immune privilege is not a general property of adult stem cells. Instead, our studies revealed that most epithelial stem cells, such as those in the gut and ovary are subject to immune clearance, but that highly quiescent stem cells, specifically in the skin and muscle, escape immune detection. This is an intrinsic property of the resting stem cells resulting from downregulation of MHC class I and other key components of the antigen presentation machinery, which results in complete protection from immune attack. These studies established that quiescent tissue stem cells hide from immune surveillance and protect their integrity. This helps to understand why mutations in long-lived stem cells do not lead to immune clearance and, suggests how cancer stem cells may evade immune surveillance.

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CIRCULATING TUMOR CELL EX-VIVO CULTURE FROM PATIENT WITH COLORECTAL CANCER DISPLAY HETEROGENEITY AND CANCER STEM CELL HALLMARKS

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The aim of the present project is to functionnaly characterize an unknown population of cancer cells responsible of tumor dissemination, namely circulating tumor cells in the context of colorectal cancer Although circulating tumor cells (ctc) have attracted a broad interest as potential markers of tumor progression and treatment response, their characterization remains minimal. Here, we designed straightforward conditions for the isolation and maintenance of colon ctcs in culture based on their self-renewing abilities. We generated the first ctc cell lines from the blood of three patients with advanced metastatic colorectal cancer (crc). These cells display cancer stem cell (csc) hallmarks and are able to generate metastasis when injected in the spleen of nude mice. Taken together our results show that ctc lines could represent a clinical useful tool to recapitulate tumor heterogeneity and to rapidly predict treatment response in patients with crc facilitating access to personalized medicine

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June 11-13, 2018 | Dublin, Ireland

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IMPACT OF HLA-G POLYMORPHISM ON THE OUTCOME OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR METASTATIC RENAL CELL CARCINOMA

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Renal cell carcinoma (RCC) is particularly sensitive to immune intervention. HLA-G, a non-classical HLA class I molecule with immunomodulatory properties, has been studied with regard to outcome after hematopoietic stem cell transplantation (HSCT), in particular the 14 bp insertion/deletion polymorphism in the 3' untranslated region. Here we analyzed n=56 patients affected by metastatic RCC who received an allogeneic HSCT between 1998 and 2006 in Milano, Marseille, Clermont-Ferrand and Stockholm. The 14 bp polymorphism was analyzed in correlation with overall survival (OS), PFS, acute and chronic GvHD. With a median follow-up of 13 years, a trend towards better outcome was observed when homozygosity for the 14bp-del allele was present: multivariate hazard ratio was 0.50 (95% confidence interval (CI): 0.23-1.13; P=0.10) and 0.57 (95% CI: 0.26-1.26; P=0.17) for OS and PFS, respectively, when 14bp-del/del was compared with 14bp-ins/X. Further exploratory analysis revealed a significant association between T/C at p3003 and improved OS (P=0.05) and PFS (P=0.006) compared with T/T. To our knowledge this is the first study on HLA-G and outcome after HSCT for a solid malignancy. After a coordinated multicenter study, we found that the more tolerogenic polymorphisms (14bp-del/del) is associated with better PFS and OS. The finding on p3003 deserves further investigation.

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microRNA-17 IS DOWNREGULATED IN ESOPHAGEAL ADENOCARCINOMA CANCER STEM-LIKE CELLS AND PROMOTES A RADIORESISTANT PHENOTYPE

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Esophageal adenocarcinoma (EAC) is an aggressive disease with an extremely poor prognosis. Resistance to neoadjuvant chemoradiation therapy (CRT) remains a critical barrier to the effective treatment of EAC. Cancer stem-like cells (CSC) are a distinct subpopulation of cells implicated in the resistance of tumors to anti-cancer therapy. However, their role in the resistance of EAC to CRT is largely unknown. In this study, using a novel *in vitro* isogenic model of radioresistant EAC, we demonstrate that radioresistant EAC cells have enhanced tumorigenicity *in vivo*, increased expression of CSC-associated markers and enhanced holoclone forming ability. Further investigation identified a subpopulation of CSC that are characterised by high aldehyde dehydrogenase (ALDH) activity, enhanced radioresistance and significantly altered microRNA (miR) expression alterations, including decreased expression of miR-17. *In vitro*, miR-17 overexpression was demonstrated to significantly sensitise radioresistant cells to X-ray radiation and promoted the downregulation of genes with miR-17 binding sites, such as C6orf120. *In vivo*, miR-17 was significantly decreased, whilst C6orf120 was significantly increased, in pre-treatment EAC tumour samples from patients who demonstrated a poor response to neoadjuvant CRT. This study sheds novel insights into the role of CSC in the resistance of EAC to CRT and highlights miR-17 as a potential biomarker of CRT sensitivity and novel therapeutic target in treatment resistant EAC.

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