Tumor-initiating and stroma-associated tumor cells within osteosarcoma, a primary bone tumor in adolescent and young adults.

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Purpose: Osteosarcoma (OS) is the most frequent primitive malignant bone tumor. It is a rather complex pathology without any specific genetic marker for diagnosis. For pathologists, OS is defined as malignant cells producing bone matrix. As mesenchymal stem cells (MSC) are precursors of osteoblasts that produce the bone matrix, they are strongly suspected to be at OS origin. We hypothesized that some MSC with cancer stem cell (CSC) characteristics may be involved in OS development, chemotherapy resistance and metastatic progression. Moreover, we have shown that exposure to pesticide mixture may promote the tumorigenic transformation in a predisposed stromal environment (Hochane et al., Stem cells 2017).

Experimental Design: adherent cells from six human OS samples were isolated after tumor dissociation. They were named OS derived cells (OSDC) and were compared to own patient bone marrow mesenchymal stem cells (BMMSC). We tested MSC characteristics (cell surface markers, differentiation capacities...), CSC characteristics (sphere formation assay, tumor formation in immunocompromised mice, karyotype, metabolism (SeaHorse®)), and tumor growth support capacities in an induced human OS mouse model.

Results: OSDC had the same morphologic aspect and membrane expression profile as BMMSC (CD90+, CD105+,CD45- and CD34-). They kept differentiation capacities toward osteoblastic lineage and to less extend toward adipogenic and chondrogenic lineage, with variability between different OSDC populations. Karyotype was normal for all 6 BMMSC and for 4 OSDC. OSDC showed CSC characteristics, with sphere formations in semi solid conditions, decrease of mitochondrial metabolism in normoxia condition (20% O2). No tumor formation was induced in immunocompromised mice (SCID), while in coinjection mouse model, all 6 OSDC increased the incidence of lung metastasis compared to osteosarcoma cells (MNNG-HOS) alone.

Conclusion: OSDC that were isolated from human OS samples did not demonstrate own tumor properties, but they were more like MSC with higher abilities to growth in unanchorage conditions (sphere) than BMMSC and changes in mitochondrial metabolism. They are highly suspected to be part of tumor microenvironment, rather than the tumor origin, and to support and modulate the tumor growth. More studies are necessary to identify which CDOS factors influence tumor growth suggesting new stromal targets for combined therapy.