Exploiting the Cross-talk between Glioblastoma Cells and Tumor-associated Macrophages with a Nano-drug for regulating Tumor Immune Microenvironment

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Glioblastoma (GBM) is the most frequent and malignant brain tumor with a high mortality rate. The tumor-associated macrophages (TAM) closely interact with the GBM cells (GC) to promote the survival, progression and therapy resistance of the GBM. Various therapeutic strategies have been devised either targeting the GC or the TAM but few have addressed the cross-talks between the two cell populations. The present study was carried out to explore the possibility of exploiting the cross-talks between the GC and TAM for regulating the tumor microenvironment through using Nano-DOX, a drug composite based on nanodiamonds bearing doxorubicin. In the in vitro work, Nano-DOX-loaded TAM were first shown to be viable and able to infiltrate three-dimensional GC spheroids and release cargo drug therein. GC were then demonstrated to encourage Nano-DOX-loaded TAM to unload Nano-DOX back into GC which consequently emitted damage-associated molecular patterns (DAMPs) that are powerful immunostimulatory agents as well as indicators of cell damage. As a result, Nano-DOX-damaged GC exhibited an enhanced ability to attract both TAM and Nano-DOX-loaded TAM. Most remarkably, Nano-DOX-damaged GC reprogrammed the TAM from a pro-GBM phenotype to an anti-GBM phenotype that suppressed GC growth. Finally, mice bearing orthotopic human GBM xenografts were intravenously injected with Nano-DOX-loaded mouse TAM which were found releasing drug in the GBM xenografts 24 h after injection. GC damage was evidenced by the induction of DAMPs emission within the xenografts and a shift of TAM phenotype was detected as well. Taken together, our results demonstrate a novel way with therapeutic potential to harness the cross-talk between GBM cells and TAM for modulation of the tumor immune microenvironment.