Retinoic acid induced chordomas as a model of differential therapy

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Chordoma, originating from the remnants of notochord during embryogenesis, is one of the major challenging tumor types of all bone sarcomas with slow growing potential and high recurrence rate. Studies indicated that *brachyury*, the expressed gene in early stages of mesodermal development in cells with high potential of differentiation; is specific to almost all chordomas. Differentiation therapy is a promising method with less toxicity for tumor types originating from stem cells. We hypothesize that the differentiation therapy will be a novel technique for curing chordomas.

The fight against cancer has been a major challenge for decades and scientists have been struggling to find new treatment models depending on the tumor type, its grade, and location. To date it is shown that the most common treatment methods are chemotherapy and radiotherapy, which are not real solutions for the treatment of cancer due to recurrence, metastasis, and drug resistance, supposedly caused by cancer stem cells.[1] This is also true in the case of chordomas, which are rare primary tumors of bone originating from the remnants of notochordal primitive mesenchymal cells, during embryogenesis. They are traditionally considered as slow growing, and locally invasive neoplasms with little tendency to metastasize and have highly potential recurrence rate after surgery.

The previous studies showed that *brachyury*, a significant marker expressed in early stages of mesoderm formation,[2] is expressed in chordomas. It has been also demonstrated that *brachyury* gene plays a key role in notochord differentiation in chordates during embryonal development. It is well-known that *brachyury* is no longer expressed after late differentiation of mesoderm. All of these findings suggested that *brachyury* is the crucial factor for the differentiation of late mesodermal development. Cells expressing *brachyury* are more likely to differentiate into other late mesodermal lineages (for example bone, cartilage, and so forth) when induced with differentiation factors. One study reported that *brachyury* expression was elevated when FGFR3 was introduced as an inducer into mesenchymal stem cell line, differentiating these cells into the chondrogenic lineage successfully *in vitro* and *in vivo* transplantations.[3] Our preliminary results showed that expression of brachyury and some of the transcriptional factor genes such as Oct4, Klf4, Nanog, which all are expressed in cancer stem cells and stem cells, were also expressed in chordoma cell line, UCH-1, and primary chordoma tissues. Therefore, chordoma cells have a promising potential to be the appropriate targets for the differentiation therapy owing to the expression of these markers.

Differentiation therapy is a promising method that makes cancer cells continue to maturate and eventually

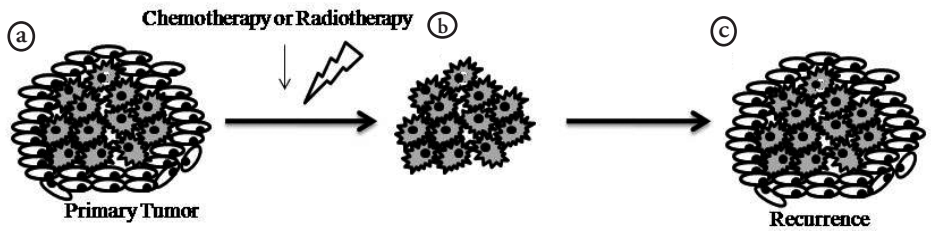

Figure 1 - Schematic representation **a)** of primary tumor cells, **b)** after chemotherapy or radiotherapy normal cancer cells die but cancer stem cells stay alive, and **c)** develops a secondary tumor.

Figure 2 - Schematic representation of **a)** primary tumors metastasize, **b)** cancer stem cells migrate to other tissues, and **c)** develop a secondary tumor.

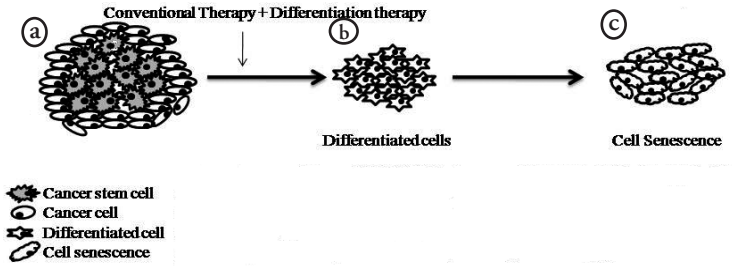

Figure 3 - When exposed to conventional therapies together with differentiation therapy, normal cancer cells will die whereas cancer stem cells will differentiate into other cells and go senescence.

restrains their proliferation. It also allows conventional therapies such as chemotherapy to become more efficient and applicable. Findings indicate that differentiation therapy (**Figures 1-3**) is less toxic than chemotherapy, therefore, a better candidate for treatment in tumor. As a differentiation factor, retinoic acid (RA), which can be used to differentiate mesenchymal originated cells, is used in acute myelogenous leukemia patients as an additional treatment method where RA blockades the proliferation and enhances differentiation.[4]

Around the globe, rare cases of chordoma have been reported so far with only one cell line, UCH-1, generated by Silke Bruederlein at University of Ulm, Ulm, Germany.[5] To date there is no trial on differentiation therapy for chordomas both *in vitro* and *in vivo*. We hypothesized that if chordoma cells, which are known to possess mesenchymal origin, are induced with either RA or osteogenic/chondrogenic factors then these cells might exit the proliferation cycle and differentiate to mesenchymal tissues. When chordoma cells are induced to differentiate into osteogenic/chondrogenic cell lineages, they might be more sensitive to the chemotherapeutic drugs and less likely to metastasize.

As a result, this method may be used as an alternative approach to the conventional therapeutics in treating chordomas.

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