

A NEW WAY TO ERADICATE TUMORS: THE STEM CELL APPROACH



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Every organ in our body is built from numerous cells ; each of them has a specific task and is therefore “differentiated” into a specific type of cell. The life time of these differentiated cells is limited and many of them are constantly lost. In order to ensure the integrity of the organ, a group of cells called “stem cells” exists. These stem cells are a very special type of cells : when needed, they have the capacity of producing all the other specialized cells that build the organ and yet maintain themselves. It is due of the presence of stem cells that, in case of injury, the organ can be repaired.

In our work we focussed on skin. This is the organ where the action of stem cells can be frequently witnessed by everyone. Each time we cut ourselves, we loose a certain amount of specialized skin cells. In this circumstance, the skin stem cells become active and replace the lost cells, with the result of reconstituting the portion of the lost tissue (Figure 1).

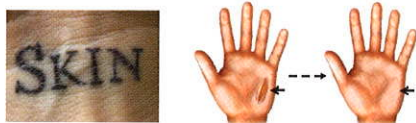


Fig. 1

We use mice as experimental model. In mouse skin the location of the stem cells has been identified : they reside within the hair structures, as shown in Figure 2. These cells can be identified and characterized by the exclusive presence of a molecule called **CD34** on their surface. Based on the presence of this molecule it is possible to separate stem cells from the other skin cells using a technique called Fluorescence Activated Cell Sorting (*FACS*). The results can be visualized as shown in the dot plot in Figure 3. Each dot represents one cell. The position

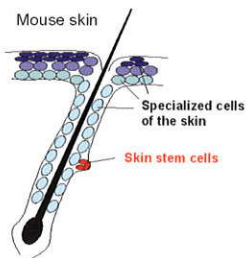


Fig. 2

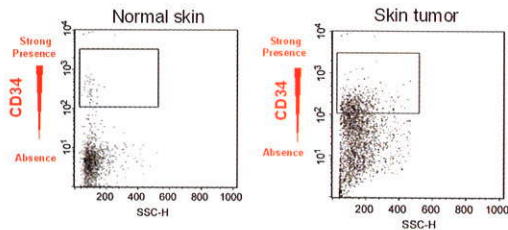


Fig. 3

of the dot on the X axis indicates the size and shape of the corresponding cell, while the position on the Y axis indicates the presence of the CD34 molecule. Therefore, the cells included in the rectangle represent the pool of stem cells of the mouse skin.

We found that the CD34 molecule was present also in a population of tumor cells (Figure4).

The idea that led our investigation was that the presence of specific molecules in both, these tumor cells and skin stem cells, could reflect a functional similarity.

As previously described, the characteristic of stem cells is to be able to generate all the other cells of the organ and even to maintain their own population. We asked, similarly to the skin stem cells, whether tumor cells presenting the surface CD34 molecule are able to generate all the other tumor cells. To answer to this question, we tested the ability of tumor cells presenting the CD34 molecule to initiate tumor growth and to reconstitute a new tumor when transplanted onto nude mice. As illustrated in Figure 4 (left), the CD34 tumor cells were hundred fold more efficient in reconstituting a tumor when compared with the total tumor cells. Importantly, tumor cells without the CD34 never initiated a tumor. Furthermore, the organization of the reconstituted tumors was identical

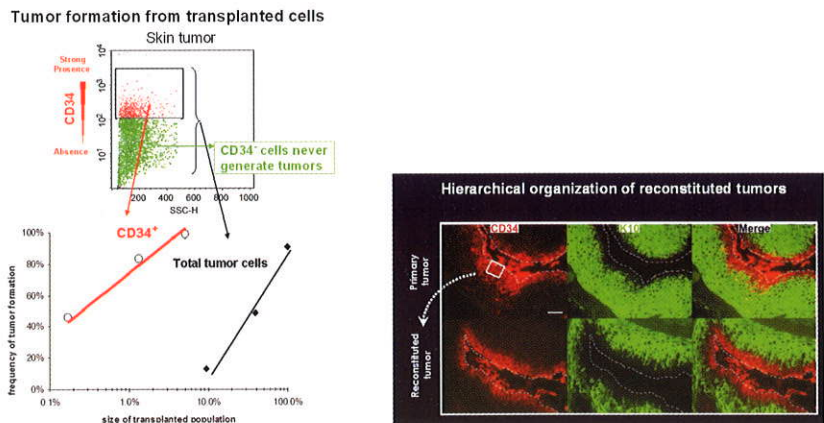


Fig. 4

to the primary tumor (Figure 4, right), indicating that cells presenting the CD34 molecule had the ability of deriving all tumor cells.

In the last years the understanding of cancer biology has evolved from a more simplistic model where cancer cells are all equal in their potential, to a more complex view where also cancer cells are diversified (Figure 5). According to this view, a tumor resembles an organ in that only a fraction of tumor cells retain the potential of sustaining tumor growth throughout time. For their similarity to stem cells these tumor cells are called “cancer stem cells”. Similarly to stem cells that can repair an injured organ, cancer stem cells can reinitiate tumor growth upon tumor therapy.

Cancer stem cell concept



Old concept :
All the cells in the tumor are equal and have the same ability in restoring a new tumor.



New cancer stem cell concept:
The tumor resemble an organ: it is organized as a hierarchy of different tumor cells and only a subpopulation of them exclusively retain the ability to sustain long term tumor growth and to reconstitute the tumor.

Fig. 5

In line with this theory, as described above, we have for the first time identified rare cancer stem cells (presenting the CD34 molecule) in skin tumors with the exclusive potential for tumor initiation. Only these cells can reconstitute an exact duplicate of the primary tumor. The relevance of this finding lies in the idea that since cancer stem cells are the cells responsible to support tumor growth, specifically targeting these cells would result in complete tumor regression without relapse (Figure 6).

Promises and challenges of the cancer stem cell concept:

Targeted elimination of cancer stem cells will induce complete tumor regression and prevent reappearance

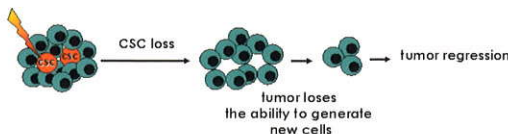


Fig. 6

We found that β -catenin, a factor involved in the regulation of several processes inside the cells, was specifically active in the tumor cells but not in the normal skin cells (blue label in Figure 7).

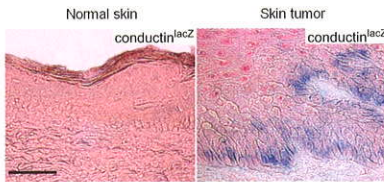


Fig. 7

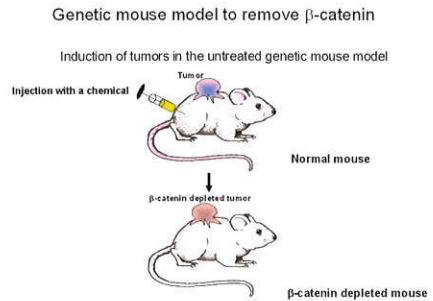


Fig. 8

We took advantage of a genetic mouse model where the β -catenin molecule could be removed exclusively from the cells of skin and skin tumor upon administration of a chemical (scheme in Figure 8). We induced tumor formation on the back skin of these mice. When the tumors reached a certain size, we induced the ablation on the β -catenin molecule by injecting the chemical. We then monitored the mice for the following weeks. As shown in Figure 9, the first week after the injection all the tumors continued to grow. After the second week, only the control tumor grew. The tumors, which at this time lacked β -catenin, arrested their growth and started to regress until they completely disappeared.

Tumor regression is induced by removal of β -catenin

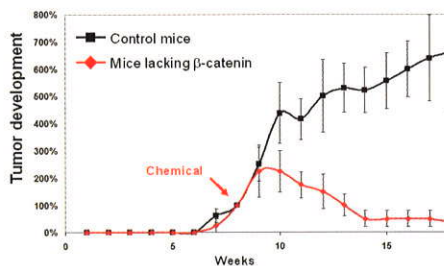


Fig. 9

Therefore, ablation of β -catenin resulted in the striking consequence of complete tumor regression. Analysis on the regressing tumors showed that the regression was not due to an increase of cell death or to a complete block in proliferation. The regressing tumor appeared completely differentiated, indicating that their long term maintenance was compromised. We tested the presence of the cancer stem cell population in the tumor where β -catenin was removed. Interestingly, we found that the amount of tumor cells with the CD34 molecule was significantly reduced (Figure 10). This finding explained the loss of long term growth of these tumors and their subsequent regression.

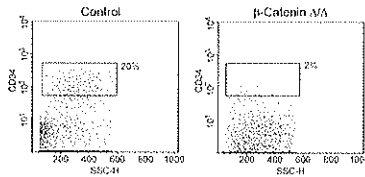


Fig. 10

In our study we have discovered a molecule being exclusively required for the function of cancer stem cells in skin tumor. Specific ablation of this molecule results in the loss of cancer stem cells, and the striking consequence is complete tumor regression. Importantly, this study proved for the first time the hypothesis that specifically targeting cancer stem cells leads to complete tumor regression.

Finally, we proved that the β -catenin molecule is also critical for the growth of human tumors. We could show that, similarly to mice, β -catenin was active in human skin tumor, but not in the normal skin. Furthermore, blocking this molecule in human skin tumor cells significantly inhibited their growth when transplanted onto mice (Figure 11).

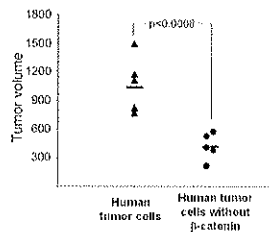


Fig. 11

Considering that this molecule it is not required for normal skin function, its essential role in tumor long term growth makes it a powerful candidate for future therapeutic applications.

Taken together, this study defines an efficient strategy to eradicate tumors and provides evidences that targeting cancer stem cells is a promising way to achieve effective tumor therapy.