Track brain tumor growth by MRI and planar bioluminescence imaging

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We demonstrated the use of MRI and bioluminescence imaging (BLI) to track tumor growth in a mouse model of human brain tumor, glioblastoma multiforme (GBM). While MRI offers high resolution and 3D structure of the brain structure, BLI has a high sensitivity and can detect as few as thousands of cells that express luciferase [1, 2]. BLI allows us to visualize genetic expression and physiological processes in living animals at the molecular level. BLI does not rely on an external excitation light as required by fluorescence imaging, because of that BLI has minimum interfering background and can detect very low levels of light. In our work, U87 cells were transfected with the firefly luciferase gene and cultured. The luciferase transfected cells (U87-Luc) were then injected into mice brain by using a stereotactic system [3]. To image the bioluminescence signal, a substrate luciferin was injected intraperitonially. When the luciferin interacts with the luciferase it causes an energy-dependent bioluminescent reaction and results in the emission of visible light. While the emitted light is very weak, it can be captured faithfully by a light detector. In addition there is virtually no light emitted from tumor-free regions and thus BLI has a high sensitivity and makes it a perfect modality to be used in combination with MRI. While BLI complements MRI in terms of early detection of small number of tumor cells, planar BLI can only capture the projected bioluminescence light from a 3D tumor. A more accurate measurement of the tumor volume can be acquired from MRI. In this sense, MRI measurement of a tumor volume is more robust to the positioning of the mouse inside the coil and the orientation of the tumor. On the other hand, planar BLI may exhibit large inter-subject variation due the projection of a 3D tumor to a 2D image. Solutions to this problem include 3D BLI tomography and using MRI as guideline to the usage of BLI. For example, a tumor resembling an ellipsoid will project different to the planar light detector depending on the orientation of the ellipsoid. While BLI can be performed quickly and more frequently than MRI, MRI can capture the orientation of an ellipsoidal tumor can allow us to normalize BLI measurement.

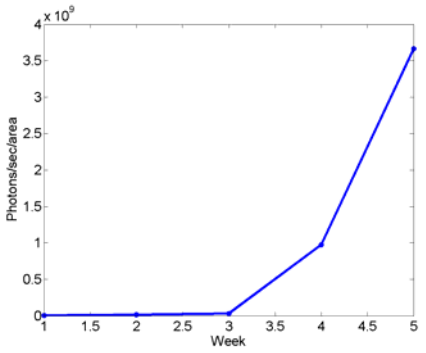

Figure 1. Changes of bioluminescscence signal over five weeks of a mouse.

Method

GBM tumor cells, U87, were transfected with luciferase and injected intracranially into mice brain. One week after the injection, we performed weekly BLI. We used a commercial bioluminescence imaging station, IVIS 100 from Xenogen Co. The system features a cooled, highly sensitive CCD camera. Mice were placed on the imaging platform and bioluminescence images were taken every 5 minutes. At the meantime, we scanned the mice by a 4.7T Bruker small animal MRI machine to verify the existence of the brain tumor.

Results

Figure 1 shows the time course over five weeks of a mouse injected with 1 million U87-Luc cells. It is observed that the BLI signal increased dramatically over the five weeks. Figure 2 shows a typical BLI result of three mice injected with the U87-Luc cells. As discussed above, there could be large inter-subject variation in BLI signals. Figure 3 shows the results of BLI signals obtained over three mice injected with the same number of U87-Luc cells. While all the three mice had an increase in BLI signal over 33 days, the absolute measurement of BLI signal in terms of photons per second per unit area were very different. Such variation could be caused by the difference in the tumor size, or by the difference in the tumor position and orientation. In order to more accurately track the tumor growth, it therefore requires researchers to carefully analyze the BLI data and use MRI data, if available, to make necessary adjustment.

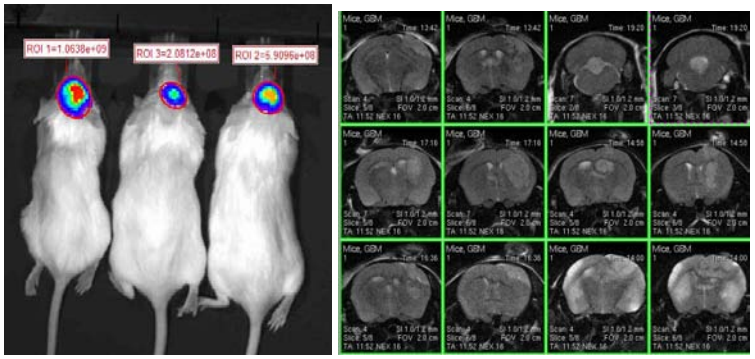

Figure 2. Left, a typical bioluminescence image of three mice injected with U87-Luc cells. Right, T2-weighted MR images of the first mouse at the fourth week. From the MRI the tumor is clearly visible.

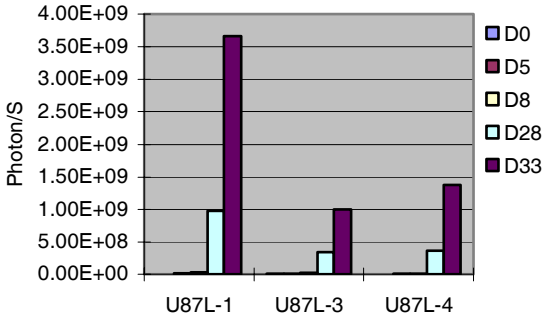

Figure 3. There is a large variation among three mice injected with same number of U87-Luc cells.

Discussions

We studied a xenograft mouse tumor model with BLI and MRI to track the tumor growth. The two modalities offer unique advantages and disadvantages in terms of sensitivity and robustness to positioning. We noted the limitation of planar BLI and proposed that using MRI we may be able to normalize the BLI measurement with respect to the tumor position and orientation, and hence reduce variation due to the measurements.

References

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