

Tissue redox activity as a sensing platform for imaging of cancer based on nitroxide redox cycle

Rumiana Bakalova¹, Zhivko Zhelev^{1,2}, Ichio Aoki¹, Daisuke Kokuryo¹, Veselina Gadjeva², and Tsuneo Saga¹

¹Molecular Imaging Center, National Institute of Radiological Sciences, Chiba, Chiba, Japan, ²Medical Faculty, Trakia University, Stara Zagora, Stara Zagora, Bulgaria

Target audience

This study is directed to the specialists in the clinical and experimental oncology.

Purpose

Redox signalling is crucial for carcinogenesis and tissue redox activity can serve as a sensing platform for cancer diagnosis and planning of therapeutic strategy.^{1,2} The present study aimed to develop an universal methodology for *in vivo* imaging of this parameter in mammals, which allows a differentiation of carcinogenesis from normal (healthy) condition.

Methods

The experiments were conducted on: neuroblastoma-bearing mice (in early or moderate stage of cancer development; n=36); colon cancer-bearing mice (in moderate stage of cancer development; n=10); and healthy mice (controls; n=38). The tissue redox activity was visualized *in vivo* by cell-penetrating nitroxides and magnetic resonance imaging (MRI) on anesthetized animals. The method is based on nitroxide redox cycle, coupled with appearance or disappearance of MRI signal.³ The half-life ($\tau_{1/2}$) of nitroxide-enhanced MRI signal in the respective tissue was used as a diagnostic marker.

Results

The tissues (cancer and non-cancer) of cancer-bearing mammals were characterized by a long-lived MRI signal ($\tau_{1/2} > 14$ min), indicating a high oxidative activity. The tissues of healthy organism were characterized by a short-lived MRI signal ($\tau_{1/2} < 3$ min), indicating a high reducing activity to the nitroxide probe. Highest signal intensity was detected in the cancer area. An enhanced oxidative activity of non-cancer tissues was observed even when the cancer is at early stage of development and cannot be visualized anatomically by high-resolution MRI.

Discussion

The results provide direct evidence on intact mammals that healthy and cancer-bearing organisms are characterized by completely different tissue redox activity, which can be a basis for cancer diagnosis using nitroxide-enhanced MRI. The tissues of cancer-bearing mammals are characterized by a high oxidative activity, while the tissues of healthy organism are characterized by a high reducing activity to the nitroxide probe.

In vivo, the nitroxide probe exists mainly in two forms – radical and hydroxylamine.⁴ Various reducers and oxidizers are involved in the formation of hydroxylamine, but only the interaction of hydroxylamine with superoxide (and/or hydrogen peroxide) seems to be a dominant process *in vivo* that can restore the nitroxide radical and MRI contrast.⁴ We assume that the long-lived nitroxide-enhanced MRI signal in cancer-bearing mice can be explained by the presence of excessive amount of superoxide (and/or hydrogen peroxide) in their tissues. This is in agreement with the widely-accepted opinion that cancer cells are characterized by increased production of reactive oxygen and nitrogen species than normal cells, which ensures genomic instability.^{1,2}

Conclusion

The study shows that the tissue redox activity can be used as a sensing platform for imaging of cancer, using nitroxide-enhanced MRI and cell-penetrating contrast agent. The proposed methodology is applicable in clinical laboratory practice on isolated biopsy specimens and blood samples for evaluation of the effectiveness of anti-cancer therapy, based on its effect on tissue redox status. The data also suggest that non-cancer tissues of cancer-bearing mammals are potential therapeutic target and its protection against oxidative stress may be essential for survival and recovery of the organism.

References

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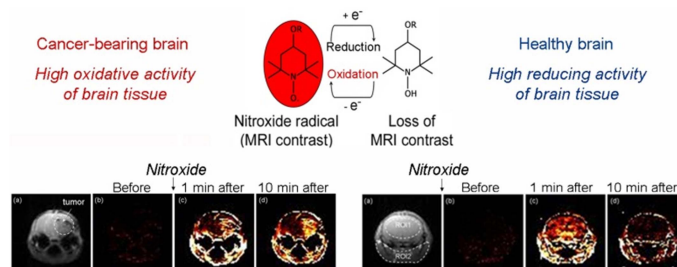


Figure 1: Dynamics of nitroxide-enhanced MRI signal in cancer-bearing and healthy mice, based on tissue redox activity.