

Abstract

Genetically Encoded Photosensitizer Targeted to Methylated DNA †

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Abstract: Genetically encoded photosensitizers are widely used in fundamental research and translational medicine due to their ability to generate reactive oxygen species (ROS) after photosensitizing. Previously, it was shown in mice that red dimeric fluorescent protein KillerRed is a potential photosensitizer that can be used for photodynamic therapy of cancer. In addition, it was demonstrated that HeLa cells expressing KillerRed fused to histone H2B cease proliferation upon illumination. A DNA repair protein, X-ray repair cross-complementing protein 1 (XRCC1), redistributed in the cell nuclei, indicating that the mechanism of phototoxic action of the construct involved DNA breaks generation. Here, we have constructed and tested a new genetically encoded photosensitizer molecule which introduces DNA breaks and activates the repair system in cancer-derived and embryonic cell lines more efficiently than previously described. The molecule consists of two parts: a SuperNova2 (monomeric mutant of KillerRed with enhanced phototoxicity) and methyl-CpG binding protein MECP2. The complex activates XRCC1 redistribution after illumination with lower power compared to the previously used construct. We suppose it can be explained by the tighter contact between photosensitizer and DNA. In addition, we hypothesize that the system should be error-prone for the expressed genes as it is targeted to the DNA which is silenced by methylation. Taking everything into consideration, the new genetically encoded construct has shown the improved ability to generate DNA breaks in the cancer cell lines.

Keywords: genetically encoded photosensitizer; KillerRed

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