Targeting hypoxic cancer cells by of checkpoint kinases ATR and CHK1

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Background

The checkpoint kinases ATR and CHK1 are considered to be promising targets for cancer treatment due to their roles in regulation of the S and G2 checkpoints and in the repair of DNA double strand breaks through homologous recombination. Interestingly, severe levels of hypoxia O₂ have been shown to activate ATR/CHK1 signaling, which could likely make hypoxic cancer cells sensitive to inhibitors of these kinases.

Aims

The aim of this project is to explore whether inhibition of ATR or CHK1 could be used to selectively target hypoxic cancer cells, both in combination with ionizing radiation and on its own.

Conclusions

• We found that hypoxia alone did not alter the sensitivity to CHK1 inhibitors, but inhibition of CHK1 after reoxygenation following periods of extreme hypoxia (0.0% O₂) did result in decreased clonogenic survival and an increased fraction of γ-H2AX positive cells.
• Hypoxic cells were also found to radiosensitize at least to the same extent as normoxic cells by CHK1 inhibition.
• Preliminary experiments performed in Osteosarcoma (U2OS) and lung cancer lines H460, A549 treated with the ATR inhibitor VE821 shows that the number of γ-H2AX positive cells after ATR inhibition was higher in cells incubated at hypoxia (0.0% O₂, 20%) compared to normoxia (21% O₂).
• The ATR inhibitor also abrogated the radiation-induced G2 checkpoint.
• These studies help determine the potential of using inhibitors of ATR and CHK1 to eradicate radiosensitive hypoxic cancer cells.

Figure 1. Exposure to 0.0%, but not 0.2% O₂ results in cell cycle delay, activation of CHK1 and phosphorylation of H2AX in S-phase cells.

Figure 2. Re-oxygenation following exposure to 0.0% O₂ sensitizes cancer cells to CHK1 inhibitors.

Figure 3. Inhibition of CHK1 sensitizes hypoxic cells to ionizing radiation (IR).

Figure 4. Preliminary experiments showing that hypoxia can sensitize cells to ATR inhibition.

References