Imaging Tumor Sensitivity to a Bioreductive Prodrug:  
Two for the Price of One!

J. Martin Brown

Hypoxia is an important characteristic of many solid tumors and has a major negative effect on treatment response. A way to combat this effect is with drugs called “bioreductive prodrugs” or “hypoxic cytotoxins,” which are metabolized under hypoxia to toxic species. However, the patients with hypoxic tumors need to be identified.

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out to address was whether there was a relationship between the activity of the enzymes that reduce EF5 to its hypoxia-binding species and those that reduce CEN-209 to its cytotoxic species. Although both require the addition of an electron from the reducing enzymes, there is no a priori reason to suppose that the same enzymes would reduce EF5 and CEN-209: The compounds are dissimilar in structure (a nitroaromatic and N-oxide, respectively) and in the severity of hypoxia required for their activation to their respective active metabolites. Yet, Wang and colleagues, using a battery of sensitive assays, which they did with great care with multiple important controls, found a very close correlation over a wide range of enzymatic activity between the reduction of EF5 and that of CEN-209, as well as cytotoxicity and DNA damage by CEN-209, under hypoxic conditions. Importantly, although they showed that the reducing enzyme CYPOR metabolized EF5 and CEN-209 to a similar extent, they showed that CEN-209 metabolism was more closely correlated with EF5 binding than with CYPOR activity, implying the presence of additional (as yet unknown) enzymes responsible for the reduction of both EF5 and CEN-209. This finding shows that EF5 binding (and, hence, strength of 18F-EF5 signal in tumors) provides a superior assessment of reductive metabolism (and, hence, cytotoxicity) of CEN-209 than does the activity of CYPOR or any other known enzymes.

These findings have important implications for the clinical use of CEN-209. As the drug kills only cells under hypoxic conditions, it is accepted that no clinical trials should be conducted without first selecting the patients with hypoxic tumors. There is a plethora of potential ways to do this, including directly measuring oxygen levels with electrodes, using immunohistochemistry of hypoxia-activated proteins such as CA9 or GLUT1, and PET imaging with nitroaromatic compounds such as 18F-EF5. However, the data presented by Wang and colleagues show that detecting hypoxia with EF5 has the major advantage over the other methods, in that it not only detects hypoxia but also assesses the level of prodrug-activating reductive enzymes needed to metabolize CEN-209 to its cytotoxic species. Thus, a tumor that “lights up” with 18F-EF5 should be sensitive to CEN-209, whereas one that might be hypoxic but shows little 18F-EF5 activity would not be expected to be sensitive to the drug (Fig. 1). In effect, EF5 potentially images tumor sensitivity to CEN-209 by simultaneously assessing tumor hypoxia and the level of reductive enzymes. It is two for the price of one.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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