Inhibiting the Hypoxia Response for Cancer Therapy: The New Kid on the Block

Commentary on Narita et al., p. 6128

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The hypoxia-inducible transcription factor (HIF)-1α inhibitor KC7F2 described in this issue of Clinical Cancer Research is the newest addition to an emerging class of antitumor agents targeting the hypoxia response. Here, we discuss the proposed mechanism of action of KC7F2 and its potential strengths and limitations in comparison with other promising HIF-1α inhibitors. (Clin Cancer Res 2009;15(19):5945–6)
cell division. For these agents, it may be difficult to determine the extent that HIF-1α inhibition plays in antitumor activity. Nevertheless, some HIF-1α inhibitors achieve their potency by inhibiting HIF-1α at multiple levels. The guanylyl cyclase activator YC-1 inhibits HIF-1α by promoting HIF-1α degradation, inhibiting HIF-1α synthesis, and disrupting its transcriptional activity by interfering with the HIF-1α/p300 interaction (5). PX-478, a HIF-1α inhibitor currently in a Phase I clinical trial, inhibits HIF-1α by decreasing HIF-1α translation and, to a lesser extent, transcription and deubiquitination of HIF-1α (6). It is interesting that KC7F2 is a disulfide compound similar to PX-12, a dual thiorodoxin and HIF-1α inhibitor that is also in early clinical trials (7).

Narita and colleagues propose that KC7F2 inhibits HIF-1α translation by reducing the phosphorylation of the translation repressor eIF4E binding protein (4E-BP1) and the ribosomal kinase S6K, thus preventing initiation of translation. As HIF-1α is one of the few proteins whose translation is maintained during hypoxia, this could be a mechanism by which KC7F2 achieves selective inhibition of HIF-1α. However, it should be noted that both 4E-BP1 and S6K, downstream targets of the mTOR pathway, are generally believed to already be inhibited in hypoxia as a means to reduce global protein translation (8). It will be interesting to see whether KC7F2 inhibits phosphorylation of these proteins in normoxia or whether the effect of KC7F2 on the translational machinery is hypoxia dependent.

Ultimately, although many agents have been shown to inhibit HIF-1α in cells, only a few have been shown to inhibit HIF-1α in vivo and to have significant antitumor activity. The higher selectivity of KC7F2 for cancer versus normal cells and its increased cytotoxicity toward these cells in hypoxia versus normoxia is promising. Further work is needed to show whether KC7F2 will live up to its potential in vivo.

Disclosure of Potential Conflicts of Interest

G. Powis is a founder, stockholder, and formerly consultant to Oncothyreon, which owns PX-12 and PX-478, two HIF-1 inhibitors mentioned in this review.

References

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doi:10.1158/1078-0432.CCR-09-1650

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