Commentary

AKT inhibition: a bad actor in liver injury and tumor development?

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Cells respond to growth signals by activating internal programs that coordinate growth, division and death. One of these, the PI3K/AKT pathway, is frequently activated in human cancer (1). The serine/threonine kinase AKT is a key actor that regulates development, metabolism and the immune response (2,3).

Two decades of intense scrutiny have given us several AKT inhibitors to test as cancer therapeutics. Some have entered clinical trial, so it is important to define mechanisms underlying their therapeutic and toxic effects. Investigators frequently model the effects of an inhibitor with a germline knockout (KO) of the inhibitor's gene target in mice. However, we know that gene KO during development may mask a role in the adult. To study how adults respond to *Akt* loss, Wang *et al.* conditionally knocked out *Akt* in adult mice, both systemically and in the liver (4). This approach unmasked unexpected potential toxicities of AKT inhibitors.

The three members of the *Akt* family are *Akt1*, *Akt2* and *Akt3*. Their genetic sequences are quite similar, but we know they have both overlapping and distinct functions and substrates (5). Wang and colleagues find *Akt1* and *Akt3* ablation does not kill adult mice. However, concomitant, systemic deletion of *Akt1* and *Akt2* cause liver inflammation, hypoglycemia and death. The authors speculate intestinal damage inhibits nutrient absorption, shifting the animal's primary energy supply to fatty acid oxidation. Once the animal exhausts fat stores, hypoglycemia and death rapidly ensue. Effects of a moderately high dose of the pan AKT inhibitor MK2206 in mice are similar but reversible. Thus, this work illuminates a possible toxicity for pan AKT inhibitors.

The surprise in this study is that liver *Akt1* ablation in adult *Akt2*$^{-/-}$ mice causes hepatocellular carcinoma (HCC). This was unexpected since *Akt* overexpression and pathway activation are implicated in HCC development (6-8). The authors find that *Akt1* and *Akt2* ablation increases liver injury and inflammation. Markers of proliferation are expressed within the hepatic tumors, while adjacent normal tissue expresses apoptotic markers. Thus *Akt1* and *Akt2* deletion in livers of adult mice induces hepatocyte cell death and liver inflammation that progresses to HCC. AKT can suppress apoptosis by inhibiting FOXO transcription factors. This cascade is largely dependent on *FoxO1* since deleting hepatic *FoxO1* along with *Akt1* and *Akt2* protects mice from liver damage, inflammation and HCC.

The authors also investigate *Akt1* and *Akt2* involvement in liver tumor development using a chemically induced model of HCC. Individual knockout of *Akt1* or *Akt2* does not change the frequency of tumor induction. Rather *Akt2* ablation increases HCC pulmonary metastasis. They speculate that high insulin levels in *Akt2* KO mice increase AKT1 activation and metastasis. So here we see an unexpected potential negative side effect of inhibiting *Akt2*—accelerated HCC progression.

Previous work indicates obesity significantly increases the risk of HCC (9,10) through stimulation of liver damage and inflammation (11). These patients also have hepatic insulin resistance and decreased AKT signaling. This study implicates reduced hepatic AKT signaling in the genesis of obesity-induced HCC. One concern is that pan-AKT inhibitors that further suppress AKT signaling will exacerbate the increase in HCC seen in obese patients.

AKT inhibitors are slowly advancing through clinical trials. These results raise the possibility that pan AKT inhibitors cause liver injury and inflammation and possibly

HCC. The work suggests that trials carefully monitor patients for liver damage and pro-tumorigenic side effects. We need further studies to determine whether there is a window where benefits of AKT anti-tumor activity outweigh risk of these serious toxicities. Furthermore, we do not know whether drugs targeting other sites in the PI3K/AKT pathway will have similar side effects. Currently tested AKT inhibitors target all isoforms and include the ATP competitive inhibitor GSK690693 and allosteric inhibitor MK2206. Second generation allosteric inhibitors with isozyme specificity are under development and may reduce toxicities associated with pan AKT inhibitors.

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Footnote

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