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RESEARCH HIGHLIGHT

What controls PTEN and what it controls (in prostate cancer)

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The standard of care for metastatic prostate cancer (PCa) is androgen deprivation therapy since almost all PCa growth is initially reliant on the androgen receptor (AR). However, almost all patients develop resistance to this therapy within 18–24 months, and current treatment for castration-resistant prostate cancer (CRPC) is extremely limited, despite the advent of new drugs that target the AR, such as abiraterone and MDV3100.[1] Multiple studies have associated the loss of phosphatase and tensin homolog deleted on chromosome 10 (PTEN), a dual lipid and protein phosphatase that is frequently lost in prostate cancer, with the development of CRPC.[2,3] Yet, multiple studies have shown that at least 20%–40% of primary PCa, which are almost always androgen sensitive, experience a loss of PTEN,[4,5] while as many as 30% of CRPC tumors are PTEN-positive.[6] The broad questions then facing researchers are: (i) How does PTEN loss cause CRPC?; (ii) What is the mechanism of CRPC development in $PTEN^{+/+}$ tumors?; and (iii) How can CRPC tumors be inhibited in PTEN-null cells? Three new publications in recent times have come up with mechanisms that answer these questions.[7–9] Two of these, both in *Cancer Cell* earlier this year, from the laboratories of Dr Charles Sawyers and Dr Hong Wu, address a novel negative feedback regulation between AR and PTEN, and all three, including the one from Dr Damu Tang, show that the loss of PTEN function is likely the first step towards the development of CRPC.

Of the various functions of PTEN, the best known is its ability to dephosphorylate phosphatidylinositol 3,4,5-trisphosphate to phosphatidylinositol 4,5-bisphosphate, which is phosphorylated by phosphatidylinositol 3-kinase (PI3K) back to phosphatidylinositol 3,4,5-trisphosphate (**Figure 1**). Thus, PTEN antagonizes the effects of PI3K. As a result, in tumors that lack significant PTEN function, Akt, the best known downsteam effector of PI3K, can easily be phosphorylated. Yet clinical trials inhibiting the activation of the PI3K/Akt axis, or its downstream target the mammalian target of rapamycin (mTOR), failed to have a substantial effect on tumor progression in men with localized or metastatic prostate cancer,[10,11] likely because inhibition of mTOR caused an upregulation of AR transcriptional activity that promoted cell survival.[12] The paper from the laboratory of Dr Charles Sawyers[7] now show that combined therapy targeting PI3K, mTOR and the AR brings substantial relief to tumor growth in $PTEN^{lox/lox}$ mice. Surprisingly, both Dr Sawyers'[7] and Dr Wu's[9] papers show that loss of PTEN is accompanied by a decrease in AR signaling. In addition, the paper form Dr Tang's group indicates a mechanism of PTEN inactivation even in $PTEN^{+/+}$ cells.[8] As a result, a better understanding of how PTEN regulates the AR, and other targets in PCa, is finally emerging.

First of all, inhibition of the PI3K/Akt/mTOR pathway induced growth arrest but no significant tumor regression in tumors grown in $PTEN^{lox/lox}$ mice.[7] This is likely because in these mice, the PI3K/Akt/mTOR pathway does not induce apoptosis, although Akt has always been known as a cell survival regulator. It could also mean that in this model, the Akt pathway regulates proliferation, whereas the AR regulates survival. Inhibition of the PI3K/Akt/mTOR pathway upregulated the receptor tyrosine kinase HER3, whereas the same group had previously shown that suppression of HER2/HER3 heterodimers prevented AR transcriptional activity in an Akt-independent manner.[13] Therefore, it is likely that PI3K/Akt/mTOR inhibition upregulates AR transcriptional activity by increasing HER3 (**Figure 1**). In turn, the AR also suppresses the Akt pathway while AR downregulation upregulates Akt by downregulating the phosphatase PHLPP[7,9] (**Figure 1**). This, interestingly, shows feedback inhibition of each pathway by the other. Why? It is likely that the AR normally suppresses the PI3K/Akt/AR pathway in order to prevent propagation of all androgen-independent signals in order to keep the PCa cells castration sensitive. However, when the AR is downregulated, such as during androgen deprivation therapy in patients with metastatic PCa, the PI3K/Akt/mTOR pathway is upregulated and takes over the control of the cell cycle and survival.[7,9]

The paper from Dr Hong Wu's laboratory reasons that the effects of PTEN loss on CRPC cell growth may result from either loss of PTEN itself or from an upregulation of pathways that PTEN suppresses, and tries to separate the two.[9] Early castration upregulated phosphorylation of Akt and S6, a downstream target of mTOR, likely indicating that simply a loss of PTEN would not cause an increase in Akt phosphorylation, but a second stimulation, such as suppression of AR activity, is required.[9] PTEN-null cells were less dependent on AR signaling and suppressed transcriptional targets of AR, and this paper shows that PTEN directly affects AR transcriptional activity by regulating the expression of various proteins known to act as AR coregulators.[9] Interestingly, the study also distinguishes between the expression of the AR in the epithelium and the stroma, and shows that epithelial AR is not required for tumor growth in $PTEN^{lox/lox}$ mice. This supports previous findings that stromal AR is of

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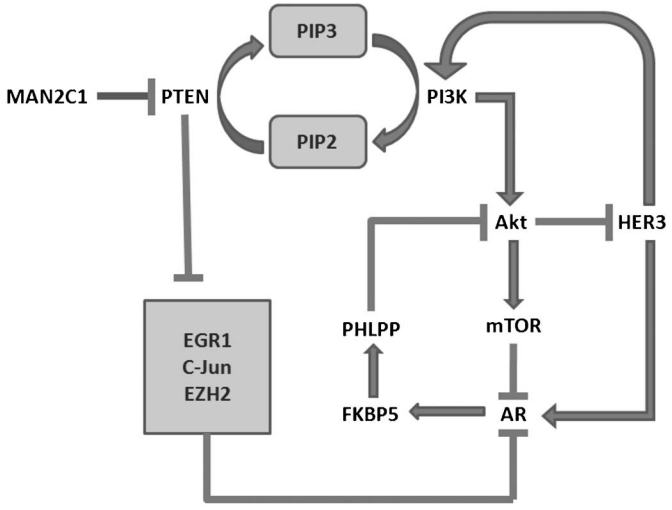

Figure 1 Schematic representation of the phosphatase and tensin homolog deleted on chromosome ten (PTEN)/Akt pathway and its relationship to the androgen receptor (AR) based on the results of three papers published recently by the laboratories of Charles Sawyers,[7] Damu Tang[8] and Hong Wu.[9] mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PIP3, phosphatidyl inositol 3,4,5-trisphosphate; PIP2, phosphatidylinositol 4,5-bisphosphate.

more importance in the development and progression of prostate cancer, and the hypothesis that epithelial AR suppresses, while stromal AR stimulates mitogenic activity.[14]

While the studies from Dr Sawyers and Dr Wu's laboratories were primarily conducted in PTEN-null cells, it is known that a large number of PCa cells that express high Akt phosphorylation in human patients are also positive for PTEN.[5] What is the cause of the increased Akt phosphorylation in these cells? Most studies assume that expression of PTEN means that it is active. Not so, says a third study from the laboratory of Dr Tang.[8] Even in cells that express high levels of PTEN, and even when that PTEN is not mutated, it can still be inactive due to the upregulation of a negative regulator of PTEN, α-Mannosidase 2C1 (MAN2C1). MAN2C1 upregulation was observed only in PCa specimen from human patients whose prostates expressed PTEN, and colocalized with PTEN. *In vitro* studies showed that MAN2C1 binds PTEN and inhibits its phosphatidyl inositol 3,4,5-trisphosphate phosphatase activity. Therefore, MAN2C1 also increased Akt phosphorylation and promoted tumor growth.[8] Since MAN2C1 belongs to a family of proteins that regulates glycoprotein maturation in the ER and in Golgi bodies, it may explain a relationship between the increased expression of glycoproteins such as MUC1 in prostate cancer.[15]

Many people just assume that a lack of PTEN causes an increase in Akt phosphorylation—that tenet is being challenged by these studies. The three studies show that Akt phosphorylation may be increased by MAN2C1-mediated PTEN inactivation even in $PTEN^{+/+}$ cells,[8] and that androgen deprivation therapy, rather than a loss of PTEN, is responsible for the increase in Akt phosphorylation.[7,9] Of course, it had been shown earlier, that PTEN-null LNCaP cells cultured in androgen-free medium show an increase in Akt phosphorylation,[16] but now the mechanism of this effect is becoming clearer. What is then obvious is that an anti-androgen, even one as powerful as MDV3100,[7] would not by itself be an effective form of therapy against metastatic prostate cancer, because each time that AR is knocked down it will activate other pathways that will want to take over[12]—resulting in AR-independent signaling. Therefore, the papers described above show that both the AR and the PI3K/Akt/mTOR pathways had to be simultaneously inhibited in order to have a substantial effect.[7,9]

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