Memo: PNC-27, a Peptide that Induces Necrosis Selectively in Cancer Cells

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Pincus and colleagues have developed a synthetic protein, PNC-27, which shows intriguing potential as a cancer therapy.[1-8] This protein is composed of a portion of the domain of p53 that binds to HMD2, linked to a pentratin sequence which enables its intracellular uptake. (A protein of similar design, PNC-28, differing slightly in the p53 domain included, has likewise shown anti-cancer activity.) The original intent behind synthesis of this protein was to prevent the binding of HMD2 to p53 in cancer cells that still expressed active p53; it was hoped that this would induce p53-mediated apoptosis in cancer cells. Other groups are working on drugs which block the p53-HMD2 interaction, likewise with the intent of inducing cancer apoptosis.[9]

When Pincus' group tested the impact of PNC-27 (or of PNC-28) on cultured cancer cells, they were gratified to note that this protein killed cancer cells, while failing to harm non-transformed cell lines.[1] However, they were startled to observe that the cancer cells died by necrosis, not apoptosis, and that the protein would also kill cancer cells that lacked functional p53.[2, 3]

Subsequent studies suggested a surprising and remarkable explanation. In cancer cells, PNC-27 was binding to HMD2 situated near the plasma membrane, and the protein was then assuming a helical conformation within the membrane that formed a pore. If enough of these pores formed, the osmotic balance of the cell was lethally disrupted, leading to cell necrosis.[3, 5] The apparent reason for the cancer-selectivity of this mechanism is that cancers, especially those that are advanced and aggressive, are prone to express HMD2 at their plasma membranes, whereas little HMD2 is found at the surface of non-transformed cells.[6] The mechanistic basis of this phenomenon remains unclear, although it had previously been documented.[10] Association of HMD2 with the plasma membrane in cancer cells enables this protein, which functions as an E3 ubiquitin ligase, to catalyse the ubiquitination and subsequent proteasomal degradation of E-cadherin, an effect which aids the epithelial-mesenchymal transition required for the metastatic spread of cancer.[10] Hence, membrane association of HMD2 tends to be observed in cancers that can spread aggressively. Overexpression of HDM2 is not uncommon in advanced cancers – possibly because p53 antagonism is selected for, but also because HDM2 promotes cancer growth and spread in other ways, in part by suppression of E-cadherin.[11-14]

In nude mice transplanted subcutaneously with a rat pancreatic adenocarcinoma (BMRPA1), steady infusion of 1-20 mg of PNC-28 over a period of 2 weeks was found to almost completely block growth of the cancer.[4] If the tumors were established before infusion commenced, partial regression of the cancers was observed. After the 14-day infusion period, growth remained minimal for 2 weeks thereafter, but then resumed, indicating that some cancer cells had survived the initial therapy. The therapy did not appear to harm the mice. These *in vivo* findings suggest that PNC-28 (and presumably PNC-27) may have genuine potential as a cancer therapy.

Unfortunately, no independent groups have reported studies with PNC-27, and development of this agent for drug use has so far progressed at a slow pace. It would be highly desirable for other researchers to examine the potential of this highly novel and promising strategy for cancer control.

It remains to be seen whether cancers which are initially sensitive to PNC-27 can grow resistant to it by acquiring genetic or epigenetic shifts that block the routing of HMD2 to the plasma membrane. It is important to understand why HMD2 is directed to the cell surface of aggressive cancers; it has been reported that IGF-I/MAPK/p90Rsk activity promotes the extra-nuclear transport of HMD2.[15] The possibility that repeated infusions of PNC-27 might give rise to anaphylactic shock in some patients is also a concern. And some less aggressive cancers, in which minimal amounts of HMD2 associate with the plasma membrane, may prove resistant to it. Nonetheless, PNC-27 merits considerable research attention as a potential clinical cancer therapy.

Since PNC-27 kills cancer cells via necrosis rather than apoptosis, it may be highly compatible with concurrent immunotherapy, as release of tumor antigens from necrotic cells, and their subsequent uptake by dendritic cells, is more effective for evoking antigen-specific anti-cancer immune responses – as well as innate anti-cancer immunity - than is the antigen exposure resulting from cancer apoptosis.[16] However, the fact that PNC-27 kills by necrosis means that, in patients with a substantial cancer burden, it may be desirable to moderate the dosing schedule so that the cancer cells are killed gradually, to avoid induction of sudden massive tumor necrosis that might trigger lethal shock.

References

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