Tests starve cancer cells while leaving normal cells unaffected

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Scientists seeking to make chemotherapies which are less harmful to cancer patients have reported "highly promising" results from a synthetic molecule called TPP.

Laboratory tests found a series of TPP-related compounds selectively shut down "bulk" cancer cells with little or no effect on normal healthy cells. The team at the University of Salford described their findings, published in the journal Aging, as having a promising "magic bullet effect".

Chemotherapies are generally poisonous to humans in that they not only break down cancerous cells but also harm healthy ones causing a litany of side-effects including nausea, hair loss, nerve damage and increased risk of infection, as well as inducing secondary cancers.

"To find something which is non-toxic and inexpensive, made with this kind of mitochondrial targeting mechanism is very encouraging, although it is too early to say how it might work in practice," said Professor Michael Lisanti, FRSA, Chair of Translational Medicine.

TPP, or Tri-phenyl-phosphonium, is a non-toxic compound that is used as a mitochondrial targeting signal (MTC), to send attached cargo molecules to mitochondria. Mitochondria are the powerhouse of the cells.

The Salford team, interested in TPP's behaviour as a targeting signal for

mitochondria, randomly selected nine TPP-related compounds and found that five of them depleted the molecules that transfer energy in the cell.

These studies show that certain TPP compounds can distinguish between "malignant" mitochondria and "normal" mitochondria, leaving normal cells unaffected. For example, Lisanti and colleagues directly showed that these TPP molecules only killed cancer cells and cancer stem cells, while normal cells did not show any loss in viability.

Using a Seahorse XFe96 metabolic flux analyser, they established that all five TPPs inhibited oxygen consumption rates, having little or no effect on energy transfer in normal human cells, but selectively targeted neighbouring "bulk" cancer cells. They also inhibited anchorage-independent growth, which is normally associated with a metastatic phenotype.

"By stopping the mitochondria from reproducing, we are effectively starving cancer cells, allowing their eradication," explained Lisanti. "And these TPP compounds can do this without interfering with mitochondrial function in a healthy cell."

The most effective molecule identified contained two TPP moieties and is referred to as 2-butene-1,4-bis-TPP.

"To have found something which kills both "bulk" cancer cells and cancer stem cells, while specifically minimizing or avoiding off-target side-effects in normal cells, is significant," commented Dr. Bela Ozsvari, a co-author on the study.

"It also provides evidence that "normal" mitochondria and "malignant" mitochondria are biochemically distinct, removing a significant barrier to therapeutically targeting cancer metabolism."

More information: Bela Ozsvari et al. Exploiting mitochondrial targeting signal(s), TPP and bis-TPP, for eradicating cancer stem cells (CSCs), *Aging* (2018). DOI: 10.18632/aging.101384