Antibiotics that target mitochondria effectively eradicate cancer stem cells, across multiple tumor types: Treating cancer like an infectious disease.

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Abstract

Here, we propose a new strategy for the treatment of early cancerous lesions and advanced metastatic disease, via the selective targeting of cancer stem cells (CSCs), a.k.a., tumor-initiating cells (TICs). We searched for a global phenotypic characteristic that was highly conserved among cancer stem cells, across multiple tumor types, to provide a mutation-independent approach to cancer therapy. This would allow us to target cancer stem cells, effectively treating cancer as a single disease of "stemness", independently of the tumor tissue type. Using this approach, we identified a conserved phenotypic weak point - a strict dependence on mitochondrial biogenesis for the clonal expansion and survival of cancer stem cells. Interestingly, several classes of FDA-approved antibiotics inhibit mitochondrial biogenesis as a known "side-effect", which could be harnessed instead as a "therapeutic effect". Based on this analysis, we now show that 4-to-5 different classes of FDA-approved drugs can be used to eradicate cancer stem cells, in 12 different cancer cell lines, across 8 different tumor types (breast, DCIS, ovarian, prostate, lung, pancreatic, melanoma, and glioblastoma (brain)). These five classes of mitochondrially-targeted antibiotics include: the erythromycins, the tetracyclines, the glycylcyclines, an anti-parasitic drug, and chloramphenicol. Functional data are presented for one antibiotic in each drug class: azithromycin, doxycycline, tigecycline, pyrvinium pamoate, as well as chloramphenicol, as proof-of-concept. Importantly, many of these drugs are non-toxic for normal cells, likely reducing the side effects of anti-cancer therapy. Thus, we now propose to treat cancer like an infectious disease, by repurposing FDA-approved antibiotics for anti-cancer therapy, across multiple tumor types. These drug classes should also be considered for prevention studies, specifically focused on the prevention of tumor recurrence and distant metastasis. Finally, recent clinical trials with doxycycline and azithromycin (intended to target cancer-associated infections, but not cancer cells) have already shown positive therapeutic effects in cancer patients, although their ability to eradicate cancer stem cells was not yet appreciated.

KEYWORDS: antibiotics; cancer stem cells; mitochondria; mitochondrial biogenesis; tumor initiating cells

Comment in

Drug therapy: Can the mitochondrial adverse effects of antibiotics be exploited to target cancer metabolism? [Nat Rev Clin Oncol. 2015]