

Unveiling the Potential of Repurposing FDA-Approved Drugs in Pancreatic Cancer

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Editorial

Therapeutic options for pancreatic ductal adenocarcinoma (PDAC) and, in particular, for unresectable cases are still limited. Hence, overall survival rates remain low and estimates suggest that PDAC will move up the ladder to become the number two in cancer-related deaths over the next decades [1,2]. Various factors endow PDAC with this drug resistance; one of the main contributors is the cancer niche which acts as an unsurmountable fortress due to its desmoplastic and poorly vascularized nature [3] as well as the additional activation of cancer stem cell (CSC) pathways in PDAC cells [4]. Hence, alternative treatment choices are profoundly necessary and need to be evaluated. Renz and colleagues discussed FDA-approved drugs on their theoretical antineoplastic potential in their recent comprehensive review 'Repurposing Established Compounds to Target Pancreatic Cancer Stem Cells (CSCs)' [5].

The article is subdivided into two parts with a focus on metabolic modulators and CSC pathway inhibition. Cancer cells are chameleons in that they are very versatile and adjust easily to tough circumstances such as reduced nutrient supply within the microenvironment. Malignant transformation *per se* has been linked to altered metabolic pathways such as the revived concept of the Warburg effect, a kind of lactic acid fermentation in the cytosol following high rates of glycolysis instead of oxidation processes commonly found in most non-malignant cells [6]. Pancreatic CSCs seem to rely on yet another method of energy acquisition in the form of mitochondrial oxidative phosphorylation (OXPHOS) [7]. Last, another underappreciated aspect of self-sufficient metabolite production is the autolytic recycling and reusing of cell organelles by disassembling non- or dysfunctional cytoplasmic components, a process now widely known as (macro-) autophagy [8]. PDAC seems to rely heavily on this process, because comparisons to other neoplasms showed much higher levels without inducing actual cell death.

These novel insights provide opportunities to target altered metabolic pathways, especially because many FDA-approved drugs already affect many of those areas. For instance, antibiotics were shown to constrain both mitochondrial protein translation (MPT) and cancer stemness in liquid tumors [9], OXPHOS dependence might be exploitable by the combination of metformin and the BRD4 inhibitor JQ-1 in pancreatic CSCs [7], and the concept of autophagy inhibition by using chloroquine is already being evaluated in clinical phase I studies.

Recent evidence suggests that cancer stemness is not a defined state, but depends on CSC pathway activity [10] and these signals can be modulated by secreted cues of the cancer microenvironment. Moreover, FDA-approved drugs have been shown to influence certain signaling cascades, which led to an inhibitory effect on cancer growth in general. Among others, components of antibiotic medications proved to possess above-mentioned properties; however, other medical drugs, such as the NK1-R blocker aprepitant, normally applied for chemotherapy-induced nausea and vomiting (CINV), revealed potent antineoplastic behavior in colorectal, hepatic and other cancer types [11,12].

One pivotal point in PDAC is the microenvironment as described before. Multiple cell types form part of the immediate surrounding and essential functions has been ascribed to pancreatic stellate cells (PSCs), a myriad of immune cells, and neural cells. The latter ones might even be involved in a positive forward feedback loop: Here, catecholamines stimulate epithelial proliferation, upregulate neurotrophin expression, thereby inducing sympathetic innervation, which causes local norepinephrine accumulation within the tumor microenvironment. This mechanism seems to be susceptible to beta-blocker treatment [13].

In the recently published review 'Repurposing Established Compounds to Target Pancreatic Cancer Stem Cells (CSCs)', we summarize and discuss in detail the current knowledge about FDA-approved compounds with a strong potential to influence the differentiated PDAC as well its subgroup of pancreatic CSC. The list of drugs makes no claim to be complete; however, this armamentarium of substances shows we might already hold a huge medical array with potential capacity, little side effects, and high promise. Further future clinical studies will be necessary to clarify the usefulness of the mostly basic and translational scientific knowledge about those compounds.

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