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SHORT COMMUNICATION
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Factors That Influence Fenofibrate Effects On Cancer Cells

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Short Communication

A recent clinical trial for pediatric embryonal brain tumors reported encouraging results, with a treatment scheme that included peroxisome proliferator-activated receptor-α (PPARα) agonist fenofibrate [1]. The treatment scheme was aimed at inhibiting neovascularization; however, the drugs used can inhibit cancer cell growth by a number of mechanisms. In a different treatment scheme, aimed to treat a variety of recurrent or progressive tumors, fenofibrate could not demonstrate similarly encouraging effects [2].

Under which conditions can fenofibrate be effective?

In basic and clinical research, PPAR agonists are generally used to inhibit angiogenesis [1], [2], [3]. However, it has been revealed that they can stimulate angiogenesis as well, using as models human cultured endothelial cells and mouse cornea [4]. It could be argued that cell type and microenvironment determine effects on angiogenesis, and can be determined by the cell and host composition of the preclinical study model.

Downstream targets of PPAR agonists can have multiple effects on gene expression and cell physiology: The subject of PPAR ligands as anticancer drugs has been reviewed recently. Grabacka et al., note that PPARα activation can engage molecular interplay among SIRT1, AMPK, and PGC-1α [5] which could explain, at least in part, the encouraging results of the Peyrl et al., study (more on this topic in [6]). In cultured cervical cancer cells, however, fenofibrate can induce mRNA for PPARα, PPARγ and superoxide dismutase 1, with tendency to decrease radiation sensitivity [7]. In different types of gastrointestinal cancer, PPAR activity above or below normal can affect tumor growth [8]. High PPAR activity can kill cancer cells that are unable to utilize fatty acids as a source of energy, or that depend on signals mediated by transcription factors NF-kB or STAT3; on the other hand PPAR activity can support growth of cancer cells that are deficient in tumor suppressors such as APC, or cancer cells that derive energy from oxidation of fatty acids [8].

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Interestingly, in a recent mechanistic study on chronic lymphocytic leukemia (CLL), inhibitors of PPARα and fatty acid oxidation enzymes increased glucocorticoid-mediated killing of CLL cells in culture. The study authors noted a similar effect on mouse CLL xenografts, where immune-deficient mice could be rescued by combination of GCs and PPARα inhibition [9]. CLL cells may use fatty acids as a source of energy, because they express lipoprotein lipase: palmitate oxidation rates in circulating CLL cells can be similar to normal fat-burning cells such as muscle [10]. Transgenic expression of PPARα in the cell line Daudi, increased both expression of immunosuppressive factors interleukin (IL)10 and phospho-STAT3 and resistance to metabolic and cytotoxic stress; in contrast, PPARα antagonist MK886 killed circulating CLL cells directly, caused proliferating CLL cells to enter an immunogenic death pathway and cleared CLL xenografts from immunodeficient mice. [10].

Lipoprotein lipase is highly expressed in bone marrow mesenchymal stem cells of acute myeloid leukemia patients, making those marrow cells prone to adipogenic differentiation, and thereby contributing to alteration of the bone marrow as a niche [11].

It is clear that balance of metabolic function is critical to the function of bone marrow as a niche for hematopoetic cells: in normal hematopoietic stem cells, regulation of mitochondrial fatty acid oxidation is essential for their function. Inhibition of fatty acid oxidation results in symmetric commitment [12].

Inflammatory signals are an important parameter of PPAR effects on cancer development. In mouse liver, deletion of PPARα aggravates lipopolysaccharide -induced hepatic injury through activating transcription factors STAT1 and NF-κB-p65 and increasing levels of pro-inflammatory cytokines. The activities of key anti-oxidant enzymes and mitochondrial complexes decrease while lipid peroxidation and protein nitration levels increase [13]. Similarly, inhibition of PPARγ in mouse myeloid-lineage cells induces systemic inflammation, immunosuppression, and tumorigenesis [14].

The ability of nuclear receptors to interfere with specific aspects of inflammatory signals is crucial to the effects of PPAR agonists. Against Mantle cell lymphoma (MCL), fenofibrate was shown to inhibit activity of the transcription factor NF-kB, killing the malignant cells [15]. It must be noted that NF-kB has a wide range of effects on nuclear receptors [16] [17], and that nuclear receptors have a broader role in cancer cells than the one anticipated by their function in classical endocrinology of healthy tissue [18] [17].

Breast cancer cells survive due to enhancement of NF-kB activity by glucocorticoids [19]. NF-kB may also be activated by PPARα in breast cancer initiating cells [20]. Activation of NF-kB facilitates plasmacytoma cell resistance to glucocorticoids and to inhibitors of Janus kinases, and enables the cells to grow in the absence of Interleukin-6 [21]. In acute leukemia activation of NF-kB was associated with glucocorticoid treatment failure in children [22], and chemotherapy failure in adults [23]. In cell culture, persistent activation of NF-kB could protect Acute Myeloid Leukemia cells from proteasome inhibitor bortezomib [24].

The importance of regulation of inflammatory mechanisms by nuclear receptors and their ligands is also evident in comparison of the effects of fibrates and glucocorticoids between rodents and primates. Fibrates have partly different effects in the liver of a primate (cynomolgus monkey) in comparison to rodents (rats and mice). When mice and rats are given PPARα agonists, they show hepatic peroxisome proliferation, hypertrophy, hyperplasia, and eventually hepatocarcinogenesis; these effects are accompanied by a higher expression of inflammatory genes in rodent liver, in comparison to monkeys [25]. The inflammatory

effects in mice, however, can be modulated by glucocorticoids, as there appears to be a synergy of PPAR and GR against inflammatory signals [26] [27]: PPARα blocks glucocorticoid receptor-mediated transactivation but cooperates with liganded glucocorticoid receptor for transrepression on NF-kB [28]. As result, in mice with hyperinsulinemia through high-fat diet, activation of PPARα limits GC-induced Glc intolerance [28].

A synergy of nuclear receptors against inflammatory mediators can have importance for leukemic cells that are resistant to glucocorticoids [29]; such cells can be killed in vitro by proteasome in inhibitor with a gene expression signature enriched for the STAT3 signal pathway [30]. The clinically permitted exposure, however, to the proteasome inhibitor, is rather low [31], and bone marrow cells may modulate STAT3 signals [32]. Interestingly, chronic treatment with fenofibrate inhibits STAT3 activation, and prevents the IL-6-induced gene expression in wild-type but not in PPARα-deficient mice [33]. Tissue-specific modulators of PPARα could be therefore effective, to interfere with selected targets of the glucocorticoids in cancer cells in vivo [34]. For types of tumor cells that cannot integrate fatty acid oxidation in their metabolism, even fenofibrate should be studied as part of the antineoplastic drug combination, including however preferably assays not only on the malignant cells, but also on the cells that form their niche. As described, the molecular endpoint targets of PPAR pathways are useful variables in the analysis of drug interactions at the level of cell culture. In conclusion, PPAR activators like fenofibrate have a high potential as anticancer drugs; and due to interference with glucocorticoid signals, are particularly interesting in leukemia. Fenofibrate is capable, however, for negative effects in antineoplastic treatment, especially on cancer cell types that utilize fatty acid oxidation as an energy source, and as a pathway for resistance to drugs. Advance in molecular study of homeostatic mechanisms, with particular attention to aspects specific for the human organism [35], will enable progress in design of combination schemes for this type of PPAR agonists.

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