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Activation of PPARγ in myeloid cells promotes lung cancer progression and metastasis

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PPARγ activators inhibit cancer cell growth. However the role of these agents in progression/metastasis is not well-defined. Using an orthotopic model of lung cancer, we showed that pioglitazone accelerated progression/metastasis through affects on macrophages. This suggests that potential therapeutic agents may have opposing effects on cancer in different cells.

For most cancers, including lung cancer, patient survival is more closely linked to metastasis than primary tumor burden, underscoring the need to develop inhibitors of metastasis. A critical difference between tumor initiation and progression/metastasis is the role of the tumor microenvironment (TME). Cancer initiation in solid tumors largely involves changes in epithelial cells, whereas progression/metastasis depends on interactions between cancer cells and the surrounding stroma. Thus when targeting a specific molecular pathway, a potential complication is that the particular pathway may have opposing physiologic effects in different cell types. This has been demonstrated in the case of NFκB and hepatocellular carcinoma. Work from the Karin lab showed that activation of NFκB in hepatocytes protects against cancer development, whereas activation of the same pathway in myeloid lineages (Kupffer cells) promotes cancer progression.[1] Activation of the nuclear receptor peroxisome proliferator-activated receptor-γ (PPARγ) has been extensively studied in numerous cancers. This nuclear receptor is the target for the thiazolidinediones class of agents (TZDs), including rosiglitazone and pioglitazone. Studies in cell lines and animal models have demonstrated inhibition of tumor growth and promotion of a more differentiated, less invasive phenotype. In lung cancer interest in these agents was increased by a retrospective study showing decreased incidence of lung cancer in patients using TZDs to treat diabetes.[2] Our laboratory has studied effects of PPARγ activation in human non-small cell lung cancer cells (NSCLC), and shown inhibition of transformed growth and invasiveness.[3] We therefore sought to determine the effects of these agents on lung cancer progression. We used a recently developed orthotopic model in which murine lung cancer cells are injected directly into the left lobe of the lung of immunocompetent mice. These cells form tumors which progress to secondary pulmonary tumors and metastasize to the liver and brain. Our expectation was that TZDs would inhibit tumor progression in this model. Unexpectedly, we have found that administration of pioglitazone increased the rate of progression and the number of liver and brain metastasis.[4] In light of anti-tumorigenic effects on these cancer cells in vitro, we hypothesized that the pro-metastatic effects of pioglitazone were mediated through effects on the TME.

Macrophages play a critical role in cancer progression. A model has been proposed in which macrophages undergo a phenotypic modulation in the setting of tumors from a pro-inflammatory phenotype designated M1 to an alternatively activated phenotype designated M2.[5] M2 macrophages promote tumor progression through production of pro-angiogenic cytokines. In light of studies demonstrating promotion of the M2 phenotype by TZDs in the setting of atherosclerosis,[6] we focused on macrophages. Tissues from pioglitazone-treated mice showed increased numbers of M2 macrophages. In mice with targeted deletion of PPARγ in myeloid lineages, we found marked inhibition of tumor progression and metastasis, and this was associated with decreased numbers of M2 macrophages. Based on these findings we propose that activation of PPARγ plays a dual and opposing role in cancer. In cancer cells it inhibits proliferation and promotes differentiation, whereas in macrophages in promotes progression by mediating conversion of these cells to an alternatively activated phenotype. The relevance of these findings is underscored by several studies that have demonstrated an association of increased number of M2 macrophages in human lung tumors with worse outcomes.[7] Thus the potential efficacy of pioglitazone will depend on which cell type is playing a dominant role. In the setting of chemoprevention, the major target appears to be the lung epithelial cell, whereas during progression and metastasis the TME plays an increasingly important role. Our findings suggest that care needs to be taken in going forward with this class of agents, and underscores the need to be careful in extrapolating findings in chemoprevention to a therapeutic setting.

Several important questions remain unanswered. First, the pathways whereby alternatively activated macrophages promote progression of lung cancer are not well understood. Additional studies are

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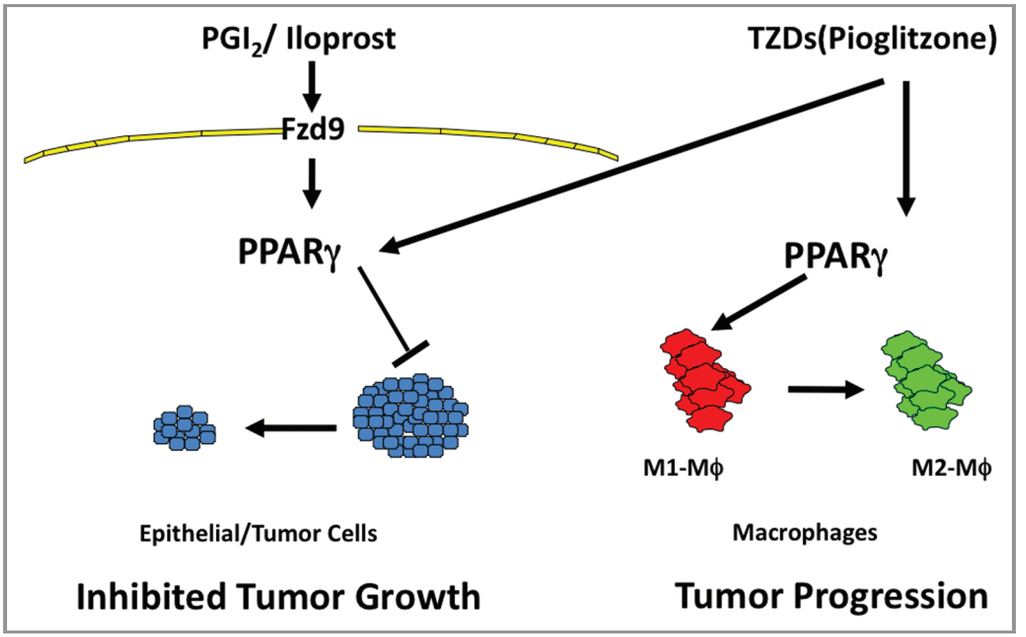

Figure 1. Activators of PPARγ have opposing effects on tumor progression in different cell types. In transformed epithelial cells or full-fledged cancer cells, this pathway is growth inhibitory. In contrast, in macrophages, these agents promote the alternatively activated (M2 phenotype), which promotes cancer progression through mechanisms which are not completely understood. The net response to an agent such as pioglitazone will depend on the balance between effects on different cell types. Prostacyclin analogs such as iloprost also activate PPARγ, but require expression of Frizzled 9 (Fzd9) on the target cells. This raises the possibility that these agents may represent targeted activators of PPARγ, and potential novel therapeutics.

required to define at what stage of metastasis these cells are important. In breast cancer, work by Condeelis and coworkers has defined a role for macrophages in multiple stages of metastasis.[8] Analogous studies need to be performed in lung cancer. These studies suggest that selective activators of PPARγ may represent novel therapeutic agents. In collaboration with Dr. Robert Winn we have demonstrated that the prostacyclin analog iloprost can activate PPARγ in human NSCLC, but that this is dependent on expression of the Wnt canonical receptor Frizzled 9.[9] Thus iloprost represents a potential targeted activator of PPARγ which will only act on Frizzled 9-positive cells. It is currently not known whether macrophages express this protein; however, it these cells lack Frizzled 9, it would be predicted that iloprost may represent a targeted activator of PPARγ with potential therapeutic efficacy (see **Fig. 1**).

Finally, an additional implication of this study relates to the role of inflammation and cancer progression. Our studies demonstrate that promotion of and alternatively activated macrophage, which is associated with the anti-inflammatory effects of pioglitazone in vascular disease actually promotes tumor progression. Analogous findings with other anti-inflammatory pathways are beginning to emerge. For example, activation of the purinergic pathway which inhibits colitis, in fact promotes colon cancer metastasis.[10] Thus a deeper understanding of the nature of pro and anti-inflammatory pathways is required to develop new therapeutics targeting cancer progression.

References

1. Maeda S, Kamata H, Luo JL, Leffert H, Karin M. IKKbeta couples hepatocyte death to cytokine-driven compensatory proliferation that promotes chemical hepatocarcinogenesis. Cell 2005; 121:977-90; PMID:15989949; http://dx.doi.org/10.1016/j.cell.2005.04.014
2. Govindarajan R, Ratnasinghe L, Simmons DL, Siegel ER, Midathada MV, Kim L, et al. Thiazolidinediones and the risk of lung, prostate, and colon cancer in patients with diabetes. J Clin Oncol 2007; 25:1476-81; PMID:17442990; http://dx.doi.org/10.1200/JCO.2006.07.2777
3. Bren-Mattison Y, Meyer AM, Van Putten V, Li H, Kuhn K, Stearman R, et al. Antitumorigenic effects of peroxisome proliferator-activated receptor-gamma in non-small-cell lung cancer cells are mediated by suppression of cyclooxygenase-2 via inhibition of nuclear factor-kappaB. Mol Pharmacol 2008; 73:709-17; PMID:18055759; http://dx.doi.org/10.1124/mol.107.042002
4. Li H, Sorenson AL, Poczobutt J, Amin J, Joyal T, Sullivan T, et al. Activation of PPARγ in Myeloid Cells Promotes Lung Cancer Progression and Metastasis. PLoS One 2011; 6:e28133; PMID:22145026; http://dx.doi.org/10.1371/journal.pone.0028133
5. Allavena P, Sica A, Solinas G, Porta C, Mantovani A. The inflammatory micro-environment in tumor progression: the role of tumor-associated macrophages. Crit Rev Oncol Hematol 2008; 66:1-9; PMID:17913510; http://dx.doi.org/10.1016/j.critrevonc.2007.07.004
6. Bouhlel MA, Derudas B, Rigamonti E, Dièvart R, Brozek J, Haulon S, et al. PPARgamma activation primes human monocytes into alternative M2 macrophages with anti-inflammatory properties. Cell Metab 2007; 6:137-43; PMID:17681149; http://dx.doi.org/10.1016/j.cmet.2007.06.010
7. Dai F, Liu L, Che G, Yu N, Pu Q, Zhang S, et al. The number and microlocalization of tumor-associated immune cells are associated with patient's survival time in non-small cell lung cancer. BMC Cancer 2010; 10:220; PMID:20487543; http://dx.doi.org/10.1186/1471-2407-10-220
8. Condeelis J, Pollard JW. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. Cell 2006; 124:263-6; PMID:16439202; http://dx.doi.org/10.1016/j.cell.2006.01.007
9. Tennis MA, Van Scoyk M, Heasley LE, Vandervest K, Weiser-Evans M, Freeman S, et al. Prostacyclin inhibits non-small cell lung cancer growth by a frizzled 9-dependent pathway that is blocked by secreted frizzled-related protein 1. Neoplasia 2010; 12:244-53; PMID:20234818
10. Künzli BM, Bernlochner MI, Rath S, Käser S, Csizmadia E, Enjyoji K, et al. Impact of CD39 and purinergic signalling on the growth and metastasis of colorectal cancer. Purinergic Signal 2011; 7:231-41; PMID:21484085; http://dx.doi.org/10.1007/s11302-011-9228-9