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Macrophage polarization: Role of PPARγ activation in chronic inflammation-associated breast cancer

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The tumor microenvironment is a complex architecture in which the functionally diverse and the heterogeneous macrophages play an important role in tumor growth and metastasis. Macrophages exhibit cellular plasticity and have various subtypes with distinct phenotypic properties depending on the micro environmental "signals". Peroxisome proliferator-activated receptor gamma (PPARγ) is a ligand-activated transcription factor expressed in macrophages and has been shown to promote macrophages to alternatively activated M2 phenotype in various cancers. This is responsible for immunosuppression and tumor growth. However, its effect on macrophage polarization in chronic inflammation-associated breast cancer is not fully understood. Herein, by using murine macrophages and a panel of breast cancer cell lines, we show exposure of macrophages to conditioned media from metastatic breast cancer cell lines prime them to adopt an M2 phenotype with dose-dependent increase in PPARγ expression along with M2 markers. Conversely, inhibition of PPARγ activity reverses this phenotype. Interestingly, treatment of macrophages with PPARγ activators that belong to the drug class of thiazolidinediones (TZDs) enhanced the M2 phenotype which was effectively blocked when used together with a PPARγ-specific antagonist. Therefore, exploring the role of PPARγ in the dynamic process of macrophage polarization and the mechanisms governing this process not only is important for our understanding of the M1–M2 paradigm of macrophage polarization but also provides insights to new treatment strategies via targeting imbalances of macrophage polarization. Moreover, a newer and safer molecule that activates PPARγ is much needed in the clinic as the TZDs do have toxic side effects. To that effect, we have recently set up a collaboration agreement with pharmaceutical company, Daiichi Sankyo USA, for the use of their pipeline Phase II-completed PPARγ activator, CS-7017, in our subsequent studies.

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Withania coagulans fruit extract protects diabetic nephropathy through inhibition of inflammatory cytokines and oxidative stress in streptozotocin-induced diabetic rats

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Diabetes nephropathy (DN) is the major determinant of morbidity and mortality in patients with diabetes. The development of DN is associated with increase in levels of inflammatory cytokines and localized tissue oxidative stress. Hyperglycemic control in diabetes is a key to prevent the development and progression of DN. Therefore, the present study was carried out to investigate the changes in oxidative and inflammatory status in streptozotocin-induced diabetic rats' kidneys and serum following treatment with *Withania coagulans*, a popular herb of ethnomedicinal significance. The key markers of oxidative stress and inflammation such as inflammatory cytokines (IL-1β, IL-6, and TNF-α) and immunoregulatory cytokines (IL-4 and IFN-γ) were increased in kidneys along with significant hyperglycemia. However, treatment of four-month diabetic rats with *Withania coagulans* (10 mg/kg) for 3 weeks significantly attenuated hyperglycemia and reduced the levels of pro-inflammatory cytokines in kidneys. In addition, *Withania coagulans* treatment restored the glutathione levels and inhibited lipid peroxidation along with marked reduction in kidney hypertrophy. This study demonstrates that *Withania coagulans* improved hyperglycemia and maintained antioxidant status and reduced the pro-inflammatory markers in kidneys, which may subsequently reduce the development and progression of renal injury in diabetes. The results of the present study are encouraging for its potential use to delay the onset and progression of diabetic renal complications. However, the translation of therapeutic efficacy in humans requires further studies.

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