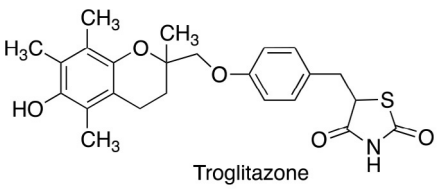
Despite the previously mentioned successes, the full potential of retinoids as anticancer agents has not yet been realized because of their potential toxicity and the problem of intrinsic or acquired resistances. Strategies to overcome this problem include their combination with other chemotherapeutic agents acting by related mechanisms and the use of nonclassical retinoids.[100] Compared with classical retinoids, the nonclassical retinoids might have lower toxicity and be able to induce apoptosis in RA-resistant cells. Retinoids are also relevant in the prevention of several cancers, including oral cavity, head and neck, breast, skin, and liver cancer.

10 PPAR LIGANDS AS ANTITUMOR AGENTS

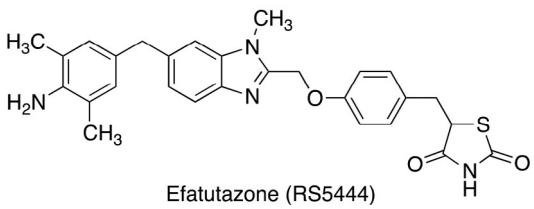
PPARs are ligand-activated transcription factors that are members of the nuclear hormone receptor superfamily. As previously mentioned, they heterodimerize with RXRs and bind to specific regions of DNA target genes known as peroxisome proliferator hormone response elements (PPREs). Their main endogenous ligands are eicosanoids and free fatty acids, and among other functions, they play essential roles in cellular differentiation and tumorigenesis. PPARα and PPARγ are the molecular targets of a number of marketed drugs, including the fibrates and the antidiabetic thiazolidinediones.

The antitumor activity of PPAR ligands against a variety of human cancers is associated with transcriptional activation of PPARγ, which could act as a tumor suppressor in several cancers. Among the PPARγ ligands studied as antitumor agents, promising results were obtained in initial clinical trials for liposarcoma and prostate cancers with troglitazone (Rezulin®). This compound was initially approved as an oral antidiabetic, but it was withdrawn from the market because of its liver toxicity. Although studies in colorectal and breast cancers have been disappointing,[101] troglitazone has shown its ability to inhibit human prostate cancer cell growth through inactivation of NF-κB via suppression of GSK-3β expression.[102]

PPARγ is also involved in some thyroid cancers. A fusion protein of PPARγ1 and the thyroid transcription factor PAX8 is present in approximately one-third of follicular thyroid carcinomas,[103] and PPARγ activation by the agonist efatutazone (RS5444) inhibits anaplastic thyroid cancer (ATC) growth. In fact, this compound is under phase I clinical testing for ATC, in combination with paclitaxel.[104] A phase II trial has been also carried out with efatutazone in patients with refractory non-small cell lung cancer, leading to the conclusion that it does not improve the efficacy of erlotinib.[105]



Troglitazone



Efatutazone (RS5444)