Piglitazone, a PPAR γ agonist, alleviates imiquimod-induced psoriasis-like skin lesions by regulating keratinocyte proliferation and differentiation through the expression of the transcription factor zinc-finger protein 1 (ZFP1) and the epigenetic modifier histone deacetylase 6 (HDAC6). Piglitazone oligodendrocyte-precursor cell (OPC) and the role of the transcription factor ZFP1 in the regulation of keratinocyte proliferation and differentiation. Piglitazone, a PPAR γ agonist, has been shown to have significant improvements when treated patients with psoriasis. However, the mechanism is still unclear. In this study, we investigated the underlying mechanisms. In vivo, we applied piglitazone to imiquimod (IMQ)-induced mouse model of psoriasis and found that piglitazone ameliorated IMQ-induced psoriasis-like dermatitis, with reduced inflammation, less K6/7-positive cells, and increased expression of keratinocyte-specific markers. Piglitazone also increased keratinocyte proliferation and differentiation. Keratinocytes were stimulated with IMQ and treated with piglitazone or vehicle. In vitro, we examined keratinocyte proliferation and differentiation. Piglitazone increased keratinocyte proliferation and differentiation. Keratinocytes were stimulated with IMQ and treated with piglitazone or vehicle. In vitro, we examined keratinocyte proliferation and differentiation. Piglitazone increased keratinocyte proliferation and differentiation.