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Review

Tacrolimus may play a role in dermatitis and radiation-induced skin injury through cellular senescence

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ABSTRACT

Skin Exposure of skin to ionizing radiation can induce acute or chronic biological effects, resulting in radiation-induced skin injury (RSI). Premature cellular senescence, caused by oxidative stress and/or DNA damage from chemical or physical agents, leads to the decrease of cellular proliferation and physiological function. Persistent DNA damage and accumulation of senescent cells are associated with the progression of radiation-induced injury. Atopic dermatitis and RSI have similar inflammatory symptoms. The treatment of tacrolimus (TAC) in atopic dermatitis may be associated with premature cellular senescence. TAC can prevent the onset of cellular senescence by inactivating the p38 mitogen-activated protein kinase (p38 MAPK). The activation of p38 MAPK can induce the senescence-associated secretory phenotype (SASP) by enhancing the transcriptional activity of nuclear factor kappa-B (NF-κB), which ultimately leads to premature cellular senescence. FK506 binding protein 51 (FKBP51) exhibits resistance to ionizing radiation, but the mechanism of TAC regulation of ionizing radiation-induced premature senescence still needs further study. This review discusses the mechanism of cellular senescence in RSI and the role of TAC in both dermatitis and RSI.

1. Introduction

Tacrolimus (TAC) has been studied since 1987, formerly known as FK506, is a macrolide antibiotic with immunosuppression.[1] It was found in the fermentation broth of Japanese soil samples containing *Streptomyces tsukubensis* in 1984.[2] In 1988, Schreiber participated in the discovery of FK506-binding protein 12 (FKBP12) and pointed out that TAC combined with FK506 binding protein (FKBP) to inhibit the phosphatase activity of calcineurin in 1991.[3] The drug inhibits calcium-dependent events, such as interleukin-2 (IL-2) gene transcription, nitric oxide synthase (NOS) activation, cell degranulation, and apoptosis. TAC is the main immunosuppressive drug administered after solid organ transplantation and plays a role in liver, kidney, heart, lung, and pancreas transplantation.[4–6] Recently, TAC has emerged as a valuable drug tool in rheumatology treatment.[7] For atopic dermatitis, a chronic inflammatory skin disease, TAC can be used with topical corticosteroids as first-line treatment.[8,9] FK506 binding protein 51 (FKBP51) promotes NF-κB activation and demonstrates resistance to ionizing radiation.[10,11] It is reported that TAC is effective in treating radiation-induced morphea (RIM), a skin complication of radiotherapy.[12] However, the mechanism underlying RSI and the role of TAC in these processes need further study. This paper reviews the mechanisms of radiation-induced skin injury (RSI) and atopic dermatitis, specifically focusing on the effects of TAC on atopic dermatitis, and discusses the potential role of TAC in RSI.

2. Mechanism of premature cellular senescence in radiation-induced skin injury

The skin is sensitive to ionizing radiation, and radiation exposure can lead to acute or chronic biological effects, known as radiation-induced skin injury (RSI).[13] RSI involves the loss of basal stem cells and progenitor cells, as well as the damage to blood vessels, due to various inflammatory factors induced by exposure to ionizing radiation.[14] Radicals and reactive oxygen species (ROS) produced by radiation can damage basal cells, inhibiting the division and proliferation of basal cells, as well as their migration and keratinization to the surface layer, and thus causing RSI.[15] Depending on the timing and severity of the injury, RSI can be categorized into acute and chronic forms. The symptoms of acute RSI include dry desquamation, moist desquamation, skin necrosis, ulcer, and bleeding.[16] The symptoms of chronic RSI include chronic ulcers, radiation keratosis, telangiectasia, fibrosis, and skin cancer.[17] Many treatment measures currently in use often lack mechanism research, and

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