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Abstract: Adenoviral vectors have provided effective methods for in vivo gene delivery in therapeutic applications. However, these vectors can induce immune responses that may severely affect the ability of vector re-application. There is limited information about the mechanisms and signal transduction pathways involved in adenoviral recognition. For optimization of cutaneous gene therapy it is necessary to investigate molecular mechanisms of virus recognition in epidermal cells. The aim of this study was to investigate the signal transduction of the innate immunity after adenoviral DNA internalization in keratinocytes. In vitro, keratinocytes were transfected with DNA, in the presence and absence of inhibitors for signalling molecules. In vivo, immunocompetent and athymic mice (n = 3 per group) were twice transduced with an Ad-vector. The results show an acute induction of type-I-interferon after in vitro transfection. Inhibition of PI3K, p38 MAPK, JNK and NFkappaB resulted in a decreased expression of type-I-interferon. In contrast to immunocompetent mice, athymic mice demonstrated a constant transgene expression and reduced inflammatory response in vivo. The results suggest an induction of the innate immunity triggered by cytoplasm localised DNA which is mediated by PI3K-, p38 MAPK-, JNK-, NFkappaB-, JAK/STAT-
and ERK1/2-dependent pathways. A stable transgene expression and a reduced inflammatory response in immunodeficient mice have been observed. These results provide potential for an effective adenoviral gene delivery into immunosuppressed skin.

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