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Apoptosis and Alterations in P21 and P27 Levels in Human Primary Aniridia Limbal Stromal Cells, in an Lps-Induced Inflammatory Microenvironment, in Vitro

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Abstract : Purpose: Congenital aniridia is a rare ocular disorder with partial or complete absence of the iris in most cases and is frequently accompanied by aniridia-associated keratopathy (AAK). Evidence from prior studies suggests increased susceptibility of corneal limbal stromal cells to inflammatory stimuli, in which an increased apoptotic rate may play a significant role. This study aimed to investigate apoptosis in primary aniridia limbal stromal cells and to assess changes in p21 and p27 levels in response to lipopolysaccharide (LPS)-induced inflammation in vitro. Methods: Primary human corneal fibroblasts were isolated from the limbal region of both aniridia (AN-LSCs; n=8) and healthy (LSCs; n=8) donors. The cells were treated with 0 µg/ml, 2.5 µg/ml, 10 µg/ml and 17.5 µg/ml LPS for 24 hours. Apoptosis was assessed by flow cytometry in each group. The expression levels of apoptosis-related genes CDKN1A (p21) and CDKN1B (p27) were measured by qPCR. p21 and p27 protein levels were analyzed by flow cytometry. Results: Flow cytometry revealed a significantly higher apoptotic rate in AN-LSCs, than in LSCs ($p<0.0001$). CDKN1A mRNA level and p21 protein level were significantly higher in AN-LSCs than in LSCs ($p=0.0232$, $p=0.0003$). In AN-LSCs, 17.5 µg/ml LPS treatment significantly increased the apoptotic rate ($p=0.0007$) but had no effect on the apoptotic rate in LSCs ($p>0.05$). In LSCs, 10 and 17.5 µg/ml LPS treatment significantly increased CDKN1B mRNA levels ($p=0.0028$, $p=0.0019$) without changes in p27 protein levels ($p>0.05$). In AN-LFC, all LPS concentrations significantly increased CDKN1B mRNA levels ($p\leq0.0051$) without changes at the protein level ($p>0.05$). Conclusions: There is an increased apoptotic rate in limbal stromal cells of congenital aniridia patients, which is accompanied by an increased p21 protein level. AN-LSCs are more sensible to LPS-induced inflammation than normal controls, and LPS treatment triggers CDKN1B mRNA levels both in AN-LSCs and LSCs Further studies should clarify the specific changes in the apoptotic cascade and identify potential therapeutic targets in limbal stromal cells of patients with congenital aniridia, aiming to prevent or delay the progression of AAK.

Keywords : limbal fibroblasts, aniridia associated keratopathy, lipopolysaccharide, apoptosis
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