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In Vitro Study of Interleukin-5 (IL-5) in Human Eosinophilic Chronic Rhinosinusitis Cell Culture

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Abstract. *Background: Eosinophilic chronic rhinosinusitis (ECRS) is an inflammatory disease in which the epithelial mesenchymal unit appears to be important in regulating the pathological mechanisms. Changes in adhesion molecule (AM) expression by inflammatory cells have been reported. The damage of respiratory epithelium in allergic diseases has a close correlation with the extent of eosinophil infiltration. In our study, we investigated the effect of IL-5 on β-catenin and E-cadherin levels in ECRS. Materials and Methods: ECRS cell cultures were incubated with IL-5 and β-catenin / E-cadherin levels were analysed after 8-72 hours using cytokine immunoassay and immunohistochemistry. Results: Eight hours of incubation with IL-5 resulted in 0.19 ng/ml E-cadherin (15.27 ng/ml β-catenin), whereas in the control 0.14 ng/ml (15.45 ng/ml β-catenin) was detectable. After 24 and 48 hours, 0.18 ng/ml (16.47 ng/ml β-catenin) and 0.33 ng/ml (17.88 ng/ml β-catenin) were measured in the incubated cell cultures, respectively; 72 hours of incubation with IL-5 resulted in 0.14 ng/ml (19.36 ng/ml β-catenin), whereas 0.17 ng/ml (20.09 ng/ml β-catenin) was determined in the controls. This study demonstrated a significant decrease in E-cadherin expression in cell cultures after stimulation with IL-5, especially in incubation-time adjusted analysis. However, the immunostaining was restricted to the membrane of the cells. Conclusion: In regard to the increased mural expression of AM, we believe that a fibrotic reaction similar to that in chronic obstructive pulmonary disease takes place in patients suffering from ECRS.*

Chronic rhinosinusitis (CRS) is defined as a disease of the nasal and paranasal sinus mucosa present for longer than 3 months, duration and is associated with mucosal changes ranging from inflammatory thickening to nasal polyps (1). Patients with CRS have long-term nasal congestion, thick mucus production, anosmia and acute intermittent exacerbations secondary to bacterial infection. Indeed, one study has suggested that their quality of life is more severely impaired than patients with congestive heart failure (2). Diagnosis is based upon the presence of typical symptoms together with clinical manifestations, but the exact pathogenesis remains unclear. The predominant histological feature of CRS is a persistent underlying eosinophilic inflammation (3). Activated eosinophils contribute to polypoid sinusitis through the release of major basic protein (MBP) in the mucus, epithelial disruption, basement membrane denudation and through the production of inflammatory cytokines (3-5). With regard to the pathogenesis, this new entity is called eosinophilic chronic rhinosinusitis (ECRS).

Maintenance of organised tissue is established by cell-to-cell mediated adhesion. The adherens junctions of keratinocytes promote homophilic cell-to-cell adhesion and are composed of cadherin, β-catenin or plakoglobin, α-catenin and p120 (6-10). β-Catenin is a 96 kDa cadherin-associated protein that mediates the anchoring of cadherins to actin by itself binding α-catenin. β-Catenin is released into the cytoplasm and is able to access the nucleus and induce transcriptional activity (11, 12). The cell-to-cell adhesion is assumed to be controlled by tyrosine phosphorylation of the adherens junction and desmosome components (13-15). It has been reported that the level of cadherin expression influences the strength of adhesion (16). In addition, the expression of different cadherins in originally identical cells could lead to cell sorting (16).

Damage to respiratory epithelium is known to contribute to the pathogenesis of airway diseases through the alteration of barrier function and permeability of the mucosa (17). Damage to the epithelium closely correlates with the degree of eosinophil infiltration and indeed eosinophil products are known to cause epithelial damage and submucosal oedema (18). In a guinea-pig model of nasal allergy, a local decrease

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of E-cadherin was observed in association with an infiltration of eosinophils (19). This result suggests that the intimate epithelial cell contact mediated by E-cadherin is compromised as a consequence of eosinophil infiltration. The key pathogenic stage of nasal polyposis seems to be the recruitment, activation and survival of eosinophils (20). Mediators such as interleukin (IL)-5 are considered to be key factors for eosinophilic accumulation and activation in nasal polyps (21). Eosinophil migration is dependent on the expression of cytokines, chemokines and adhesion molecules (AM) (22). Resident cells, such as T-lymphocytes, release IL-1β, IL-4 and tumor necrosis factor (TNF)-α and thus enhance endothelial AMs (23-25). The up-regulation of endothelial AMs results in stronger leukocyte endothelium adherence and transendothelial migration of leukocytes along a chemotactic gradient.

Endothelial AMs include intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and E-selectin. Increased expression of ICAM-1, VCAM-1 and E-selectin has been demonstrated locally after experimental nasal and bronchial allergen challenge (26, 27). The cytokine pattern in chronic polypoid sinusitis often shows neither a T-helper 1 (TH-1) nor a TH-2 type predominance because IL-4, IL-5, IL-12 and IFN-γ have all been shown to be elevated in nasal polypoid tissue without influencing the atopic status of an individual (28). In paranasal polyposis, IL-5 expression was observed in polyps and inferior turbinates, whereas no detectable IL-5 was found in serum from the same patients (29).

E-cadherin seems to play an important role in eosinophil epithelial interaction during the eosinophil migration process. Furthermore, E-cadherin and β-catenin are potent cell adhesion molecules in the architecture of epithelial cell-to-cell junctions. IL-5 plays a central role in CRS and is known to have eosinophil-selective chemoactivities. Therefore we designed an *in vitro* study to determine the influence of IL-5 on β-catenin and E-cadherin in ECRS. Further insight into the cytokines and chemokines that mediate inflammatory processes in ECRS may lead to the development of new therapeutic approaches.

Materials and Methods

Tissue collection and culture of human chronic rhinosinusitis cells. All ECRS cells were obtained from 4 patients suffering from CRS and undergoing functional endoscopic sinus surgery at the Department of Otorhinolaryngology at the University Hospital of Mannheim, Germany in 2006. Prior to surgery, written consent was obtained from all patients to take tissue samples of the resected paranasal mucosa and turbinates. This study was approved by the Ethics Committee of the Faculty of Medicine, Mannheim, University of Heidelberg, Germany.

After surgery, the tissue samples were examined by a pathologist and diagnosed as eosinophilic and noneosinophilic CRS according to the levels of eosinophilic granulocytes within the samples. In consequence; eosinophil and noneosinophil cells were cultured. An epithelial and a fibroblast culture for each sample of paranasal sinus mucosa and inferior nasal turbinate was set up. After removal of connective tissue, the tissue specimens were cut into small pieces and incubated in trypsin solution (0.25% trypsin in phosphate-buffered saline, PBS) overnight at 4˚C. For primary culture of epithelial cells, the suspension was added onto mitomycin-treated (23.9 μM) human fibroblast monolayers and cultured in FAD2-medium (Dulbecco's modified Eagle's medium and Ham's F12 in a 3:1 ratio supplemented with fetal calf serum, insulin, triiodothyronine hydrocortisone, epidermal growth factor, cholera toxin and penicillin or streptomycin) at 37˚C in a 10% CO_2 atmosphere. On reaching subconfluency, the feeder layer was removed by incubation with 0.02% ethylenediamine tetraacetic acid (EDTA) in PBS for 4 min at 37˚C and the sinus epithelial cells were further cultured in serum-free keratinocyte/fibroblast growth medium (KGM, Clonetics, San Diego, CA, USA / Fisher Scientific Co., Pittsburgh, PA, USA). Cells were passsaged by trypsinisation (0.1% trypsin and 0.02% EDTA dissolved in PBS for 5 min at 37˚C).

Treatment with IL-5. After 8, 24, 48 and 72 hours of incubation with 0.4 ng/ml human recombinant IL-5 (catalogue number 205-IL; R&D Systems, Wiesbaden, Germany), the expression of the β-catenin and E-cadherin protein in the supernatants of the IL-5 and untreated culture cells was analysed, respectively. The untreated cells of the control groups received incubation without IL-5.

Cytokine immunoassay. Cell culture supernatants were collected in sterile test tubes and stored at –20˚C until used. The concentrations of the two examined AM's were determined by an ELISA technique (R&D Systems, Wiesbaden, Germany). The system used a solid-phase monoclonal antibody and an enzyme-linked polyclonal antibody raised against recombinant cytokines. According to the manufacturer's directions, each ELISA assay determined β-Catenin and E-cadherin in 100 μl of supernatant. The cells were grown in 96-well plates with 12 strips of 8 walls coated with mouse antibody against either β-catenin or E-cadherin. After 8-72 hours' incubation, the expression of β-catenin and E-cadherin in the supernatants of the IL-5 treated an untreated culture lines was analyzed.

Immunohistochemistry. Immunohistochemical analysis was performed using a monoclonal mouse anti-human antibody directed against β-catenin and E-cadherin (Clone β-catenin-1 M3539 and E-cadherin clone NCH-38; DAKO, Hamburg, Germany). Immunostaining was performed using the alkaline phosphatase–anti-alkaline phosphatase method (APAAP). The fibroblasts and epithelial cells were cultured on glass coverslips overnight before immunohistochemistry. When confluent, cells underwent fixation with acetone and alcohol (2:1), were washed with PBS and received a microwave pre-treatment, which required boiling for 15 min at 600 W using citrate buffer for AM. The following steps were performed by an automated staining system, DAKO TechMate 500 (DAKO, Hamburg, Germany). Cells were incubated with the primary antibody solution for 25 min at room temperature, using a working dilution of antibody to AM of 1:300. Slides were rinsed once in buffer (Buffer Kit, DAKO). Immunoreaction was demonstrated with the DAKO ChemMate Detection Kit (APAAP, Mouse, Code No. K 5000; DAKO), according to the specifications of the manufacturer. Slides were incubated with the chromogen alkaline-phosphatase substrate (Neufuchsin; DAKO)

Table I. *Incubation of paranasal ECRS with 0.4 ng/mL IL-5.*

	E-Cadherin (ng/ml)			
Incubation time (h)	FIB	Control	EP	Control
	median±standard division (ng/ml)			
8	0.1873±0.0325	0.1380±0.0290	0.4593±0.2075	0.3035±0.0047
24	0.1793±0.0643	0.2138±0.0409	0.4320±0.0770	0.3417±0.0706
48	0.3255±0.3201	0.2050±0.0648	0.5948±0.2392	1.2500±1.1378
72	0.1442±0.0104	0.1693±0.0330	1.2655±0.9853	1.7958±1.5156
	E-Cadherin as percentage of total protein (%)			
8	0.00026	0.00015	0.00011	0.00009
24	0.00017	0.00009	0.00005	0.00003
48	0.00031	0.00049	0.00021	0.00029
72	0.00023	0.00014	0.00006	0.00006

ECRS: eosinophilic chronic rhinosinusitis, FIB: fibroblast cell culture, EP: epithelial cell culture.

for 20 min at room temperature. Finally, cells were counterstained by Harris-hematoxylin for 3 min, dehydrated in graded ethanol and coverslipped. Controls were carried out by omitting the primary antibody.

Analysis of β-catenin / E-cadherin immunostaining. The rates of expression were analysed semi-quantitatively. The number of positively marked epithelial cells was graded from 1 to 3 with 0 (no positive cells), 1(<20% positive cells), 2 (20-50% positive cells) and 3 (>50% positive cells). The intensity was noted as I (faint) or II (strong). The combination of these immunohistochemical reaction patterns resulted in 7 possible scores: 0, 1/I, 1/II, 2/I, 2/II, 3/I and 3/II. The reaction scores 0 to 2/I were classified as negative or low expression and 2/II to 3/II as high expression of β-catenin and E-cadherin. To ensure the observer reliability of the assessment, the specimens were blindly assessed by two independent reviewers unaware of all clinical data. Differences between the two investigators were resolved by consensus.

Statistical analysis. Statistical analysis was performed using the SAS programme (SAS/STAT, Version 8; SAS Institute Inc., Cary, NC, USA). Student's *t*-test was used to calculate *p*-values ($p<0.05$). The influence of IL-5 and incubation time was analysed using the the general linear model (GLM) procedure (SAS/STAT).

Results

E-cadherin. After 8 hours of incubation, 0.19 ng/ml E-cadherin was determined in the supernatants of the treated fibroblast (FIB) cultures [0.46 ng/ml in epithelial culture (EP)], whereas in the controls, a level of 0.14 ng/ml (EP: 0.30 ng/ml) was detectable. After 24 and 48 hours the level in FIB was 0.18 ng/ml (EP: 0.43 ng/ml) and 0.33 ng/ml (EP: 0.54 ng/ml), respectively (Table I). E-cadherin as a percentage of total protein dropped from 0.000057% (EP: 0.00021%) after 8 hours to 0.000025% (EP: 0.00032%) after 72 hours in the treated FIB cultures, whereas EP cultures showed an increase from 0.00021% to 0.00032% (Figure 1A-D). Student's *t*-test did not reveal any significant difference in E-cadherin expression of the treated FIB and EP cultures compared to their respective controls (FIB: $p=0.5814$, EP: $p=0.5265$).

Further statistical analysis was performed in order to evaluate the influence of tissue origin (mucosa of sinus or inferior turbinate), eosinophils and hours of incubation. The analysis of variance following the GLM procedure revealed no significant influence of eosinophils ($p=0.9196$), incubation time ($p=0.8632$) or tissue origin ($p=0.8557$) in the treated FIB cultures. However, incubation time had a significant influence on E-cadherin expression in the non-treated FIB cultures ($p=0.0016$). Furthermore, incubation time-adjusted repeated measures analysis of variance showed a significant increase in E-cadherin concentration in the treated FIB cultures compared to the nontreated FIB cultures ($p=0.0418$). The treated EP cultures failed to reveal any significant difference in E-cadherin expression ($p=0.1770$).

β-Catenin. With regard to the β-catenin concentration in FIB culture of ECRS mucosa, an increase over 72 hours of incubation with 0.4 ng/ml IL-5 was found. After 8 hours incubation with IL-5, β-catenin was measured to be 15.27 ng/ml in the FIB cultures of eosinophilic paranasal mucosa, while after 72 hours this value had risen to 19.36 ng/ml. On the other hand, the treated EP cultures showed a decrease in β-catenin expression (Table II). The percentage of β-catenin as a proportion of total protein dropped in FIB cultures from 0.0046% (EP: 0.0084%) after 8 hours to 0.0033% (EP: 0.0038%) after 72 hours (Figure 2A-D). Student's *t*-test did not show a significant difference in β-catenin concentration in the cultures compared to their respective controls (FIB: $p=0.1634$, EP: $p=0.1870$). The GLM procedure with repeated measures and analysis of variance showed no significant

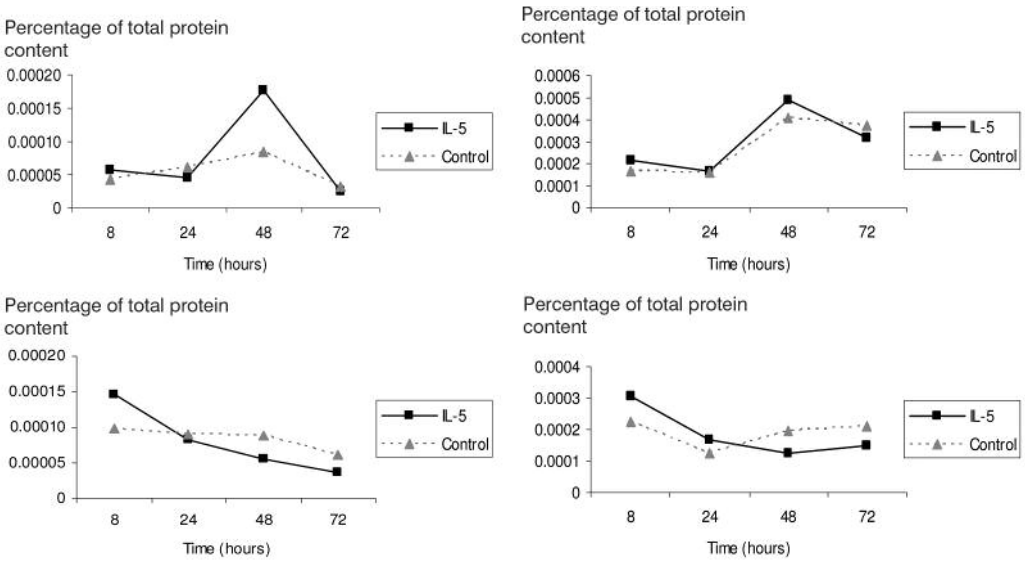

Figure 1. *Effects of IL-5 on expression of E-cadherin. After 8, 24, 48 and 72 hours of incubation with 0.4 ng/ml IL-5 the expression of E-cadherin in the supernatants of the IL-5 treated and untreated control fibroblast (A, B) and epithelial (C, D) cultures was analysed.*

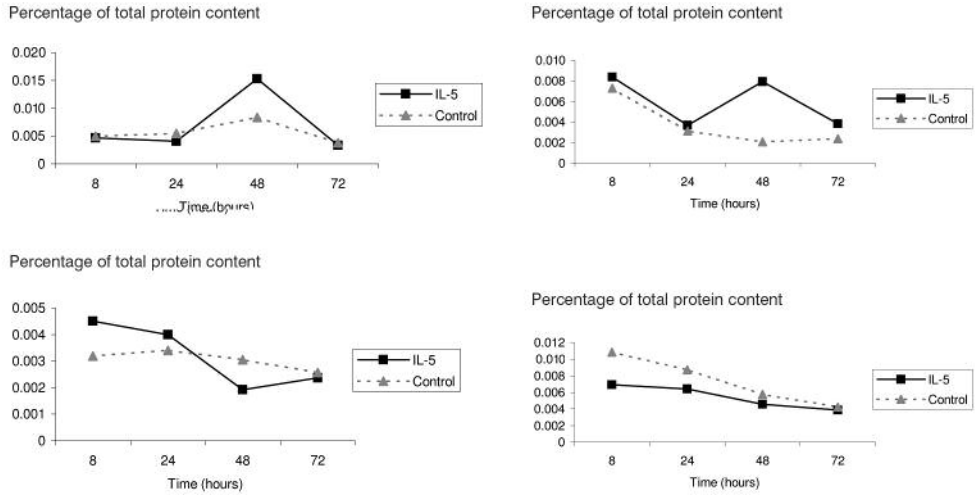

Figure 2. *Quantification of β-catenin expression after IL-5 incubation. After 8, 24, 48 and 72 hours of incubation with 0.4 ng/ml IL-5 the expression of the β-catenin in the supernatants of the IL-5 treated and untreated control fibroblast (A, B) and epithelial (C, D) cultures was analysed.*

influence of the incubation time (FIB: p=0.8315, EP: p=0.8627), tissue origin (FIB: p=0.9897, EP: p=0.1049) or eosinophils (FIB: p=0.7676, EP: p=0.0073) on the β-catenin concentration in the cultures.

Immunhistochemistry. Immunostaining was restricted to the membrane of the cells. After 48 hours of incubation with IL-5, reactivity to β-catenin was observed at the membranes of ECRS cells. In contrast, the untreated ECRS cells showed a lower reactivity to β-catenin at the membranous borders in comparison to the treated cells. There was no difference in β-catenin and E-cadherin expression when comparing the immunoreactivity of the basal layer of non eosinophilic paranasal mucosa with the eosinophilic paranasal mucosa in CRS. However, the eosinophilic paranasal mucosa samples showed a high mural expression of β-catenin. The results are presented in Figure 3 and Table III.

Discussion

Trafficking of lymphocytes and granulocytes from the blood vessels to the site of the immunological reaction requires

Table II. *Incubation of paranasal ECRS with 0.4 ng/mL IL-5.*

	β-Catenin (ng/ml)			
Incubation time (h)	FIB	Control	EP	Control
	median±standard division (ng/ml)			
8	15.2725±1.8495	15.4390±3.8862	16.8305±1.3704	13.9898±3.6608
24	16.4678±0.8573	18.5668±3.1109	12.4445±8.5160	11.1395±8.5401
48	17.8825±2.0922	19.1590±1.5503	07.1563±5.3888	08.0725±7.1186
72	19.3583±2.1471	20.0852±2.1904	13.6890±5.8532	12.3190±9.3342
	β-catenin as percentage of total protein (%)			
8	0.00456	0.00406	0.00765	0.00907
24	0.00402	0.00442	0.00504	0.00594
48	0.00858	0.00570	0.00624	0.00391
72	0.00284	0.00316	0.00386	0.00332

ECRS: eosinophilic chronic rhinosinusitis, FIB: fibroblast cell culture, EP: epithelial cell culture.

adhesion to endothelial cells, migration through capillary walls, leukotaxis along matrix proteins and attachment to epithelial walls, and finally release of enzymes, cytokines and inflammatory molecules. This is facilitated by the expression and alteration of adhesion molecules. The expression of various adhesion molecules is associated with general inflammatory conditions and can be found in all different kinds of inflammation. As significant alterations in E-cadherin expression by IL-5 were restricted to FIB culture in this study, other cytokines, as for example IL-13 and VCAM would seem to play a more pivotal role in the pathologic changes of the epithelial barrier in CRS. Nevertheless, IL-5 is well recognised as being an eosinophil chemoattractant as well as having a role in inducing their production and promoting the release of granular proteins (30, 31). Previous studies have reported an up-regulation of IL-5 in patients suffering from nasal polyposis (1). IL-5 belongs to the chemokines of the β-chemokine family (CC) that activate and attract eosinophils. In nasal polyposis, IL-5 has been found to be one of the key factors for eosinophilic accumulation and activation (21). This emphasises the importance of IL-5 in the type of inflammation found in ECRS. Immunohistochemical analysis revealed IL-5-positive eosinophils in nasal polyposis but could not detect IL-5-positive cells; the authors explained that the lack of IL-5-positive T-cells could be due to a cytokine storage limitation in T-cells (32). In chronic polypoid sinusitis, various authors have described a mixed profile of TH-1 and TH-2 type cells (28, 29).

In our study, IL-5 was able to induce significant changes in E-cadherin levels in supernatants of fibroblasts but failed to do so in other examined components of the extracellular matrix (ECM). This is consistent with previous studies indicating that anequilibrium exists between the nasal polyp

Table III. *Immunoreactivity score (IRS): Grading of ECRS and NCRS after detection of E-cadherin and β-catenin in primary (0 h) and cultured (24 and 72 hours) fibroblast and epithelial culture.*

Tissue	Immunohisto-chemical σcore[a]	Immunoreactivity n=4/4			
		ECRS/Control		NCRS/Control	
		FIB[b]	EP[c]	FIB[b]	EP[c]
Paranasal tissue					
0 h / β-Catenin	0 – 1/II	x*/4	x*/4	x*/4	x*/4
	2/I – 3/II	x*/0	x*/0	x*/0	x*/0
0 h / E-Cadherin	0 – 1/II	x*/4	x*/4	x*/4	x*/4
	2/I – 3/II	x*/0	x*/0	x*/0	x*/0
24 h / β-Catenin	0 – 1/II	4/4	4/4	1/4	1/4
	2/I – 3/II	0/0	0/0	3/0	3/0
24 h / E-Cadherin	0 – 1/II	0/3	2/4	4/4	4/4
	2/I – 3/II	3/1	2/0	0/0	0/0
72 h/ β-Catenin	0 – 1/II	1/4	3/3	4/4	1/4
	2/I – 3/II	3/0	1/1	0/0	3/0
72 h/ E-Cadherin	0 - 1/II	1/3	3/4	4/4	1/4
	2/I – 3/II	3/1	1/0	0/0	3/0
Inferior turbinate					
0 h / β-Catenin	0 – 1/II	x*/4	x*/4	x*/4	x*/4
	2/I – 3/II	x*/0	x*/0	x*/0	x*/0
0 h / E-Cadherin	0 – 1/II	x*/4	x*/4	x*/4	x*/4
	2/I – 3/II	x*/0	x*/0	x*/0	x*/0
24 h / β-Catenin	0 – 1/II	3/4	4/4	1/4	3/4
	2/I – 3/II	1/0	0/0	3/0	1/0
24 h / E-Cadherin	0 – 1/II	4/4	4/4	4/4	4/4
	2/I – 3/II	0/0	0/0	0/0	0/0
72 h/ β-Catenin	0 – 1/II	1/1	2/2	4/4	4/4
	2/I – 3/II	3/3	2/2	0/0	0/0
72 h/ E-Cadherin	0 - 1/II	1/4	2/2	4/4	4/4
	2/I – 3/II	3/0	2/2	0/0	0/0

[a]0-1/II: negative to low expression of E-cadherin/β-catenin; 2/I-3/II: strong expression of E-cadherin/β-catenin; ECRS: eosinophilic chronic rhinosinusitis, NCRS: noneosinophilic chronic rhinosinusitis; Incubation: 0.4 ng/ml IL-5; [b]Fibroblast and [c]epithelial cell culture. *Primary cell culture without IL-5 incubation.

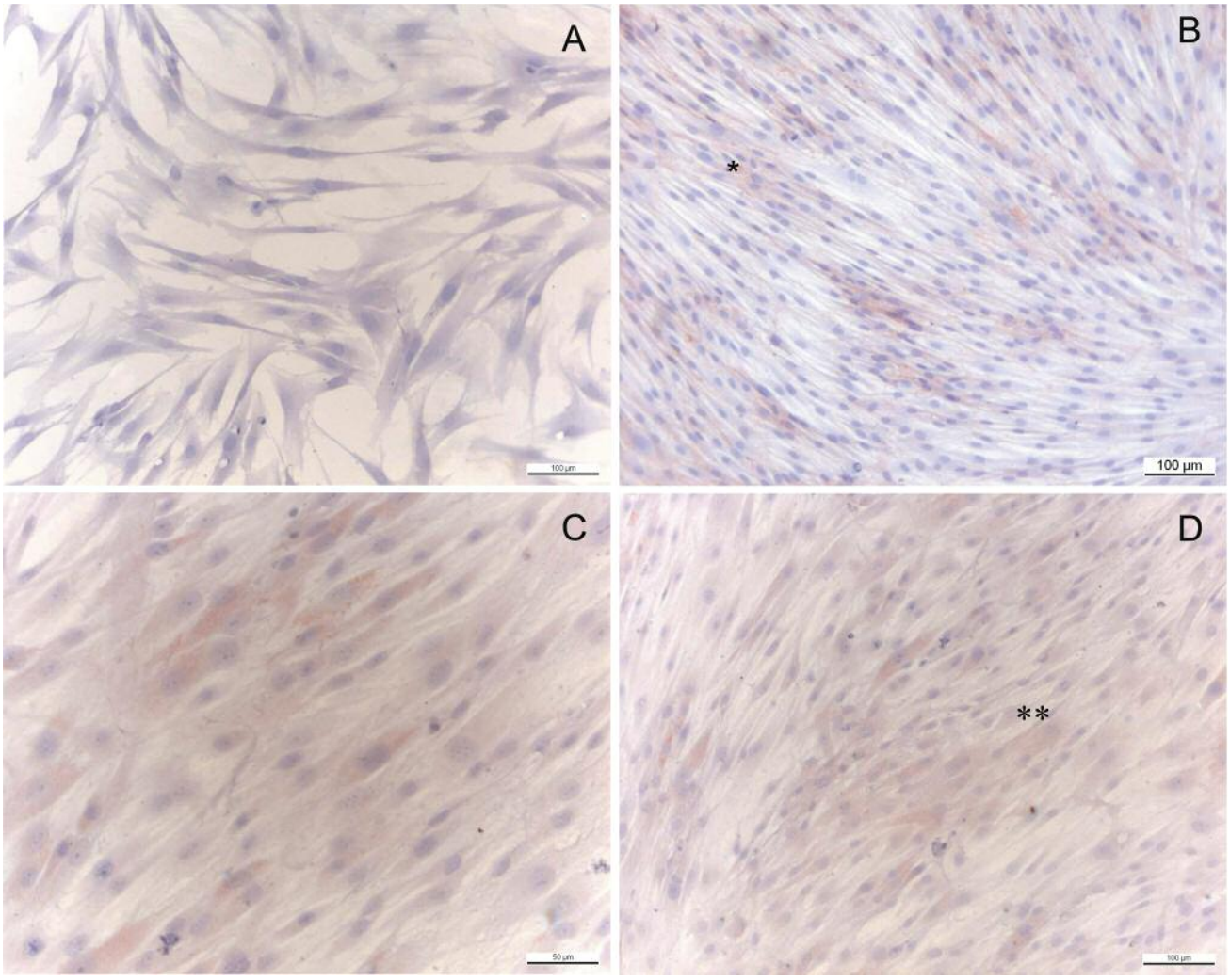

Figure 3. *Immunhistochemical staining against β-catenin in fibroblasts after 8 and 72 hours of cell culture. β-Catenin after incubation with 0.4 ng/mL IL-5 at A, 8 hours and B, 72 hours. Homogenous immunostaining for β-catenin at the cell-membrane (*). β-Catenin in untreated NCRS after C, 8 hours and D, 72 hours of cell culture. Here, β-catenin staining showed a reduced reactivity to β-catenin on the membranous site (**) of the cells and the majority of the fibroblasts show a faint immunoreactivity.*

itself and the surrounding tissue with regard to the IL-5 concentration (29).

The up-regulation of other cytokines such as IL-6, Il-12 and IL-13 seems to indicate polyp growth and thus these are overexpressed in polyps (29). In nasal polyp fibroblasts, the expression of the cytokine eotaxin is highly sensitive to the synergistic action of IL-4 and lipopolysaccharide (33). In our study, we were unable to investigate an alteration in the expression of all examined ECM components by IL-5. The supporting connective tissue in paranasal mucosa is porous and its ECM components play an essential role in inflammatory reactions. The inflammation occuring in this tissue type leads to structural changes in the epithelium and the lamina propria. In lower airway diseases, such as asthma and chronic obstructive pulmonary disease, chronic inflammation induces a certain degree of ECM deposition and remodelling of the lower airway tissue (34). In CRS, subepithelial collagen deposition is significantly greater than in normal tissue (35). Connexin 43, abundant in subepithelial fibroblasts, was found to be inversely correlated with eosinophil infiltration in nasal polyps (36). In CRS, fibroblasts embedded in the oedematous framework present abundant interdigitating cytoplasmic processes and solitary cilia. The injury to the barrier function and change in permeability of the sinus mucosa is closely correlated with the extent of eosinophil infiltration and eosinophil products (17, 18).

Interepithelial junctions play a crucial role in the regulation and sustainment of endothelial and epithelial functions. Adherens junctions of epithelial layers are involved in promoting homophilic cell-to-cell adhesion and are composed

of cadherin, β-catenin or plakoglobin, α-catenin and p120 (6-11). In embryonic liver culture, β-catenin was even able to modulate cell proliferation and apoptosis. Monga *et al*. reported that an inhibition of β-catenin reduced cell proliferation in these cultures (37). Although we would assume there to be an up-regulation of β-catenin and E-cadherin in ECRS culture, we were unable to detect a significantly higher accumulation of β-catenin or E-cadherin in eosinophilic tissue compared to noneosinophilic CRS tissue. The only exception was a significant decrease of E-cadherin expression in the supernatants of fibroblast cultures compared to the untreated cultures.

With reference to the previous observation of Monga *et al*., it is possible that in ECRS the increase in mural β-catenin activity might have enhanced cell proliferation in the suprabasal layer of the matrix and thus resulted in growth of polyps as the pathomorphological correlate.

In the present study, we demonstrated that the incubation of eosinophil paranasal mucosa with IL-5 did not significantly increase or decrease the expression of epithelial E-cadherin. But incubation time-adjusted repeated measures analysis of variance showed a significant difference in E-cadherin concentration in the treated FIB cultures compared to the untreated FIB cultures. No significant increase in β-catenin expression was observed in fibroblast and epithelial cell cultureS compared to the control. These results suggest the possibility that the eosinophil epithelium interactions in CRS are not only IL-5-dependent. Similarities in the cellular nature of remodelling and in the severity of airway inflammation might further enable comparisons to be made between lower and upper airway remodelling. Based on our experiments, we were unable to determine a common pathogenic principle in upper and lower airway inflammation in terms of IL-5.

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