

# Correlation Between Interleukin 6 with Nasopharyngeal Carcinoma in the Minangkabau Ethnic Group

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## ABSTRACT

Nasopharyngeal carcinoma (NPC) is a malignant tumour of nasopharyngeal epithelium that has a unique distribution pattern. Nasopharyngeal carcinoma is not only geographically specific but also ethnically. Some ethnic groups tend to suffer NPC. Multifactorial interactions are presumed to be the cause of NPC. One of them is interaction with interleukin 6 (IL-6). Interleukin 6 is a glycoprotein that not only links between chronic inflammation and progression of the tumour, but also a role as an important regulator to immune response and the growth factor of NPC. This study aimed to determine the correlation of IL-6 with NPC in the Minangkabau ethnic group. This study was an analytical study with a cross-sectional comparative study. A total of 21 plasma of NPC patients of the Minangkabau ethnic group and 21 plasma sex and aged-matched  $\pm 3$  years controls participated in this study. Plasma IL-6 levels were measured with ELISA (Enzyme-Linked Immunosorbent Assay). All data were subjected to a normality test with Shapiro Wilk and a log 10 transformation test. Then performed an independent t-test in both groups. The plasma level of IL-6 in the NPC group was higher ( $46.16 \pm 73.10$  pg/ml) than the plasma control group ( $23.16 \pm 25.84$  pg/ml), but it was not statistically significant ( $p > 0.05$ ).

**Keywords:** interleukin 6, nasopharyngeal cancer, Minangkabau.

## 1. INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignant tumor originating from the nasopharyngeal mucosa [1]. Anatomically, the nasopharynx begins anteriorly at the posterior choana and extends along the airway plane to the level of the free border of the soft palate [2]. There is an increase in the number of cases of nasopharyngeal carcinoma. Based on Global burden cancer (Globocan) 2018, 129,079 new cases of the nasopharynx with a death rate of 72,987 cases. This data had increased compared to Globocan 2012, which was 87,000 new cases of nasopharynx with 51,000 of death [3,4]. Nasopharyngeal cancer is 2-3 times more common in men than women. This cancer is more common in Southeast Asian countries. The five countries with the highest incidence in the world are China, Indonesia, Vietnam, India and

Malaysia. Although nasopharyngeal cancer has been treated with various treatments, the prognosis is not improving satisfactory. The prognosis varies widely due to biological heterogeneity. The researchers believe that research in biomarker field can improve the prognosis of patient [5].

Interleukin 6 is one of the biological markers in inflammation-associated malignancy. Interleukin 6 is a pleiotropic cytokine involved in the pathogenesis of head and neck cancer, one of the hallmarks of inflammations-associated malignancy [6]. The secretion of IL-6 in the tumor microenvironment, on the one hand, acts as an immune defense against tumors, but on the other hand promotes tumor cell proliferation when Signal Transducer and Activator of Transcription-3 (STAT-3) is activated. Previous studies had shown that IL-6 is

elevated in head and neck cancers due to overproduction in the tumor microenvironment. The reflection is an increase in the level of IL-6 in the blood as a biological characteristic of tumor. In nasopharyngeal cancer, it is known that there is an increase in the level of IL-6 in the plasma of NPC patients, which reflect tumor progression and the concentration of IL-6 increases in the plasma of NPC patients [7]. Interleukin 6 supports the occurrence of latent Epstein Barr infection (EBV) through the activation of STAT-3 signal [8]. Signal Transducer and Activator of Transcription-3 activation in EBV- infected cells promotes the transcription of latent EBV genes, such as cyclin D1, c-myc, snail, etc.

Currently, several target therapies that work inhibited IL-6 signaling have been researched. Siltuximab and Tocilizumab are IL-6 signaling inhibitors that have been approved by Food and Drug Administration (FDA) in Castleman's disease and rheumatoid arthritis. In head and neck cancer, the use of Pembrolizumab and Nivolumab are targeted therapies that are currently in phase III clinical trial stage [9,10].

## 2. METHOD

This study was an analytical study with a cross-sectional comparative study. A total of 21 plasmas of nasopharyngeal cancer of the Minangkabau ethnic group and 21 plasmas sex and aged-matched  $\pm 3$  years controls participated in this study. Plasma IL-6 levels were measured using the ELISA (Enzyme-Linked Immunosorbent Assay) method. All data obtained were processed using Statistical Package for Social Sciences (SPSS) program version 23.0. The Correlation between IL-6 with nasopharyngeal carcinoma in Minangkabau ethnic group was analyzed using a normality test with Shapiro Wilk and a Log 10 transformation test. Then performed an independent t-test in both groups. It was declared significant if  $p < 0.05$  (CI 95%).

## 3. RESULT AND DISCUSSION

### 3.1. Result

The characteristics of respondents, based on gender, the incidence of NPC is more common in men (61.90%) than in women (38.09%). The age group of most NPC respondents was 40-69 years (80.95%). The youngest respondent diagnosed NPC was 20 years old, while the oldest was 69 years old. The histopathology examination showed that the most common type was undifferentiated squamous cell carcinoma (WHO III) with 66.67%, followed by undifferentiated non-keratinized carcinoma (WHO II) with 33.33% and no keratinized carcinoma (WHO I). In this study, the majority of NPC patients came already at stage IV (76.19%), followed by stage III (19.04%), stage II (4.76%), and no patient was diagnosed

at stage I. Most primary tumor status at the time of diagnosis of NPC was T4 (61.90%), followed by T2 (23.80%), T3 (14.28%), and no patient came with T1. Meanwhile, the status of most lymph nodes is the enlargement of lymph node (76.19%) compared to without enlargement of lymph node (23.80%).

Based on Table 1, the mean level of IL-6 was not significant ( $p > 0.05$ ). Higher in the NPC group compare to the control group. Table 2 showed that the highest level of IL-6 was in the stage IV group followed by the stage III group, then the stage II group, and there was no stage I found in this study. The higher the tumor stage, the higher the mean level of IL-6. However, the One-Way ANOVA test revealed that it was not statistically significant ( $p > 0.05$ ).

**Table 1** The differences mean levels of interleukin 6 between NPC and control groups

Group	n	Mean level of IL-6 $\bar{x} \pm SD$ (pg/ml)	p
NPC	21	46.16 $\pm$ 73.10*	0.119
Control	21	23.16 $\pm$ 25.84	

Independent T-test method. \*not significant different

**Table 2** The differences mean levels of interleukin 6 among NPC staging in the Minangkabau ethnic group

Group	n	Mean level of IL-6 $\bar{x} \pm SD$ (pg/ml)	p
Stage II	1	4.46	0.439
Stage III	4	37.52 $\pm$ 24.66	
Stage IV	16	50.92 $\pm$ 82.73	

The statistical analysis used the One-Way ANOVA

**Table 3** The differences mean levels of IL-6 among primary tumor status group of NPC in the Minangkabau ethnic group

Group	n	Mean Levels of IL-6 $\bar{x} \pm SD$ (pg/ml)	p
Primary tumor of T2	5	26.38 $\pm$ 24.44	0.892
Primary tumor of T3	3	30.38 $\pm$ 15.85	
Primary tumor of T4	13	57.40 $\pm$ 91.13	

The statistical analysis used the Independent T-test method

In the Table 3, the highest mean level of IL-6 was in the T4 primary tumor group, followed by T3 and T2. There was no T1 tumor group found in this study. The higher grade of the primary tumor group, the higher the mean level of IL-6. However, after the One Way Annova test, there was no statistically significant difference ( $p > 0.05$ ).

The mean level of IL-6 was higher in the enlargement lymph node group compared to without enlargement lymph node group. After the Independent t-test was

performed in the 2 groups, there was no statistically significant difference,  $p > 0,05$  (Table 4).

**Table 4** The differences in the mean levels of IL-6 between regional lymph node status of NPC in the Minangkabau ethnic group

Group	n	Mean Levels of IL-6 $\bar{x} \pm SD$ (pg/ml)	p
Enlargement lymph node (-)	5	41.53 $\pm$ 33.44	0.832
Enlargement lymph node (+)	16	47.60 $\pm$ 82.57	

The statistical analysis used the Independent T-test method

The mean level of IL-6 was higher in the WHO type II group compared to the WHO type III. The Independent t-test statistical analysis performed that there was no significant difference,  $p > 0,05$  (Table 5).

**Table 5** The differences in the mean levels of IL-6 in the subtypes of NPC pathology in the Minangkabau ethnic group

Group	n	Mean Level of IL-6 $\bar{x} \pm SD$ (pg/ml)	p
WHO type II	7	77.11 $\pm$ 121.21	0.515
WHO type III	14	30.68 $\pm$ 2.,83	

The statistical analysis used the Independent T-test method

### 3.2. Discussion

In this study, the mean level of IL-6 in NPC patients was higher (46.16 $\pm$ 73.10pg/ml) than the mean level of IL-6 in the control group (23.16 $\pm$ 25.84pg/ml). This result was similar with research in Malaysia by Tan et al. [11] but in significant difference between IL-6 plasma level of 78 NPC patients who had not been treated before and control plasma group that had been matched for age and sex, which was 164 $\pm$ 37pg/ml in NPC patients compared to 31 $\pm$ 13pg/ml in the control group. Interleukin 6 is a cytokine that has been studied in various solid tumor. The high level of IL-6 explained that the possibility of inflammation caused by EBV infection triggers the development of tumor cells. Colotta et al. [12] explained that IL-6 was one of the keys in cancer-associated inflammation, which was the main effector molecule required for antiapoptotic tumor cells through activation of the STAT-3 and Nuclear Factor Kappa Beta (NF- $\kappa$ B) pathways. There was a correlation between NPC, IL-6, and EBV. Latent Membrane Protein-1 (LMP-1), one of the EBV genes that had the ability to induced the production of IL-6, besides that IL-6 was a pro-inflammatory cytokine that regulated the latent infection of EBV through the activation of STAT-3 signal. After STAT-3 phosphorylation occurred, LMP-1 will be induced, which will increase the expression of IL-6.

Interleukin 6 was also detected in control plasma because IL-6 is a cytokine produced by various types of cells that are spread in the body that worked locally and was found systemically. In addition to its role in the inflammatory response and growth factors of various types of tumors, IL-6 also plays a protective function in various infections [13]. Deficiency of IL-6 can lead to disturbances in innate and adaptive immune function. Classical signaling of IL-6 through mIL-6R is associated with a protective effect against infection and regenerative activity, so IL-6 can still be detected in healthy people but in lower amounts [14].

Previous studies found IL-6 levels in healthy people with different values among different ethnicities. Gong et al. [15] in China concluded that the plasma of IL-6 in healthy people is 36.6 $\pm$ 13.33pg/ml. Zergoun [16] in North Africa concluded that the plasma levels of IL-6 in healthy people were 15.51 $\pm$ 5.14pg/ml. Dahl [10] in United States obtained an average plasma IL-6 level of 1.82 $\pm$ 0.30pg/ml. This study did not explore the condition of control plasma respondents of the Minangkabau ethnic group, such as menstrual cycle and body weight status. Whether this can affect IL-6 levels in the NPC and control groups cannot be ruled out. For this reason, further research is needed.

The mean level of IL-6 increased according to the stage but not statistically significant. Research results in some countries showed various results. In Italy, Gallo et al. [17] reported that IL-6 levels in the advanced stage were higher than in the early stage (68.3 $\pm$ 2.4pg/ml vs. 45.0 $\pm$ 1.8pg/ml) but not statistically significant. Meanwhile, Cao et al. [18] in China found a significant correlation between IL-6 levels and NPC stage ( $p < 0,001$ ) at the time of diagnosis before receiving any therapies with the highest IL-6 level at stage IV 76.9 $\pm$ 37.57pg/ml and the lowest at stage I. Interleukin 6 induces the proliferation and migrations of cancer cells and increases the expression of adhesive factors resulting in the spread of cancer cells.

Increasing levels of IL-6 were seen in advanced cancer patients, especially patients with regional enlargement of the lymph node. IL-6 could induce cell migration and promote tumor cell proliferation, increasing the expression of adhesion factors that cause NPC cells to diffuse and metastasis [18]. Increased blood level of IL-6 reflects IL-6 level in the tumor microenvironment and indicated the progression of disease. Dahl [10] explained that a STAT-3 played a role in oncogenic activity in tumors, such as mutations that would cause Janus Kinase/ Signal Transducer and Activator of Transcription-3 (JAK/STAT-3) signal activations. JAK/STAT-3 signaling mediated by IL-6 cause positive feedback of IL-6 synthesis that promote tumor growth, proliferation and metastasis.

The mean level of IL-6 was highest in the T4 primary tumors compared to T3 and T2 primary tumor status but not statistically significant. So far, not many studies have explored the correlation between IL-6 and primary tumor status of NPC patients. Ke et al. [19] in China performed a study in 290 patients newly diagnosed with NPC reported no significant difference of IL-6 between the T3/T4 primary tumor group and the T1/T2 primary tumor group ( $p=0.647$ ). Riedel et al. [20] in Germany researched IL-6 in head and neck cancer in 90 samples and concluded no significant correlation between IL-6 and primary tumor status ( $p=0.21$ ). Meanwhile, Sparano et al. [21] in Illinois explained a positive correlation between IL-6 and T3/T4 primary tumor status in head and neck cancer patients. Interleukin 6 is a cytokine produced by Th2 cells. Patients with T3 primary tumor and T4 showed a stronger Th2 immune response and decreased the Th1 immune response so IL-6 production is increased and Th1 function as a driver of cell-mediated immunity and tumoricidal effects is impaired. Elevated levels of IL-6 in the blood of head and neck cancer patients are the result of overproduction in the tumor which reflects the biological characteristics of the tumor and the progression of cancer [20,21].

In this study, IL-6 levels were higher in the lymph node enlargement status compare to without lymph node enlargement but not statistically significant. Research on the correlation between IL-6 levels and lymph nodes in the NPC patients showed different results. Ke et al. [19] reported that there was no significant correlation between IL-6 levels and lymph nodes enlargement of NPC patients. Interleukin 6 in the N3/N4 lymph node group compare to N0/N1 lymph node group,  $p=0.976$ . Lotfi et al. [22] also did not find a significant correlation between IL-6 levels and lymph node enlargement status in squamous cell carcinoma patients ( $p=0.757$ ). On the other hand, Riedel et al. [20] found a significant correlation between IL-6 and lymph node status in head and neck cancer patients ( $p=0.045$ ).

Tumor cells access circulation and surround soft tissue by releasing growth factors or cytokines to stimulate lymphangiogenesis. VEGF-C or Vascular Endothelial Growth Factor-C is major regulator of lymphangiogenesis [23]. Huang et al. [24] explained that in colorectal cancer VEGF-C worked through VEGF receptor-3 (VEGFR-3) which was predominantly expressed on lymphatic endothelial cells. The binding of VEGF-C and VEGFR-3 causes the proliferation and migration of cells. IL-6 and sIL-6R act through the Steroid receptor coactivator/ Focal Adhesion Kinase/ Signal Transducer Activator Transcription-3 (Src/FAK/STAT-3) cascade to induce and increase the phosphorylation of VEGF-C. Further research about VEGFR and Src/FAK/STAT-3 signal is needed in nasopharyngeal carcinoma.

The results of the study regarding the correlation of IL-6 with pathological sub type showed that IL-6 level was higher in WHO type II than WHO type III but statistically not significant. The results of previous showed different results. Kadir et al. [25] in cohort study of 16 NPC patients also found that IL-6 levels were not affected by histopathology type. In other hand, Elhabashy [26] explained there was a correlation between NPC, IL-6 and EBV.

WHO type II and III are dominantly EBV (+), especially WHO type III and most often occurs in endemic countries. In NPC, the virus is in a latent state in tumor cells. The interaction between lymphoid stroma found in undifferentiated NPC and surrounding carcinoma cell is an important contributing factor in the development of malignant NPC cells. In addition, infected lymphoblastoid cells contain a variety of extra-chromosomal viral DNA (episomes) that express latent proteins including Epstein Barr Nuclear Antigen (EBNA) and LMP. LMP-1 acts as a classic oncogene and is important for B-cell transformation induced by EBV and stimulates the production of IL-6 cytokines that activate the STAT-3 signal. Meanwhile, LMP-2A modulates STAT and NF- $\kappa$ B signal in EBV-infected epithelial cells through transcription and secretion of IL-6 [27, 28].

In addition, the transcription factor of nanog through phosphorylation of STAT-3 triggered by IL-6 kept the stem cells in a stable state of undifferentiated [29]. Whereas in the keratinized type IL-6 induced aggregation of keratin formation. When keratinocytes are exposed to pro-inflammatory cytokines, there will be changes in the expression and synthesis of cytoskeletal proteins. Interleukin-6 stimulates the redistribution and aggregations of keratin K16 which is a marker that is expressed in pathological conditions [30]. Based on this explanation, there is possible role of transcription factor nanog and keratin K16 in regulation of IL-6 by interacting with NPC sub type so further research is needed.

#### 4. CONCLUSION

The main conclusion of this research, there was no significant correlation between level of IL-6 and incidence of NPC in Minangkabau ethnic group. Besides, plasma level of IL-6 in NPC patients of Minangkabau ethnic was higher than healthy plasma, plasma level of IL-6 in WHO type II was higher than WHO type III, and there was a tendency of increasing plasma level of IL-6 to NPC stages, primary tumor status, and regional lymph node status but no significant correlation among them. Our result suggests further research in the correlation between immune response to plasma level of IL-6 in NPC, other pathway that play role in the regulations of

IL-6, such as the Src/FAK/STAT-3 signal and regulation of transcription factor to plasma level of IL-6.

## REFERENCES

- [1] MLK Chua, JTS Wee, EP Hui, ATC Chan, "Nasopharyngeal carcinoma," *The Lancet*, 387(10022):1012–24, 2016.
- [2] S Edge, D Byrd, C Compton, AJCC (American Joint Committee on Cancer). *Cancer Staging Manual*. Vol. 7, Springer-Verlag, 2010.
- [3] F Bray, J Ferlay, I Soerjomataram, RL Siegel, LA Torre, A Jemal, "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries." *CA: A Cancer Journal for Clinicians*, vol. 68, no. 6, pp. 394-424, 2018.
- [4] SM. Naomi, YA. Dewi, H. Agustina, "Association between Histopathological Grading and Clinical Staging in Nasopharyngeal Carcinoma Hubungan Derajat Histopatologi dengan Stadium Klinis pada Karsinoma Nasofaring \*\* Departemen Telinga Hidung Tenggorokan-Kepala Leher" *Journal of Medicine and Health*, vol. 2, no. 2, pp. 730-7, 2018.
- [5] JM. Bauml, C. Aggarwal, RB. Cohen, "Immunotherapy for head and neck cancer: where are we now and where are we going?" *Annals of Translational Medicine*, 7(S3):S75–S75, 2019.
- [6] J. Rajčáni, F. Bánáti, K. Szenthe, H. Helmut Niller, J. Minarovits, L. Stipkovits, et al, "Detection of Interleukin 6 (IL-6) antigen in the head and neck carcinoma cells" *Clinical and Medical Investigations*, vol. 4, no. 2, pp. 1-8, 2019.
- [7] EL. Tan, G. Selvaratnam, R. Kananathan, CK. Sam, "Quantification of Epstein-Barr virus DNA load, interleukin-6, interleukin-10, transforming growth factor- $\beta$ 1 and stem cell factor in plasma of patients with nasopharyngeal carcinoma" *BMC Cancer*, vol. 6, no. 49, pp. 1-8, 2006.
- [8] SW. Tsao, YL. Yip, CM. Tsang, PS. Pang, VMY. Lau, G. Zhang, et al., "Etiological factors of nasopharyngeal carcinoma," *Oral Oncology*, vol 50, no. 5, pp. 330-8, 2014.
- [9] DE. Johnson, RA O'Keefe, JR Grandis. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. *Nature Reviews Clinical Oncology*. 15(4):234–48, 2018.
- [10] RA Dahl. Targeting interleukin-6 trans-signaling in head and neck squamous cell carcinoma. 2018.
- [11] EL Tan, G Selvaratnam, R Kananathan, CK Sam, "Quantification of Epstein-Barr virus DNA load, interleukin-6, interleukin-10, transforming growth factor- $\beta$ 1 and stem cell factor in plasma of patients with nasopharyngeal carcinoma," *BMC Cancer*, vol. 6, no. 49, pp. 1-8, 2006.
- [12] F Colotta, P Allavena, A Sica, C Garlanda, A Mantovani. "Cancer-related inflammation, the seventh hallmark of cancer: Links to genetic instability". *Carcinogenesis*. 30(7):1073–81, 2009.
- [13] Y Gong, S Liang, L Zeng, Y Ni, S Zhou, X Yuan. "Effects of blood sample handling procedures on measurable interleukin 6 in plasma and serum," *Journal of Clinical Laboratory Analysis*. 33(7):1–7, 2019.
- [14] E Choy, S Rose-John, "Interleukin-6 as a multifunctional regulator: Inflammation, immune response, and fibrosis," *Journal of Scleroderma and Related Disorders*.;2(Suppl 2):S1–5, 2017.
- [15] Y Gong, S Liang, L Zeng, Y Ni, S Zhou, X Yuan, "Effects of blood sample handling procedures on measurable interleukin 6 in plasma and serum," *Journal of Clinical Laboratory Analysis*, vol. 33(7), pp. 1–7, 2019.
- [16] A Zergoun, A Zebboudj, SL Sellam, N Kariche, D Djennaoui, S Ouraghi, et al. patients.37(3):3505–14, 2017.
- [17] O Gallo, AM Gori, M Attanasio, F Martini, B Giusti, T Brunelli, et al. Interleukin-6 and acute-phase proteins in head and neck cancer. *European Archives of Oto-Rhino-Laryngology*.252(3):159–62, 1995.
- [18] W Cao, X Chen, L Lin, W Ma, D Wang, L Zhou. "Associations of serum CD62P and IL-6 levels with nasopharyngeal carcinoma staging and prognosis," *International Journal of Clinical and Experimental Pathology*. 9(9):9631–5, 2016.
- [19] L Ke, Y Xiang, W Xia, J Yang, Y Yu, Y Ye, et al. "A prognostic model predicts the risk of distant metastasis and death for patients with nasopharyngeal carcinoma based on pre-treatment interleukin 6 and clinical stage," *Clinical Immunology*. 164:45–51, 2016.
- [20] F Riedel, I Zaiss, D Herzog, K Götte, R Naim, K Hörmann, "Serum levels of interleukin-6 in patients with primary head and neck squamous cell carcinoma," *Anticancer Research*. 25(4):2761–6, 2005.
- [21] A Sparano, DMR Lathers, N Achille, GUYJ Petruzzelli, "Modulation of Th1 and Th2 cytokine profiles and their association with advanced head and neck squamous cell carcinoma," (II):573–6.

- [22] A Lotfi, N Shahidi, G Bayazian, S Abdollahi Fakhim, R Estakhri, A Esfahani, et al, "Serum level of interleukin-6 in patients with oral tongue squamous cell carcinoma," *Iranian Journal of Otorhinolaryngology*. 27(80):207–11, 2015.
- [23] A Yadav, B Kumar, J Datta, TN Teknos, P Kumar, "IL-6 promotes head and neck tumor metastasis by inducing epithelial-mesenchymal transition via the JAK-STAT3-SNAIL signaling pathway," *Molecular Cancer Research*, 9(12):1658–67, 2011.
- [24] SCM Huang, SW Tsao, CM Tsang, "Interplay of viral infection, host cell factors and tumor microenvironment in the pathogenesis of nasopharyngeal carcinoma" *Cancers*. 10(4), 2018.
- [25] A Kadir, K Retnowati, M Amsyar Akil, A Usman. "The Evaluation of Serum Il-6 Changes as Proliferative Cytokines in Patients With Nasopharyngeal Carcinoma Before and After the Ionizing Radiotherapy," *Global Journal of Health Science*. 10(8):55, 2018.
- [26] H Elhabashy. Applicability of Serum Interleukin-6 as a Screening Tool for Nasopharyngeal Carcinoma. 2017;(December 2012).
- [27] G Zhang, CM Tsang, W Deng, YL Yip, VWY Lui, SCC Wong, et al. "Enhanced IL-6/IL-6R Signaling Promotes Growth and Malignant Properties in EBV-Infected Premalignant and Cancerous Nasopharyngeal Epithelial Cells," *PLoS ONE*. 8(5):1–13, 2013.
- [28] LS Young, CW Dawson, "Epstein-Barr virus and nasopharyngeal carcinoma," *Chinese Journal of Cancer*. 33(12):581–90, 2014.
- [29] N Gawlik-Rzemieniewska, I Bednarek "The role of NANOG transcriptional factor in the development of malignant phenotype of cancer cells," *Cancer Biology and Therapy*, 17(1):1–10, 2016.
- [30] M Hernández-Quintero, W Kuri-Harcuch, A González Robles, F Castro-Muñozledo, "Interleukin-6 promotes human epidermal keratinocyte proliferation and keratin cytoskeleton reorganization in culture," *Cell and Tissue Research*. 325(1):77–90, 2006.