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ESTIMATION OF MIRNA-183 EXPRESSION AND TGF-B LEVEL IN CHRONIC MYELOID LEUKEMIA

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ABSTRACT

Background: MicroRNA-183 and Transforming Growth Factor Beta (TGF-β) have emerged as significant players in the pathophysiology of Chronic Myeloid Leukemia (CML). Research indicates that miRNA-183 may play a role in the regulation of cell proliferation and apoptosis in CML cells, potentially influencing disease progression and response to therapy. Elevated levels of miRNA-183 have been associated with poor prognosis, suggesting it could serve as a biomarker for disease severity. **Objective:** In this study, we aimed to analyze the expression of miR-183 and TGF- β level and investigate the relationship between miR-183 and level of TGF- β in CML patients. **Material and Methods:** The study has been carried out on 60 Iraqi patients (37 males and 23 females at age range 17 - 69 year) with chronic myeloid leukemia at chronic phase, who are referred to the National Center of Hematology/ Mustansiriyah University, Baghdad during the period from January to November 2023. Twenty of them are newly diagnosed (T0), and the other 40 patients are under treatment with TKIs (T+), Thirty age and gender-matched healthy subjects were enrolled to act as control group. TGF-β level estimates by ELISA while micrRNA-183 detection using RT- PCR. **Conclusion:** The elevated levels of TGF-β and miRNA-183 in CML patients, coupled with their positive correlation.

KEYWORDS: CML, imatinib, nilotinib, miRNA-183 and TGF-β.

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative disorder recognized by detection of abnormal chromosome called Philadelphia chromosome (Ph). The Ph chromosome is formed as result of reciprocal of translocation between the long arm chromosome 9 and 22 [9,22] (q34; q11) [1,2]. The chimeric oncogene BCR-ABL1 which is resulting from fusion of Breakpoint Cluster Region (BCR) and Abelson Tyrosine – Protein Kinase 1 (ABL1) genes [3]. Oncogene BCR-ABL1 is responsible for encoding BCR-ABL oncoprotein. This oncoprotein interferes with cellular signaling pathways, resulting in tumor progression [4]. Micro RNAs (miRNAs) are a class of small non-coding RNAs that have a crucial role in cellular processes such as differentiation, proliferation, migration, and apoptosis [5,6]. miRNAs may act as oncogenes or tumor suppressors; therefore, they prevent or promote tumorigenesis, and abnormal expression has been reported in many malignancies. The role of miRNA in leukemia pathogenesis is still emerging, but several studies have suggested using miRNA expression profiles as biomarkers for diagnosis, prognosis, and response to therapy in leukemia [7,8]. The miR-183 cluster, a trio of microRNAs

(miRNAs) comprising miR-183, miR-96, and miR-182, is transcribed as a polycistronic unit [9]. Notably, these miRNAs often exert oncogenic effects via distinct molecular pathways. Exosomes, extracellular vesicles, facilitate intercellular communication and modulate the tumor microenvironment. Intriguingly, the miR-183 cluster is detectable within exosomes and plays a functional role in tumor progression [10]. miR-183 plays a central role in transforming growth factor beta (TGF-β) which is a potent immunosuppressive factor abundant in the tumor microenvironment and inhibit Natural Killer cells (NK) function by reduced or restored DAP12 levels in NK cells[11,12]. TGF-β considered regulatory cytokine any defect in T regulatory cells lead to decrease in level of TGF-β and cause suppression to immune system [13]

In this study, we aimed to analyze the expression of miR-183 and TGF- β and investigate the relationship between miR-183 and level of TGF- β in CML patients.

MATERIAL AND METHODS

Subjects:

This research involved 60 individuals diagnosed with chronic myeloid leukemia (CML). Twenty of these patients were newly diagnosed and had not begun treatment (T0), while the remaining 40 were already undergoing treatment (T+). The T+ group was further divided into two subgroups: 20 patients treated with imatinib and 20 treated with nilotinib. A control group of 30 healthy individuals was also included. All participants, both patients and controls, were recruited from the National Center of Hematology at Mustansyriah University between January and November 2023.

Study design:

This study is a case-control study that was performed in a diagnostic laboratory setting.

Inclusion criteria: Subject with age >17, Newly diagnosed CML, CML patients treated different tyrosine kinase inhibitor

Exclusion criteria: Subjects who were excluded from this study include: All subjects under the age of 17 years, Patients with crisis and accelerated phase of CML after performing blood film test based on percentage of blast cells protocol.

METHODS

Collected samples: About 5 ml of blood were aspirated from all subjects (apparently healthy controls and patients) by using peripheral vein punctures and dispensed into two aliquots; the first one was prepared by transferring 2 ml of whole blood into anticoagulant tubes containing EDTA For detection miRNA-183 using RT-PCR .However, the second aliquot was prepared by transferring 3 ml of whole blood into a non-heparinized gel tube, and left for 15 minutes at 40C to clot, then centrifuged at 4100 rpm for 10 minutes to separate serum, which is dispended into three aliquots in an eppendorf tubes and stored in -80C until being used to determine the serum level of certain biomarkers (TGF- β) by means of Enzyme Linked Immunosorbent Assay (ELISA) technique.

Detection of Transforming Growth Factor beta (TGF-β)

In this study the detection of TGF-β in CML patients and controls groups using sandwich ELISA techniques (Sunlong Biotech, China) and read the result by semi-automated ELISA reader (Mindray, China).

Detection of miR-183:

First step extraction of miRNA (EasyPure miRNA kit, TRAN, Korea), then Stem-loop RT-PCR is one of the most used real-time PCR approaches to quantify small non-coding RNAs such as microRNAs. The quantification method is divided into two steps. First, RNA is reverse transcribed using a specific stem-loop primer, and the resulting RT product is subsequently used as a template for quantitative real-time PCR. This fast and simple method provides quantitative data with high sensitivity and specificity to study miRNAs and their functions [14]. The reverse transcriptase (Easy script One step gDNA removal and cDNA synthesis, TRAN, Korea) using stem loop primers (IDT, Korea) table 1, the step using thermal cycler (Bio-Rad, USA). The Protocol used for synthesis cDNA illustrates in table 2

Table 1: *(Stem loop primer sequence for miRNA.)*

miRNA	Stem loop for miRNA (5′-3′)
miRNA-183	**5'-** GTC GTA TCC AGT GCA GGG TCC GAG GTA TTC GCA CTG GAT ACG ACC ACT GG -3'
Universe stem loop	GAAAGAAGGCGAGGAGCAGATCGAGGAAGAAGACGGAAGAATGTGCGTCTCGC CTTCTTTCNNNNNNNN

Table 2: *(Thermal cycler steps for cDNA synthesis.)*

	Step 1	Step 2	Step 3
Temperature	41ºC	83 ºC	4 ºC
Time	15 min	30 sec	5 min

Primers preparation (IDT,Korea): Upon dissolving in nuclease free water as manufacturer instruction , a primary working solution was prepared from lyophilized primers to prepare a stock solution with concentration 100µM for each primer and store at (-20ºC). From stock solution prepared working primers with concentration 10 µM by diluting 10 µl of primers stock solution in 90 µl nuclease free water store at (-20ºC) before usage.

Quantitative Real time PCR (qRT-PCR).

miRNA (miRNA-183), the forward and reverse primers, table 3, for miRNA illustrated in table 4, were detected the gene expression using RT-PCR SYBR Green assay (Bio-Rad 96X thermal cycler ,Korea), PerctStartTM Green qPCR Supermix kit (TRAN,Korea).

The U6 gene is used as endogenous control for normalization. The sequence of U6 primers is also illustrated in table 3.

Table 3: *(The forward and reverse primers for miR-183 and Housekeeping gene U6.)*

miRNA	Forward primer (5′-3′)	Reverse primer (5′-3′)
miRNA-183	5'-TCT CCC AAC CCT TTA GCA -3'	5'- CCA GTG CAG GGT CCG AGG TA-3'
U6 housekeeping gene	5' CTCGCTTCGGCAGCA 3'	5' AACGCTTCACGAATT 3'

Table 4: *(Steps of RT-PCR for detection micRNA-183 expression.)*

Steps	Temperature	Time	Cycles
Enzyme reaction (Initial denaturation)	94ºC	30 min	1
Denaturation	94ºC	5 sec	38
Annealing	58ºC	14 sec	
Extend	72ºC	10 sec	
Melting curve analysis	95 ºC	1 min	1
	55 ºC	30 sec	

To determined miR-183 gene expression it was reported as fold change ΔCt calculation, Using Ct (threshold cycle) method quantification 2- ΔCt method for calculation expression micro RNA, calculate ΔCt for target gene (Ct target gene - Ct endogenous gene) for patient and ΔCt for control (Ct for target gene - Ct fore endogenous gene). Then calculation 2- ΔCt For patient and control, application the calculation (Patient 2 -ΔCt / Control 2 -ΔCt) there result mean fold of gene expression [15].

Statistical analysis

The statistical analysis was conducted using the software package SPSS IBM Corp., Released 2021. IBM SPSS Statistics for Windows, Version 28.0. (IBM Corp., Armonk, NY). Demographic data were characterized using descriptive statistics ANOVA test, Ratio and person correlation (r). Estimated p-values <0.05 were considered significant.

RESULTS

This study is conducted on 60 patients with CML, 20 patients of them are newly diagnosed and before starting treatment regime (abbreviated as T0), while the rest 40 patients are previously diagnosed and under treatment (abbreviated as T+), half of them are treated with Gleevec (imatinib) and the other are treated with Tasigna (nilotinib). All patients of T0 and T+ groups are at chronic phase of CML. Along with those patients, 30 healthy looking persons are enrolled to act as control group with matched age and gender. The age means showed non-significant differences between control group (39.2 ± 12.1 year) and patients of T0 and T+ (35.6 ± 12.2 and 43.3 ± 13.9 year respectively). Also, male-female ratio (MFR) in CML patients is 1.6:1, thus the distribution of male: female in control group (1.5:1) is conducted to be matched with that in patients and with non-significant difference table 5.

Table 5: *(Age and gender of patients and control groups.)*

Character		Control (n=30)	Patients		P value
			T0 (n=20)	T+ (n=40)	
Age (years)	Range	19 - 61	17 - 55	14 – 65	0.103
	M±SD	39.2 ± 12.1	35.6 ± 12.2	43.3 ± 13.9	
Gender (n, %)	Male	12 (60%)	12 (60%)	25 (62.5%)	0.975
	Female	8 (40%)	8 (40%)	15 (37.5%)	
	MFR	1.5	1.6		
M±SD: Mean ± standard deviation; MFR: male/female ratio					

Estimation TGF-β level

Serum TGF-β levels were significantly elevated in both newly diagnosed (T0) and treated (T+) CML patients compared to healthy controls (P-value < 0.001). Specifically, the T0 group exhibited the highest TGF-β levels, followed by the T+ group. These findings suggest a role for TGF-β in the pathogenesis of CML, table 6.

Table 6: *(Serum level TGF-β, in CML patients' groups and controls group.)*

Parameter/ Serum level	Range (Median ± SD)			
	CML Patients		Control no.=30	p-value
	T0 no.=20	T+ no.=40		
TGF-β (pg/ml)	(232±31.3)	(221.7±17.0)	(150.3±19.0)	<0.001
significant p value <0.05				

Gene expression of miRNA-183

miRNA-183 expression was significantly upregulated in CML patients compared to controls. The fold change in miRNA-183 expression was approximately 10 and 10.5 in the T0 and T+ groups, respectively. This indicates a substantial increase in miRNA-183 levels in CML patients, table 7.

Table 7: *(Gene expression miRNA-183 among CML patients' groups and control subject.)*

Groups	Mean of Ct of miR-183	Mean CT of U6	ΔCt	$2^{-\Delta Ct}$	fold of gene expression
T0	33.6	29.3	4.3	0.050	10
T+	34.0	30.0	4.0	0.062	10.5
Control	35.9	28.5	7.4	0.0059	1
Ct: cycle threshold, ΔCt: (Ct of target gene - Ct of control gene)					

Correlation between miRNA-183 and TGF-β in CML patients' groups

A strong positive correlation was observed between miRNA-183 expression and serum TGF-β levels in both newly diagnosed and treated CML patients. This suggests a potential regulatory relationship between these two factors. When TGF-β level increases the miRNA-183 expression will increase and verse versa, Figure 1 & 2.

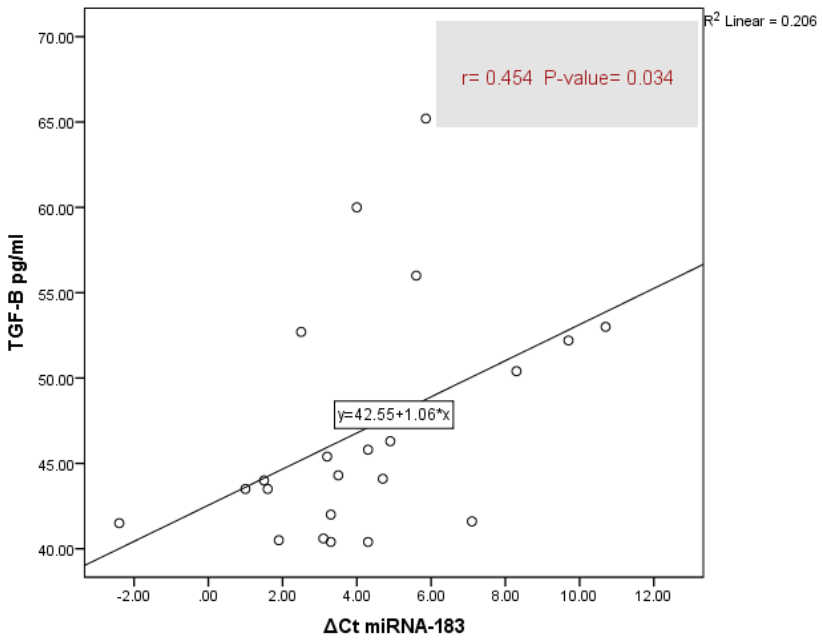

Figure 1: *(Correlation of ΔCt miRNA -183 and TGF-β among Newly diagnosed CML patients.)*

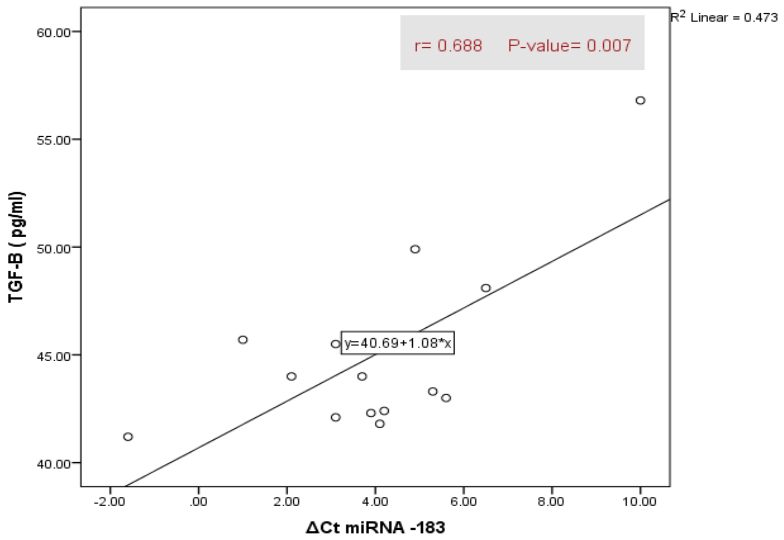

Figure 2: *(Correlation of ΔCt miRNA -183 and TGF-β among Treated CML patients.)*

DISCUSSION

The TGF-β signaling pathway plays a crucial role in various cellular processes, including growth, differentiation, cell death, movement, invasion, production of extracellular matrix, blood vessel formation, and immune responses [16,17]. In this study, the TGF-β levels were significantly higher in CML patients compared to controls, with a more pronounced elevation in the newly diagnosed group. TGF-β signals play critical roles in the regulation of the Tumor Microenvironment (TME), which has a complex impact on the progression of cancers. TGF-β may be used as a biomarker in cancer [18]. TGF-β plays dual roles in the TME based on the divergent stages of the tumor progression and genetic alteration background. In early-stage tumors, the TGF-β pathway induces apoptosis and inhibits the proliferation of cells including carcinoma cells as a tumor suppressor. Paradoxically, in late stage, it has pro-tumor effects by modulating genomic instability, the transition of epithelial cells to a mesenchymal cell type (EMT), neo-angiogenesis, immune evasion, and metastasis [19]. The statement suggests that TGF-β, which is released from the extracellular matrix of a bone marrow microenvironment (BMM) that is actively remodeling, may have an inhibitory effect on the progression of chronic myeloid leukemia (CML) [20]. This aligns with the complex role of TGF-β in cancer biology, where it can exhibit both tumor-suppressive and tumor-promoting effects depending on the context and stage of the disease [21].

The elevated levels of TGF-β and miRNA-183 in CML patients, coupled with their positive correlation, suggest a potential role for miRNA-183 in the TGF-β-mediated signaling pathways involved in CML pathogenesis. Further investigations are warranted to elucidate the specific mechanisms by which miRNA-183 regulates TGF-β signaling and contributes to CML progression.

Recently, increasing evidence suggests that miRNAs play a crucial role in maintaining normal cellular function and dysregulation of miRNA expression is associated with tumorigenesis and tumor progression [22,23].

MicroRNA-183 (miR-183) exhibits abnormal expression patterns across various tumors and plays a significant role in tumor initiation and progression. Its expression is regulated by multiple pathways, and the mechanisms through which miR-183 functions in cancer are diverse, often leading to conflicting conclusions. Specifically, miR-183 has been found to be upregulated in 18 different types of cancer,

while it is downregulated in 6 types. Furthermore, there are instances in 7 types of cancer where both upregulation and downregulation have been reported. Evidence indicates that miR-183 can act as either an oncogene or a tumor suppressor, in addition to influencing the expression of other oncogenes and tumor suppressor genes across various cancer types [24]. The current study found that elevated TGF-β causes upregulation of miRNA-183 which may cause deactivation of NK cells, which is consistent with another study that found that TGF-β induces improved expression of miRNA-183 and blocks expression of DNAX-activating protein 12 kDa (DAP12). Inhibition of DAP12 creates an immunosuppressive tumor microenvironment by inhibiting NK cell function. Downregulation of DAP12 is a common feature in all types of lung cancer and its expression is lower in intertumoral NK cells than in peritumoral NK cells [25,26].

Understanding the interplay between TGF-β and miRNA-183 in CML could lead to the development of novel therapeutic strategies. Targeting either TGF-β or miRNA-183 could potentially have therapeutic benefits in CML patients. For instance, inhibiting TGF-β or miRNA-183 might attenuate CML progression by disrupting aberrant signaling pathways.

CONCLUSION

The elevated levels of TGF-β and miRNA-183 in CML patients, coupled with their positive correlation, suggest a potential role for miRNA-183 in the TGF-β-mediated signaling pathways involved in CML pathogenesis.

Recommendation:

Future studies could focus on:

Investigating the specific molecular mechanisms by which miRNA-183 regulates TGF-β signaling in CML. Exploring the potential therapeutic effects of targeting TGF-β or miRNA-183 in CML patients. Identifying additional factors that may influence miRNA-183 expression or function in CML.

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REFERENCES

1. Rudich A, Garzon R, Dorrance A. Non-Coding RNAs Are Implicit in Chronic Myeloid Leukemia Therapy Resistance. Int J Mol Sci 2022, Vol 23, Page 12271 [Internet]. 2022 Oct 14 [cited 2024 Oct 10];23(20):12271. Available from: https://www.mdpi.com/1422-0067/23/20/12271/htm
2. Patterson SD, Copland M. The Bone Marrow Immune Microenvironment in CML: Treatment Responses, Treatment-Free Remission, and Therapeutic Vulnerabilities. Curr Hematol Malig Rep [Internet]. 2023 Apr 1 [cited 2024 Oct 12];18(2):19–32. Available from: https://link.springer.com/article/10.1007/s11899-023-00688-6
3. Osman AEG, Deininger MW. Chronic Myeloid Leukemia: Modern therapies, current challenges and future directions. Blood Rev. 2021 Sep 1;49:100825.
4. Singh P. MicroRNA based combinatorial therapy against TKIs resistant CML by inactivating the PI3K/Akt/mTOR pathway: a review. Med Oncol [Internet]. 2023 Oct 1 [cited 2024 Oct 10];40(10):1–15. Available from: https://link.springer.com/article/10.1007/s12032-023-

02161-z
5. Gaál Z. Implication of microRNAs in Carcinogenesis with Emphasis on Hematological Malignancies and Clinical Translation. Int J Mol Sci 2022, Vol 23, Page 5838 [Internet]. 2022 May 23 [cited 2022 Aug 30];23(10):5838. Available from: https://www.mdpi.com/1422-0067/23/10/5838/htm
6. Hameed AM, Amira Z, Al-Alwany SHM, Mtashar BA. Biochemical and breakpoint cluster region-c-ABL oncogene 1 polymorphism study among Iraqi patients with chronic myeloid leukemia. Iraqi J Hematol [Internet]. 2023 [cited 2024 Oct 12];12(2):176–83. Available from: https://journals.lww.com/ijhm/fulltext/2023/12020/biochemical_and_breakpoint_cluster_region_c_abl.10.aspx
7. Anelli L, Zagaria A, Specchia G, Musto P, Albano F. Dysregulation of miRNA in Leukemia: Exploiting miRNA Expression Profiles as Biomarkers. Int J Mol Sci 2021, Vol 22, Page 7156 [Internet]. 2021 Jul 2 [cited 2024 Oct 10];22(13):7156. Available from: https://www.mdpi.com/1422-0067/22/13/7156/htm
8. Wang X, Zuo D, Yuan Y, Yang X, Hong Z, Zhang R. MicroRNA-183 promotes cell proliferation via regulating programmed cell death 6 in pediatric acute myeloid leukemia. J Cancer Res Clin Oncol 2016 1431 [Internet]. 2016 Oct 13 [cited 2022 Aug 30];143(1):169–80. Available from: https://link.springer.com/article/10.1007/s00432-016-2277-2
9. Li H, Kloosterman W, Fekete DM. MicroRNA-183 Family Members Regulate Sensorineural Fates in the Inner Ear. J Neurosci [Internet]. 2010 Mar 3 [cited 2024 Oct 12];30(9):3254–63. Available from: https://www.jneurosci.org/content/30/9/3254
10. Li S, Meng W, Guo Z, Liu M, He Y, Li Y, et al. The miR-183 Cluster: Biogenesis, Functions, and Cell Communication via Exosomes in Cancer. Cells 2023, Vol 12, Page 1315 [Internet]. 2023 May 5 [cited 2024 Oct 10];12(9):1315. Available from: https://www.mdpi.com/2073-4409/12/9/1315/htm
11. Wosniaki DK, Marin AM, Oliveira RN, Koerich GM, Munhoz EC, Farias JS de H, et al. The Screening of microRNAs in Chronic Myeloid Leukemia: A Clinical Evaluation. Int J Mol Sci 2024, Vol 25, Page 3363 [Internet]. 2024 Mar 16 [cited 2024 Oct 10];25(6):3363. Available from: https://www.mdpi.com/1422-0067/25/6/3363/htm
12. Donatelli SS, Zhou JM, Gilvary DL, Eksioglu EA, Chen X, Cress WD, et al. TGF-β-inducible microRNA-183 silences tumor-associated natural killer cells. Proc Natl Acad Sci U S A [Internet]. 2014 Mar 18 [cited 2024 Oct 10];111(11):4203–8. Available from: https://www.pnas.org/doi/abs/10.1073/pnas.1319269111
13. Shabeeb Z, Faraj Y, Mahmood M, Mtashar B. Interplaying of regulatory T-cells and related chemokines in immune thrombocytopenic purpura patients. Iraqi J Hematol [Internet]. 2020 [cited 2024 Oct 12];9(2):138. Available from: https://journals.lww.com/ijhm/fulltext/2020/09020/interplaying_of_regulatory_t_cells_and_related.17.aspx
14. Abel Y, Rederstorff M. Stem-Loop qRT-PCR–Based Quantification of miRNAs. Methods Mol Biol [Internet]. 2021 [cited 2022 Apr 10];2300:59–64. Available from: https://link.springer.com/protocol/10.1007/978-1-0716-1386-3_6
15. Rao X, Huang X, Zhou Z, Lin X. An improvement of the 2ˆ(-delta delta CT) method for quantitative real-time polymerase chain reaction data analysis. Biostat Bioinforma Biomath [Internet]. 2013 [cited 2022 Apr 15];3(3):71–85. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25558171%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4280562
16. Kim BG, Malek E, Choi SH, Ignatz-Hoover JJ, Driscoll JJ. Novel therapies emerging in oncology to target the TGF-β pathway. J Hematol Oncol 2021 141 [Internet]. 2021 Apr 6 [cited 2024 Oct

11];14(1):1–20. Available from: https://link.springer.com/articles/10.1186/s13045-021-01053-x
17. Castriconi R, Dondero A, Bellora F, Moretta L, Castellano A, Locatelli F, et al. Neuroblastoma-Derived TGF-β1 Modulates the Chemokine Receptor Repertoire of Human Resting NK Cells. J Immunol [Internet]. 2013 May 15 [cited 2022 May 23];190(10):5321–8. Available from: https://www.jimmunol.org/content/190/10/5321
18. Tie Y, Tang F, Peng D, Zhang Y, Shi H. TGF-beta signal transduction: biology, function and therapy for diseases. Mol Biomed 2022 31 [Internet]. 2022 Dec 19 [cited 2024 Oct 11];3(1):1–29. Available from: https://link.springer.com/article/10.1186/s43556-022-00109-9
19. Zhao H, Wei J, Sun J. Roles of TGF-β signaling pathway in tumor microenvirionment and cancer therapy. Int Immunopharmacol. 2020 Dec 1;89:107101.
20. Pendse S, Chavan S, Kale V, Vaidya A. A comprehensive analysis of cell-autonomous and non-cell-autonomous regulation of myeloid leukemic cells: The prospect of developing novel niche-targeting therapies. Cell Biol Int [Internet]. 2023 Oct 1 [cited 2024 Oct 12];47(10):1667–83. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/cbin.12078
21. Minciacchi VR, Kumar R, Krause DS. Chronic Myeloid Leukemia: A Model Disease of the Past, Present and Future. Cells 2021, Vol 10, Page 117 [Internet]. 2021 Jan 10 [cited 2024 Oct 11];10(1):117. Available from: https://www.mdpi.com/2073-4409/10/1/117/htm
22. Wu W, He X, Kong J, Ye B. Mir-373 affects human lung cancer cells' growth and its E-cadherin expression. Oncol Res [Internet]. 2012 Jan 1 [cited 2024 Oct 11];20(4):163–70. Available from: https://europepmc.org/article/med/23461063
23. Mehta A, Baltimore D. MicroRNAs as regulatory elements in immune system logic. Nat Rev Immunol 2016 165 [Internet]. 2016 Apr 28 [cited 2022 May 23];16(5):279–94. Available from: https://www.nature.com/articles/nri.2016.40
24. Cao D, Di M, Liang J, Shi S, Tan Q, Wang Z. MicroRNA-183 in Cancer Progression. J Cancer [Internet]. 2020 [cited 2024 Oct 11];11(6):1315. Available from: /pmc/articles/PMC6995398/
25. Bugide S, Janostiak R, Wajapeyee N. Epigenetic Mechanisms Dictating Eradication of Cancer by Natural Killer Cells. Vol. 4, Trends in Cancer. Cell Press; 2018. p. 553–66.
26. Pesce S, Greppi M, Ferretti E, Obino V, Carlomagno S, Rutigliani M, et al. miRNAs in NK Cell-Based Immune Responses and Cancer Immunotherapy. Front Cell Dev Biol [Internet]. 2020 Feb 25 [cited 2021 Oct 10];8. Available from: /pmc/articles/PMC7053181/