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NF-kB-p50-TFBS-complementary and c-myc-TFBS-complementary motifs in miRNAs involved in pathogenesis of different lympho- and myeloproliferative diseases

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In our previous works, there were discovered different kinds of the c-myc-TFBS-complementary and NF-kB-p50-TFBS-complementary motifs in the stem-loop forms of the human, mouse and rat miRNAs. Also, there were described different types of the stem-loop miRNA informational redundancy as to these motifs. We have hypothesized these motifs, being the elements of the stem-loop miRNA degradome, can function as the alternative transcription factors. In the present paper, this methodology was applied to analysis of the characteristic miRNA expression profiles of different B-lymphoproliferative and myeloproliferative diseases. There were found the following main regularities: 1) significant part of the stem-loop miRNAs involved in pathogenesis of different hematologic diseases contain complementary motifs to the binding sites of c-myc and NF-kB-p50 transcription factors. Agreeably to this, the degradome elements of these stem-loop miRNAs are potentially able to function as alternative transcription factors; 2) each nosological unit has its own characteristic spectra of the TFBS-complementary motifs in its characteristic miRNA set, showing their real participation in the cell differentiation pathways; 3) different types of the stem-loop miRNA informational redundancy as to the TFBS-complementary motifs correlate with different directions of the cell differentiation. Also, our results permit to formulate the following recommendations for the differential diagnosis: 1) hyperexpression of miR-320a and miR-323b in the leukemia cells may be a weighty argument to diagnose chronic myelocytic leukemia (CML); 2) hyperexpression of the miRs 495 and 543 — alone and, moreover, in combination with hypoexpression of such miRs as 134, 542, 623, 671, 1182 — in the leukemia cells may be a weighty argument to diagnose CML; 3) hypoexpression of the miR-126 in the leukemia cells may be a weighty argument to diagnose acute myelocytic leukemia; 4) hyperexpression of the miR-185 and miR-324 in the lymphoma cells may be a weighty argument to diagnose Burkitt's lymphoma; 5) hyperexpression of the miR-192a-2 in the lymphoma cells may be a weighty argument to diagnose mantle-cell lymphoma.

Key words: *lymphoproliferative diseases; myeloproliferative diseases; microRNA; transcription factor binding sites; differential diagnosis.*

For today, an important role of miRNA up- and downregulation in pathogenesis and differential diagnosis of the malignancies, including different lympho- and myeloproliferative diseases, is completely proved and generally known. At the same time, it is known that certain miRNAs affect expression of certain transcription factors (TF), including, especially, ones being involved into transcription self-control of these miRNAs [1–3]. But we are still a long way from completeness of a list of such regulation. Thus, it would be logical to suppose these facts point to the imbalance of the corresponding miRNA-TF interrelations as one of the leading events in a malignancy pathogenesis. However, what is the mechanism of this imbalance appearance? Is the commonly known miRNA-caused disruption of translation enough for this? Most probably, not. Indeed, the crucial moment of any imbalance is *differential* disruption of the homeostasis supporting functions/agents [4].

Looking at the problem have been described above, it is rational to pay a special attention to such TFs as NF-kB (especially, its p50 protein subunit) and c-myc. Both these TFs are widely multifunctional and commonly known to be involved into regulation of all main biological functions, such as cell proliferation, inflammation, immune response, malignization, apoptosis, etc. c-myc expression is NF-kB-dependent [5] and, moreover, their expression may be cross-regulated [6]. c-myc is well known as an oncoprotein, but modulations of its expression appear to be important not only for those malignancies in which it executes its direct oncoprotein's function [7, 8]. NF-kB-p50 is not known as an oncoprotein, but its expression and activity play a distinguished role in practically all kinds and stages of oncogenesis [9, 10]. Especially, both these TFs play indirect but quite important role in development of different kinds of leukemia and lymphoma [11, 12]. At last, NF-kB TF was firstly discovered in proliferating lymphocytes [13]. In this connection, we must point the followings.

In our previous papers [14, 15], we have described the NF-kB-p50-TFBS-complementary and c-myc-TFBS-complementary motifs in all *Homo sapiens*, *Mus musculus* and *Rattus norvegicus* stem-loop formed miRNAs, known up to October 2016. We have supposed these motifs enable the stem-loop miRNA degradome to function as a set of the alternative TF.

Note. The term «degradome» was not so long ago applied to the side products of protein processing, but now it is widely enlarged to the side products of different RNAs processing [16–18]. As we think, it is expedient to enlarge it up to the side products of any macromolecule processing.

Thus, the aim of our investigation was a search for any characteristic differences in distribution of the TFBS-complementary motifs named above between the stem-loop forms of the miRNAs involved in pathogenesis of the lymphoproliferative and myeloproliferative diseases.

We are fully aware of the incompleteness of modern information on these issues and, accordingly, the imperfection of our attempt to systematize this information. Therefore, we consider this article mainly as a draft algorithm for analyzing available and newly received information.

MATERIALS AND METHODS

This search was performed using the literature data and miRBase. We have used only such papers in which the authors have compared miRNA spectra in the leukemia/lymphoma cells obtained immediately from the patients versus their normal homologues obtained

from the healthy donors [19–26]. The papers describing the *in vitro* cultured leukemia/lymphoma cells were not used because of significant biochemical disturbances appearing in all kinds of cells under *in vitro* conditions.

Distribution of the corresponding TFBS-complementary motifs in the whole set of the human stem-loop miRNAs have been discovered up to the end of October 2016 is shown in our previous papers [14, 15] and the supplementary materials to them. So, our task in the present work was to compile a list of miRNAs involved in the pathogenesis of the corresponding diseases, compare it with these supplementary tables and analyze the results using the criteria described in [14, 15].

Statistical analysis. Statistical significance of the final results was estimated using the Fisher's exact method. In these calculations, we used the total number of all — both upregulated and downregulated — miRNAs involved in the pathogenesis of B-lymphoproliferative diseases have been studied here and the analogous number for myeloproliferative diseases. The approximate values of high number factorials were taken from the [26] tables.

RESULTS AND DISCUSSION

It is very important to note that we have initiated the present research without any

Table 1. List of miRNAs involved in pathogenesis of some hematological diseases and containing c-myc-TFBS-complementary motifs

Diagnosis	Upregulated miRNAs	Downregulated miRNAs	References
Lymphoproliferative diseases			
B-lymphoid			
Diffuse large B-cell lymphoma (BCL)			
Activated B-cell-like subtype and germinal center B-cell-like subtype (ABC+GCB)	miR-17, miR-18a, miR-19a, miR-19b, miR-20a, miR-92a, miR-145, miR-150, miR-328 1 del, 2 ins/9 miRs	Not found	[19]
Transformed from follicular lymphoma (FL)	let-7b, let-7i, miR-217, miR-221, miR-222, miR-223 2 del, 1 ins/6 miRs	Not found	
Other B-lymphoproliferative diseases			
FL	miR-9, miR-54, miR-193a, miR-193b, miR-213, miR-301a, miR-338, miR-345, miR-513b, miR-574, miR-663, miR-1287, miR-1295, miR-1471 1 del, 1 ins/13 true miRs	miR-17, miR-30a, miR-33a, miR-106a, miR-141, miR-202, miR-205, miR-222, miR-301b, miR-431, miR-570 1 del, 1 ins/11 miRs	
Burkitt's lymphoma (BL)	miR-9, miR-26a, miR-26b, miR-93, miR-105(-1), miR-124, miR-185, miR-192, miR-193a, miR-202, miR-324,miR-326, miR-328, miR-339, miR-340, miR-371a, miR-429, miR-448, miR-483, miR-485, miR-497 1 conv, 1 del, 1 ex, 2 ins/20 miRs	miR-23a, miR-23b, miR-26a, miR-26b, miR-29b, miR-30a, miR-30d, miR-34b, miR-103, miR-107, miR-142, miR-146a, miR-146b, miR-155, miR-221, miR-222, miR-342 4 del/18 miRs	[19]
Mantle-cell lymphoma (MCL)	miR-17, miR-18a, miR-19a, miR-19b, miR-20a, miR-25, miR-92a, miR-93, miR-106b, miR-124a, miR-155, miR-302c, miR-370, miR-617, miR-654 2 del, 3 ins/14 true miRs	miR-27b, miR-31, miR-142, miR-148a, miR-150 1 conv, 1 del/5 miRs	
B-cell chronic lymphocytic leukemia (B-CLL)	miR-21, miR-150, miR-155, mir-195, miR-222 5 miRs	miR-15a, miR-16-1, miR-29c, miR-34a 4 miRs	[19], [20], [21], [22], [23], [24]
B-cell acute lymphocytic leukemia (B-ALL)	miR-34a, miR-222, miR-511 3 miRs	miR-26a, miR-199a, miR-221, miR-223 1 ex/4 miRs	
Myeloproliferative diseases			
Chronic myelocytic leukemia (CML)	miR-9, miR-18a, miR-21, miR-51, miR-92a-1, miR-96, miR-105-1, miR-128-1, miR-154, miR-181b-1, miR-193b, miR-299, miR-320a, miR-323b, miR-323a, miR-329, miR-335, miR-337, miR-338, miR-365, miR-379, miR-382, miR-409, miR-410, miR-411, miR-431, miR-432, miR-486, miR-493, miR-495, miR-543, miR-654, miR-758 2 conv, 6 del, 3 ins, 2 in.inv/32 true miRs	hcmv-miR-US4, miR-22, miR-28, miR-30e, miR-34a, miR-98, miR-134, miR-135a, miR-142, miR-143, miR-145, miR-148b, miR-149, miR-150, miR-155, miR-181c, miR-186, miR-188, miR-191, miR-193a, miR-193b, miR-196b, miR-197, miR-198, miR-199a, miR-199b, miR-200c, miR-202, miR-221, miR-222, miR-320c, miR-342, miR-361, miR-363, miR-371a, miR-424, miR-491, miR-513a, miR-513c, miR-518a-1, miR-520f, miR-542, miR-557, miR-564, miR-582, miR-584, miR-588, miR-595, miR-601, miR-605, miR-622, miR-623, miR-650, miR-652, miR-659, miR-663, miR-664, miR-665, miR-671, miR-760, miR-765, miR-874, miR-1180, miR-1182, miR-1183,miR-1224, miR-1225, miR-1299, miR-1300, miR-1323, miR-1469, miR-1471 3 conv, 13 del, 1 ins/70 true miRs	[20], [24], [25]
Acute myelocytic leukemia (AML)	miR-146a 1 miR	miR-15a, miR-16, miR-29b, miR-93, miR-124-1, miR-125a, miR-126overlap, miR-130a, miR-203 3 del, 2 ins / 9 miRs	

Notes. In this and next tables:
miR-xxx – stem-loop miRNA containing conventional motif(s);
miR-xxx – stem-loop miRNA containing motif(s) with an exchange;
miR-xxx – stem-loop miRNA containing motif(s) with a deletion;
miR-xxx – stem-loop miRNA containing motife(s) with an insert;
miR-xxx – stem-loop miRNA containing inner inversion;
miR-xxx – miRNAs not known in human (most probably, the contaminants); pseudo-miRNAs (indeed tRFs or other short RNAs);
miR-xxx* – mature (not stem-loop) miRNA, especially -5p; but its hyper- or hypoexpression indirectly testifies the corresponding stem-loop form expression modulations;
miR-xxx, miR-xxx, etc – stem-loop miRNA containing all kinds of motifs signed with the corresponding colors;
miR-xxxoverlap, etc. – stem-loop miRNA containing the motifs of the different kinds, overlapping one another;
miR-xxx, etc. – stem-loop miRNA containing 2 motifs of the same kind.

preliminary hypothesis. Thus, all results described below were obtained only owing to the search algorithm have been elaborated in our previous papers [14, 15].

The primary results of our search are presented in the Tables 1 and 2.

As one can see, the main regularities of the TFBS-complementary motifs distribution in the set of pathogenesis-involved miRNAs are the same as ones in the total set of human, mouse and rat miRNAs have been described previously [14, 15]. Namely:

- in total, c-myc-TFBS-complementary motifs were found much more frequently than NF-kB-p50-TFBS-complementary ones;
- in both these groups, the modified motifs (with nucleotide deletion, insertion, exchange or inner inversion) were found, in total, much more frequently than conventional ones.

It is of a special interest that NF-kB-p50-TFBS-complementary motifs in B-lymphoproliferative diseases occur only in 2 of 7 listed nosological units (in BL and MCL) and in both cases — in upregulated miRNAs. In controversial, in CML all NF-kB-p50-TFBS-complementary motifs occur only in downregulated miRNAs.

Adding the Tables 3 and 4 to the analysis, one can see that the miRNA sets involved in pathogenesis of different nosological units are quite not equal in composition of their TFBS-complementary motifs.

Especially:

- not one of the miRNAs in the CLL characteristic set has not any c-myc-TFBS-complementary motifs, while other 6 of 7 listed B-lymphoproliferative diseases contain different kinds of such motifs in 3–50% of miRNAs involved in their pathogenesis;
- between 9 listed nosological units, only CML has c-myc-TFBS-complementary motifs with inner nucleotide inversion in its characteristic miRNA set — namely, in the hyperexpressed miR-320a and miR-323b;
- between the listed B-lymphoproliferative diseases, only BL and MCL contain NF-kB-p50-TFBS-complementary motifs in their characteristic miRNA sets — namely, in the hyperexpressed miR-185 and miR-324 (BL) and in miR-92a-2 (MCL);
- CML characteristic miRNA set contain all possible kinds of the NF-kB-p50-TFBS-complementary motifs but AML miRNA set does not contain any motifs of this group, etc.

Cross-links between the characteristic miRNA sets of listed nosological units are shown in the Tables 5 and 6.

As to the c-myc-TFBS-complementary motifs (see Table 5), the characteristic miRNA sets of B-CLL and AML have not any cross-links with any of other listed nosological forms.

Only BL, MCL and CML characteristic miRNA sets have cross-links with more than one other nosological forms. It is notable that the most frequent of these cross-links is miR-142.

Table 2. List of miRNAs involved in pathogenesis of some hematological diseases and containing NF-κB-p50-TFBS-complementary motifs

Diagnosis	Upregulated miRNAs	Downregulated miRNAs	References
Lymphoproliferative diseases			
B-lymphoid			
Diffuse large BCL			
ABC+GCB	miR-17, miR-18a, miR-19a, miR-19b, miR-20a, miR-92a, miR-145, miR-150, miR-328 9 miRs	Not found	[19]
Transformed from FL	let-7b, let-7i, miR-217, miR-221, miR-222, miR-223 6 miRs	Not found	
Other B-lymphoproliferative diseases			
FL	miR-9, miR-9*, miR-54, miR-193a, miR-193b, miR-213, miR-301, miR-338, miR-345, miR-513b, miR-574, miR-663, miR-1287, miR-1295, miR-1471	miR-17, miR-30a, miR-33a, miR-106a, miR-141, miR-202, miR-205, miR-222, miR-301b, miR-431, miR-570	
BL	miR-9, miR-26a, miR-26b, miR-93, miR-105, miR-124, miR-185, miR-192, miR-193a, miR-202, miR-324, miR-326, miR-328, miR-339, miR-340, miR-371, miR-429, miR-448, miR-483, miR-485, miR-497 2 del/20 miRs	miR-23a, miR-23b, miR-26a, miR-26b, miR-29b, miR-30a, miR-30d, miR-34b, miR-103, miR-107, miR-142, miR-146a, miR-146b, miR-155, miR-221, miR-222, miR-342 29 miRs	[19]
MCL	miR-17, miR-18a, miR-19a, miR-19b, miR-20a, miR-25, miR-92a-2, miR-93, miR-106b, miR-124a, miR-155, miR-302c, miR-370, miR-617, miR-654 1 ex/14 true miRs	miR-27b, miR-31, miR-142, miR-148a, miR-150 5 miRs	
B-CLL	miR-21, miR-150, miR-155, mir-195, miR-222 5 miRs	miR-15a, miR-16-1, miR-29c, miR-34a 4 miRs	[19], [20], [21], [22], [23], [24]
B-ALL	miR-34a, miR-222, miR-511 3 miRs	miR-26a, miR-199a, miR-221, miR-223 4 miRs	
Myeloproliferative diseases			
CML	miR-9, miR-18a, miR-21, miR-51, miR-92a-1, miR-96, miR-105, miR-128, miR-154, miR-154, miR-181b, miR-193b, miR-299, miR-320a, miR-323, miR-329, miR-335, miR-337, miR-338, miR-365, miR-379, miR-382, miR-409, miR-410, miR-411, miR-431, miR-432, miR-486, miR-493, miR-495, miR-543, miR-654, miR-758 32 true miRs	hcmv-miR-US4, miR-22, miR-28, miR-30e, miR-34a, miR-98, miR-134#, miR-135a, miR-142, miR-143, miR-145, miR-148b, miR-149, miR-150, miR-155, miR-181c, miR-186, miR-188, miR-191, miR-193a, miR-193b, miR-196b, miR-197, miR-198, miR-199a, miR-199b, miR-200c, miR-202, miR-221, miR-222, miR-320c, miR-342, miR-361, miR-363, miR-371, miR-424, miR-491, miR-513a, miR-513c, miR-518a-1, miR-520f, miR-542, miR-557, miR-564, miR-582, miR-584, miR-588, miR-595, miR-601, miR-605, miR-622, miR-623overlap, miR-650, miR-652, miR-659, miR-663, miR-664, miR-665, miR-671overlap, miR-760, miR-765, miR-874, miR-1180, miR-1182, miR-1183, miR-1224, miR-1225, miR-1299, miR-1300, miR-1323, miR-1469, miR-1471 1 conv, 2 del, 3 ex, 2 ins / 70 true miRs	[20], [24], [25], [26]
AML	miR-146a 1 miR	miR-15a, miR-16, miR-29b, miR-93, miR-124-1, miR-125a, miR-126, miR-130a, miR-203 9 miRs	

Table 3. Number of c-myc-TFBS-complementary motifs in the stem-loop human miRNAs involved in pathogenesis of the hematological diseases listed above

Diagnosis	Total number of the motifs (% of total miRNA number)					
	Conventional	Deletion	Exchange	Insertion	Inner inversion	Σ
Diffuse large BCL						
ABC+GCB	0	1 (11%)	0	2 (22%)	0	3 (33%)
GCB	0	1 (17%)	0	2 (33%)	0	3 (50%)
Transformed from FL	0	2 (33%)	0	1 (17%)	0	3 (50%)
Other B-lymphoproliferative diseases						
FL	0	2 (8%)	0	2 (8%)	0	4 (17%)
BL	1 (3%)	5 (13%)	1 (3%)	2 (5%)	0	9 (24%)
MCL	1 (5%)	3 (16%)	0	3 (16%)	0	7 (37%)
B-CLL	0	0	0	0	0	0
B-ALL	0	0	1 (14%)	0	0	1 (14%)
Myeloproliferative diseases						
CML	5 (5%)	18 (18%)	0	4 (4%)	2 (2%)	29 (28%)
AML	0	3 (30%)	0	2 (20%)	0	5 (50%)

Table 4. Total number of NF-κB-p50-TFBS-complementary motifs in the stem-loop human miRNAs involved in pathogenesis of the hematological diseases listed above

Diagnosis	Total number of the motifs (% of total miRNA number)				
	Conventional	Deletion	Exchange	Insertion	Σ
Diffuse large BCL					
ABC+GCB	0	0	0	0	0
GCB	0	0	0	0	0
Transformed from FL	0	0	0	0	0
Other lymphoproliferative diseases					
FL	0	0	0	0	0
BL	0	2 (5%)	0	0	2 (5%)
MCL	0	0	1 (5%)	0	1 (5%)
B-CLL	0	0	0	0	0
B-ALL	0	0	0	0	0
Myeloproliferative diseases					
CML	1 (1%)	2 (2%)	3 (3%)	2 (2%)	8 (8%)
AML	0	0	0	0	0

Table 5. Cross-links between the hematological diseases listed above in c-myc-TFBS-complementary motif containing miRNAs involved in their pathogenesis

Diagnosis	ABC+GCB	BCL, transformed from FL	FL	BL	MCL	B-CLL	B-ALL	CML	AML
ABC+GCB	All present in the set	0	0	0	17, 19a, 20a	0	0	0	0
BCL, transformed from FL	0	All present in the set	0	0	0	0	223	0	0
FL	0	0	All present in the set	0	0	0	0	9	0
BL	0	0	9	All present in the set	142	0	105(-1)	9,142, 342, 371(a)	0
MCL	17, 19a, 20a	0	0	142	All present in the set	0	0	142	0
B-CLL	0	0	0	0	0	0	0	0	0
B-ALL	0	223	0	105(-1)	0	0	All present in the set	0	0
CML	0	0	9	142, 342, 371(a)	142	0	0	All present in the set	0
AML	0	0	0	0	0	0	0	0	All present in the set

As to the NF-kB-p50-TFBS-complementary motifs (see Table 6), only MCL and ABC+GCB have a single cross-link between one-another, and it is miR-92-a.

At last, Table 7 demonstrate distribution of the miRNAs, stem-loop forms of which have the signs of the informational redundancy as to c-myc-TFBS-complementary and NF-kB-p50-TFBS-complementary motifs.

As one can see in the Table 7, such miRNAs were found to be involved only in myeloproliferative diseases (CML and AML) and in BL. Accordingly to the Fisher's exact method (using approximate factorial values), this difference between B-lymphoproliferative (without BL) and myeloproliferative diseases is statistically significant under $P \approx 0.003$. It is notable that in most cases these miRNAs are downregulated. Upregulated from them are only miR-192 in BL; miR-495 and miR-543 in CML.

Thus, analysis of the TFBS-complementary motifs in the characteristic miRNA sets of different lympho- and myeloproliferative diseases demonstrate a series of signs which may be useful for both fundamental understanding of the leukemia genesis and differential diagnosis.

CONCLUSIONS

The conclusions of this work naturally divide in two groups — fundamentally biological (1–3) and diagnostic (4–8) ones.

1. Significant part of the stem-loop miRNAs involved in pathogenesis of different hematologic diseases contain complementary motifs to the binding sites of such TF as c-myc and NF-kB-p50. Agreeably to this, the degradome elements of these stem-loop miRNAs are potentially able to function as alternative TF.

2. Each nosological unit has its own characteristic spectra of the TFBS-complementary motifs in its characteristic miRNA set, showing their real participation in the cell differentiation pathways.

3. Different kinds of the stem-loop miRNA informational redundancy as to the TFBS-complementary motifs correlate with different directions of the cell differentiation.

4. Hyperexpression of miR-320a and miR-323b in the leukemia cells may be a weighty argument to diagnose CML.

5. Hyperexpression of the miRs 495 and 543 — alone and, moreover, in combination with hypoexpression of such miRs as 134, 542, 623, 671, 1182 — in the leukemia cells may be a weighty argument to diagnose CML.

Table 6. Cross-links between the hematological diseases listed above in NF-κB-p50-TFBS-complementary motif containing miRNAs involved in their pathogenesis

Diagnosis	ABC + GCB	BCL, transformed from FL	FL	BL	MCL	B-CLL	B-ALL	CML	AML
ABC+ GCB	All present in the set	0	0	0	92a-2	0	0	0	0
BCL, transformed from FL	0	0	0	0	0	0	0	0	0
FL	0	0	0	0	0	0	0	0	0
BL	0	0	0	All present in the set	0	0	0	0	0
MCL	92a-2	0	0	0	All present in the set	0	0	0	0
B-CLL	0	0	0	0	0	0	0	0	0
B-ALL	0	0	0	0	0	0	0	0	0
CML	0	0	0	0	0	0	0	All present in the set	0
AML	0	0	0	0	0	0	0	0	0

Table 7. Different kinds of informational redundancy in the TFBS-complementary-motif-containing stem-loop miRNAs involved in pathogenesis of the hemathological diseases listed above

Kind of redundancy	Disease, miRNA name, kind of motifs
c-myc-TFBS-complementary motifs	
Two identical motifs in one miR	CML 134↓ del+del, 1182↓ del+del
Two different motifs in one miR	BL 192↑ conv+del; CML 495↑ del+conv, 543↑ del+conv; AML 126↓ del/ins (overlapped), 130a↓ ins+del
Three different or identical motifs	CML 542↓ del+conv+del
Overlaps	AML 126↓ del/ins
NF-κB-P50-TFBS-complementary motifs	
Two identical motifs in one miR	Absent
Two different motifs in one miR	CML 623↓ ex/ins (overlapped)
Three different or identical motifs	CML 671↓ del/conv/ins (overlapped)
Overlaps	CML 623↓ ex/ins, CML 671↓ del/conv/ins

6. Hypoexpression of the miR-126 in the leukemia cells may be a weighty argument to diagnose AML.

7. Hyperexpression of the miR-185 and miR-324 in the lymphoma cells may be a weighty argument to diagnose BL.

8. Hyperexpression of the miR-192a-2 in the lymphoma cells may be a weighty argument to diagnose MCL.

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Мотиви, комплементарні сайтам зв'язування факторів транскрипції NF-kB-p50 та c-myc, в миРНК, залучених до патогенезу декількох лімфо- та мієлопроліферативних захворювань

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Резюме. У наших попередніх дослідженнях у складі пре-миРНК (stem-loop форм) людини, миші і щура виявлено різні типи мотивів, комплементарних сайтам зв'язування факторів транскрипції (ФТ) c-myc та NF-kB-p50. Також описано різні типи інформаційної надлишковості пре-миРНК щодо таких мотивів. Сформульована гіпотеза, що такі мотиви, будучи елементами деградому пре-миРНК, можуть функціонувати як альтернативні ФТ. У наведеній роботі ця методологія була застосована для аналізу характерних профілів експресії миРНК різних В-лімфопроліферативних і мієлопроліферативних захворювань. Виявлено такі основні закономірності: 1) значна частина пре-миРНК, залучених до патогенезу різних гематологічних захворювань, містить комплементарні мотиви до сайтів зв'язування ФТ c-myc і NF-kB-p50. Відповідно, елементи деградому таких пре-миРНК потенційно здатні функціонувати як альтернативні ФТ; 2) кожній нозологічній формі властивий певний характерний спектр ФТ-комплементарних мотивів у її профілі експресії миРНК, що свідчить про їх реальну участь у механізмах диференціювання клітин; 3) різні типи інформаційної надлишковості пре-миРНК відповідають різним напрямкам диференціювання клітин. Одержані результати дають змогу також сформулювати такі рекомендації для диференційної діагностики: 1) гіперекспресія miR-320a та miR-323b у бластних клітинах може бути вагомим аргументом для діагностики хронічної мієлоцитарної лейкемії; 2) гіперекспресія miRs 495 та 543 — сама по собі або, тим більше, у комбінації з гіпоекспресією miR-134, -542, -623, -671,

-1182 — у бластних клітинах може бути вагомим аргументом для діагностики хронічної мієлоцитарної лейкемії; 3) гіпоекспресія miR-126 у бластних клітинах може бути вагомим аргументом для діагностики гострої мієлоцитарної лейкемії; 4) гіперекспресія miR-185 та miR-324 у клітинах лімфоми може бути вагомим аргументом для діагностики лімфоми Беркітта; 5) гіперекспресія miR-192a-2 у клітинах лімфоми може бути вагомим аргументом для діагностики мантійно-клітинної лімфоми.

Ключові слова: лімфопроліферативні захворювання; мієлопроліферативні захворювання; мікроРНК; сайти зв'язування факторів транскрипції; диференційна діагностика.

Мотивы, комплементарные сайтам связывания факторов транскрипции NF-kB-p50 и c-myc, в миРНК, вовлеченных в патогенез различных лимфо- и миелопролиферативных заболеваний

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Резюме. В наших предшествующих исследованиях в составе пре-миРНК (stem-loop форм) человека, мыши и крысы выявлены различные типы мотивов, комплементарных сайтам связывания факторов транскрипции (ФТ) c-myc и NF-kB-p50. Также описаны различные типы информационной избыточности пре-миРНК относительно таких мотивов. Сформулирована гипотеза о том, что такие мотивы, будучи элементами деградома пре-миРНК, могут функционировать как альтернативные ФТ. В данной работе эта методология была применена для анализа характерных профилей экспрессии миРНК различных В-лимфопролиферативных и миелопролиферативных заболеваний. Выявлены следующие основные закономерности: 1) значительная часть пре-миРНК, вовлеченных в патогенез различных гематологических заболеваний, содержит комплементарные мотивы к сайтам связывания ФТ c-myc и NF-kB-p50. Соответственно, элементы деградома таких пре-миРНК потенциально способны функционировать как альтернативные ФТ; 2) каждой нозологической форме свойственен определенный характерный спектр ФТ-комплементарных мотивов в ее профиле экспрессии миРНК, что указывает на их реальное участие в механизмах дифференцировки клеток; 3) различные типы информационной избыточности пре-миРНК соответствуют разным направлениям дифференцировки клеток. Полученные результаты дают основание также сформулировать следующие рекомендации для дифференциальной диагностики: 1) гиперэкспрессия miR-320a и miR-323b в бластных клетках может быть весомым аргументом для диагностики хронической миелоцитарной лейкемии; 2) гиперэкспрессия miRs 495 и 543 — сама по себе или, тем более, в сочетании с гипоэкспрессией miR-134, -542, -623, -671, -1182 — в бластных клетках может быть весомым аргументом для диагностики хронической миелоцитарной лейкемии; 3) гипоэкспрессия miR-126 в бластных клетках может быть весомым аргументом для диагностики острой миелоцитарной лейкемии; 4) гиперэкспрессия miR-185 и miR-324 в клетках лимфомы может быть весомым аргументом для диагностики лимфомы Беркитта; 5) гиперэкспрессия miR-192a-2 в клетках лимфомы может быть весомым аргументом для диагностики мантийно-клеточной лимфомы.

Ключевые слова: лимфопролиферативные заболевания; миелопролиферативные заболевания; микроРНК; сайты связывания факторов транскрипции; дифференциальная диагностика.

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