Biochemical and Biophysical Research Communications 430 (2013) 1005–1010

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Identification of preferentially reactivated genes during early G1 phase using nascent mRNA as an index of transcriptional activity

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ARTICLE INFO

Article history:
Received 8 December 2012
Available online 19 December 2012

Keywords:
Cell cycle
Mitosis
Early G1
Transcription
Nascent mRNA

ABSTRACT

During mammalian mitosis, transcription is silenced due to dissociation of transcription factors from DNA and chromosome condensation. At the end of mitosis, transcription is reactivated through chromosome relaxation and reloading of these factors to the DNA. Early G1 genes, which are preferentially reactivated during M/G1 transition, are important for maintenance of cellular function and are known to be strictly regulated. As only few early G1 genes have been identified to date, screening for early G1 genes by genome-wide analysis using nascent mRNA could contribute to the elucidation of the regulatory mechanisms during early G1. Here, we performed a detailed expression analysis for the M/G1 transition of mammalian cells by microarray analysis of nascent mRNA, and identified 298 early G1 genes. Analysis of these genes provides two important insights. Firstly, certain motifs are enriched in the upstream sequences of early G1 genes; from this we could predict candidate cognate transcription factors, including Sp1, which is recruited to the DNA in the early G1 phase. Secondly, we discovered that neighboring genes of early G1 genes were also frequently up-regulated in the G1 phase. Information about these numerous newly identified early G1 genes will likely contribute to an understanding of the regulatory mechanisms of the early G1 genes.

1. Introduction

Transcription of genes expressed in interphase is silenced during mammalian mitosis [1,2]. Generally, the transcriptionally silent state occurs when RNA polymerase II and other transcription factors dissociate from chromatin because of chromosome condensation. At the end of mitosis, these factors are reloaded onto the chromatin after relaxation of the chromosomes. Thus, transcription of genes that are expressed in interphase is reactivated in daughter nuclei at the G1 phase.

Although the genes expressed at the early G1 phase are believed to play an important role in maintaining cellular functions such as stress response and proliferation, little is currently known of them. Among these genes, heat shock protein (Hsp) family genes are a well known example [3]. Transcription of HSP genes at the early G1 phase is unsurprising since Hsp genes are understood to defend daughter cells against external diverse stress [4]. *Egr1* and *c-fos* are also expressed at the early G1 phase and have been shown to play roles in cell growth, proliferation, differentiation, and tumorigenesis [3,5].

Not only is the number of known early G1 genes few, research on the regulatory mechanisms of early G1 gene expression is not fully understood. However, one known mechanism termed "mitotic gene bookmarking" has been described [6]. During mitosis, mitotic gene bookmarking factors such as HSF2 [3], MLL [7], RUNX2 [8], and TBP [9] remain bound to promoter regions of early G1 genes. This binding permits the genes to be maintained in a transcriptionally active state [6]. Phosphorylation of transcription factors, including C_2H_2 zinc finger proteins, is also a known regulatory mechanism and this modification reduced DNA binding ability during mitosis [2,10]. Binding ability is recovered after dephosphorylation, and these factors translocate to the DNA and reactivate transcription in the early G1 phase. In addition, transcriptionally active histone modifications and histone variants are incorporated in some regions at or near the transcription start sites (TSS) during mitosis, and contribute to early G1 gene expression [6,11,12].

As these mechanisms are derived from small number of observation with limited number of early G1 genes, comprehensive identification of many early G1 genes is valuable in elucidation of the regulatory mechanisms of early G1 genes. Previously, genome-wide analysis of the M/G1 transition based on total mRNA has been performed [13]. However, a weakness of conventional microarray analysis in detecting changes of early G1 genes lies in the abundance of mRNAs carried over from the previous cell cycle,

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0006-291X/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bbrc.2012.12.048

and nascent mRNA levels for the majority of the genes are low by comparison. If small changes in nascent mRNA levels at the early G1 phase could be detected comprehensively, it might be possible to precisely identify early G1 genes on a genome-wide scale. We previously established a method of genome-wide analysis using nascent mRNAs specifically isolated from living mammalian cells [14]. In this method, cells were cultured in medium containing bromouridine, which substitutes the 5′ of uridine for bromine, and cellular nascent RNAs are Br-labeled. The nascent RNAs are then specifically isolated by immuno-precipitation using an anti-BrdU antibody. By this method, it is possible to precisely analyze the genome-wide expression profiles of early G1 genes.

In this study, we performed genome-wide analysis of early G1 genes using nascent mRNA and analyzed the common properties of the genes. We could detect variations in genes that failed to be detected by the conventional microarray method, obtained detailed expression profiles during the M/G1 transition, and identified valuable early G1 genes. We discovered two types of the common properties of the genes. Firstly, by analyzing upstream sequences, we discovered the motifs that are enriched in upstream sequences of early G1 genes and predicted the cognate transcription factors. Next, focusing on the relationship between early G1 genes and genomic regions, we discovered that genes in the neighborhood of early G1 genes were frequently up-regulated in the G1 phase.

2. Materials and methods

2.1. Cell culture of tsFT210 cells and labeling nascent RNA with BrU

tsFT210 cells, a *Cdc2* temperature sensitive mutant strain of mouse mammary FM3A cells [15,16], were cultured in RPMI 1640 Medium (Invitrogen, CA) with 10% bovine serum (Invitrogen) which was dialyzed 0.1 mM MEM non-essential amino acid (Invitrogen), 100 U/ml penicillin, and 100 mg/ml streptomycin (Invitrogen) at 32 °C in 5% CO_2.

For labeling of nascent RNAs, tsFT210 cells were cultured in medium containing 0.5 mM Bromouridine (Sigma–Aldrich, MO) for 30 min in the dark.

2.2. Cell synchronization

tsFT210 cells were arrested in the G2 phase by incubation for 17 h at a non-permissive temperature (39 °C). Secondly, for mitotic arrest, G2 arrested cells were treated with 50 nM nocodazole (Sigma–Aldrich) for 7 h at a permissive temperature (32 °C), followed by two washes with PBS (−), and then cells were cultured at 2.0×10^5 cells/ml.

2.3. Identification of the early G1 genes

Highly up-regulated genes (298 genes) between 0.5 h and 1.0 h after release were extracted by analysis of variance (Student's *t*-test, $p < 0.05$, FDR < 0.05) and Tukey's post Hoc test using Gene Spring (Agilent technologies, CA). These genes were used for GO analysis as early G1 genes. To extract more highly up-regulated genes at the early G1 phase, 48 genes whose base 2 logarithm of expression ratios relative to control were greater than 0 at 1 h after release were extracted from the 298 early G1 genes.

Materials and methods for measurement of mitotic index, flow cytometry, whole cell run-on assay, immunoprecipitation of BrU-labeled RNA, DNA microarray, quantitative RT-PCR, Gene Ontology analysis, motif analysis of the early G1 genes, data mapping on the mouse genome, and statistical analysis of transcription of neighboring genes of the early G1 genes were described in "Supplementary materials and methods".

3. Results

3.1. Isolation of nascent RNA from cells in the M/G1 transition that represent transcriptional reactivation

To synchronize cell cycle progression in the M/G1 transition, we combined inactivation of CDC2 with inhibition of microtubule polymerization. Firstly, we arrested tsFT210 cells in the G2 phase at restrictive temperature (39 °C) [15,16]. Secondly, the cells were released from arrest by shifting to a permissive temperature (32 °C), and then treating the cells with nocodazole to induce arrest at prometaphase. Finally, the cells were given normal medium following nocodazole washout. To assess the synchrony of M/G1 transition, we analyzed the transition of DNA content and mitotic index of the cells. A large proportion of the cells completed telophase at 1 h after release from nocodazole treatment (Fig. 1A), and seventy percent of cells exited cytokinesis and entered into G1 from mitosis at 2 h (Fig. 1B). Using whole cell run-on assay [17], we confirmed transcriptional reactivation occurred at 1 h after release from nocodazole arrest (Supplementary Fig. 1). Thus, this method enables cells to entry to the G1 phase with high synchrony.

To precisely obtain expression profiles of early G1 genes, we isolated nascent RNA. We labeled cells with 0.5 mM BrU for 30 min. The concentration of BrU did not affect both G2/M transition and transcription (Supplementary Figs. 2 and 3). The nascent RNAs were specifically isolated from total RNA by immuno-precipitation using anti-BrdU antibody. Subsequently, both total RNA and nascent RNA were isolated from mitotic and G1 cells, and quantified (Fig. 2). Changes in total RNA were rarely observed, whereas nascent RNA levels were clearly elevated in proportion to the increase in G1 cells. The increase in isolated nascent RNA correlated with transcriptional activity measured by whole cell run-on assay (Fig. 2 and Supplementary Fig. 1).

3.2. Microarray analysis of nascent mRNA distinguishes M/G1 up-regulated genes from total mRNA

Next, we tested whether DNA microarray analysis of nascent mRNA could precisely detect transcriptional reactivation of M/G1. We arrested cells in mitosis and then released the cells for 2 h from mitotic arrest, and both total RNA and nascent RNA were isolated from these cells, and used for analysis of expression profiles. As there was a large difference in the amount of nascent RNA between mitotic cells and G1 cells (Fig. 2), we used external controls that appropriately normalize the microarray data (Supplementary Fig. 4). In the case of total mRNA, few genes that were up-regulated in the G1 phase (two genes) (Supplementary Fig. 5). In the case of nascent mRNA, we detected many genes (190 genes) that were up-regulated (Supplementary Fig. 5). Additionally, quantitative RT-PCR (qRT-PCR) profiles of most of the genes correlated with the microarray profiles for these genes (Supplementary Fig. 5C). Furthermore, using whole cell run-on assay, we confirmed transcriptional reactivation of genes in the G1 phase (Supplementary Fig. 6). These results show that microarray analysis of nascent RNA can detect the expression profile at the M/G1 transition more accurately than total mRNA.

3.3. Identification and biological attributes of the early G1 genes

Using nascent mRNA of highly synchronized the G1 phase cells, we next tried to identify early G1 genes. We treated the cells with BrU for 30 min and collected cells every 30 min for 3 h and obtained nascent mRNA expression profiles during the M/G1 transition (Supplementary data). We defined up-regulated genes between release

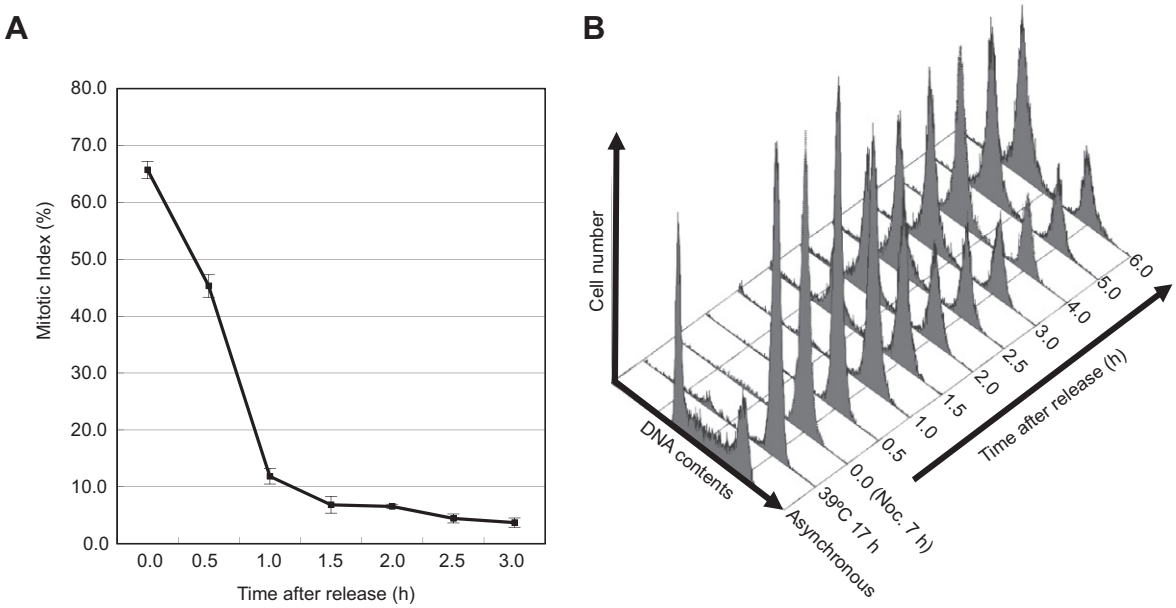

Fig. 1. Cell cycle synchronization for analysis of early G1 genes. tsFT210 cells were arrested in the G2 phase by incubation for 17 h at a non-permissive temperature (39 °C). Secondly, for mitotic arrest, the G2-arrested cells were treated with 50 nM nocodazole for 7 h at a permissive temperature (32 °C). The cells were then released from mitotic arrest, following nocodazole washout. (A) Mitotic index of the cells was measured. A minimum of 100 cells was counted from each compartment on the slides, and the average of 5 compartments was plotted. Error bars represent standard deviation of the average. (B) Cells were stained with propidium iodide. DNA content of these cells was analyzed by flow cytometry.

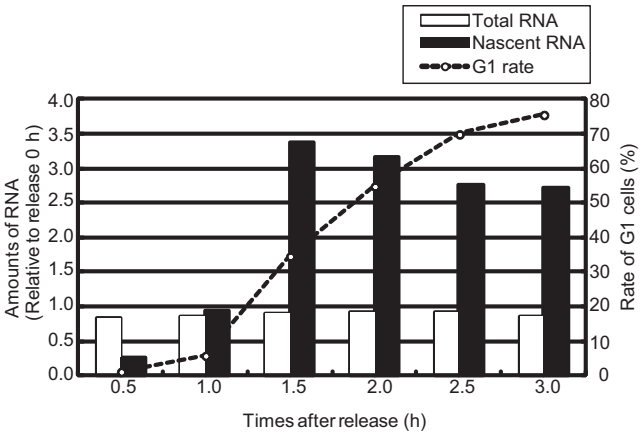

Fig. 2. Isolation of nascent RNA from cells in the M/G1 transition. The cells were cultured in medium containing 0.5 mM BrU for 30 min before harvesting the cells. Total and nascent RNA were isolated from the cells. Black bar shows the relative amounts of nascent RNA at release, 0 h, and white bar shows that of total RNA. Line graph shows the rate of G1 cells.

0.5 h and 1.0 h as the early G1 genes. We identified as many as 298 early G1 genes using statistical analysis (Fig. 3A, Supplementary data). Known early G1 genes such as *Hsp90ab1* [3] and *c-Myc* [7] were included among the identified early G1 genes, indicating that our analysis is highly efficient with respect to identification of early G1 genes. We validated the expression profiles of these genes by quantitative RT-PCR and those expression profiles correlated well with the microarray data (Fig. 3B).

Reportedly, the biological attributes of a few known early G1 genes included cellular protection and proliferation. We conducted Gene Ontology analysis for the early G1 genes that were identified in the current study (Supplementary Table 1). The analysis of biological attributes suggests that many housekeeping genes, including translation (e.g. ribosomal protein subunit) and mitochondrial proteins (e.g. NADH dehydrogenase complex subunit), were reactivated in the early G1 phase.

3.4. Motif analysis of up-stream sequences of early G1 genes

As it is possible that co-up-regulated genes contain common regulatory elements for binding of transcription factors, we performed a motif analysis of the upstream sequences of early G1 genes to predict the transcription factors that might regulate early G1 genes. Using MEME, a tool for discovering motifs in a group of DNA sequences [18], 16 motifs were preferentially found in the upstream sequences of these genes (Table 1 and Supplementary Table 2). Additionally, for motifs observed specifically in the upstream sequences of early G1 genes, we used FIMO, a tool for analysis of the occurrence of individual motifs (Supplementary Table 2). We identified nine motifs specific to the upstream sequences of early G1 genes ($p < 0.01$, Fisher's test) (Table 1). These obtained motifs were then compared with known motifs registered in the database, and we predicted the transcription factors whose motif sequences were similar to the obtained motif (Table 1). For example, motif 2, motif 4, and motif 11 were similar to the binding motif of PITX2, PAX6, and Sp1 respectively (*E*-Value < 0.01). Interestingly, previous reports indicate that Sp1 regulates some genes that are required at the G1 phase [19], telling us that other factors may have some important role in the transcriptional regulation at the early G1 phase through binding to the upstream sequences of these genes.

3.5. Genes in the neighborhood of early G1 genes tend to be up-regulated in the G1 phase

Generally, in mammalian cells, genes are transcribed randomly in the genome. Only a small number of examples position effects or expression as a cluster have been reported such as the HOX cluster [20] and the MHC class II locus [21]. When transcription of genes begins to be reactivated at the end of mitosis, higher-order chromatin structures are dramatically reconstituted, and highly condensed chromatin relaxes. This phenomenon motivated us to analyze the order of gene expression in the mammalian genome from the early G1 phase.

To address the question whether there is any relationship between transcription of the early G1 genes and some specific

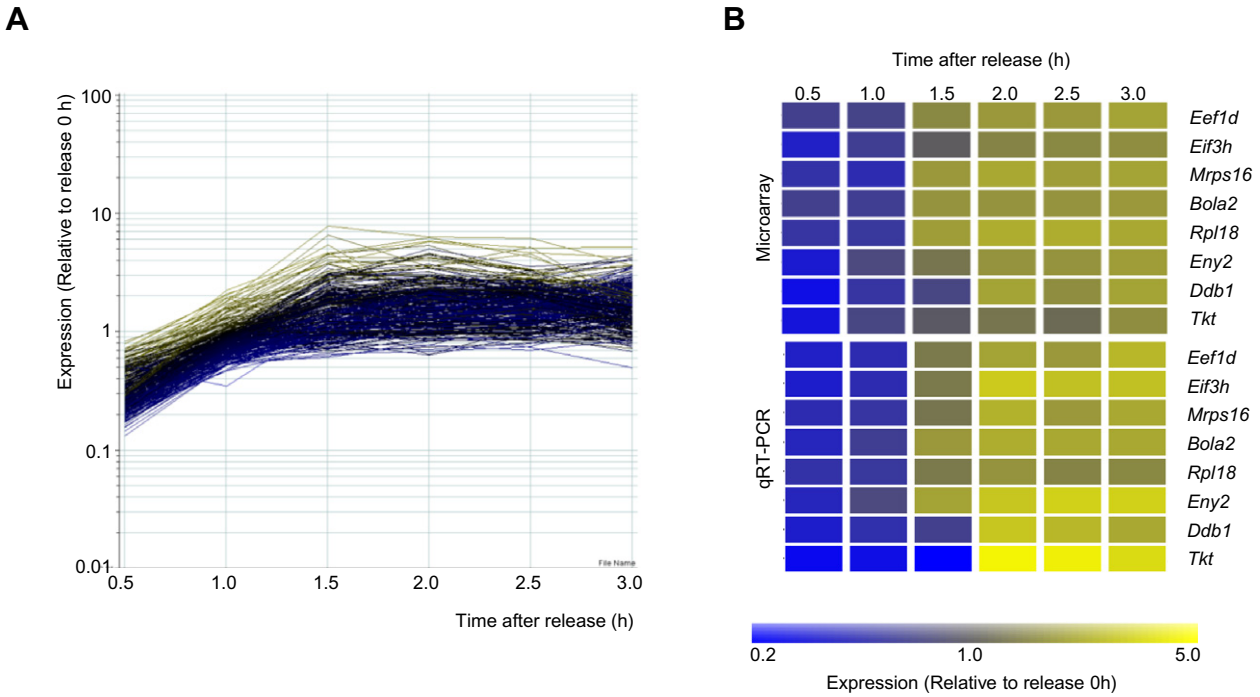

Fig. 3. Identification of the early G1 genes. (A) Line graph indicates the expression profile of the early G1 genes that were identified by microarray analysis of nascent mRNA isolated from M/G1 cells. (B) Validation of microarray data. The expression profiles of 8 early G1 genes were analyzed by qRT-PCR.

Table 1
Motif analysis of upstream sequences of early G1 genes.

No.	Motif sequence	MEME analysis			TOMTOM analysis Predicted TF	*E*-Value	*p*-Value	*q*-Value	Motif ID
		E-Value	Width	Sites[a]					
1	AAAAAAAAA(A/G)(A/C)AAAA	2.0×10^{-60}	15	36	FOXP1	0.105	1.3×10^{-4}	0.124	M00987
2	(A/G)GTGCTGGGATTA(A/G)A	1.4×10^{-29}	15	20	PITX2	6.7×10^{-3}	8.2×10^{-6}	0.013	M00482
4	AGTTCCAGG(A/C)CAGC(C/G)	1.6×10^{-25}	15	16	PAX6	7.2×10^{-5}	8.9×10^{-8}	1.4×10^{-4}	M00979
5	ACCCTGTCTC(A/G)AAAA	1.6×10^{-18}	15	14	ARF	0.360	4.4×10^{-4}	0.720	M00438
7	A(G/A)(G/A)(G/A)CTACACAGAGA	1.6×10^{-9}	15	13	RSRFC4	4.366	5.4×10^{-3}	1.000	M00026
8	GAACTCAGAAATCC	5.7×10^{-9}	14	9	SEF1	0.379	4.7×10^{-4}	0.630	M00214
10	(A/T)(A/G/T)(C/A)TT(T/A)AAA(A/C)AA(A/G)A(A/G)	6.5×10^{-12}	15	37	Srf_secondary	0.015	1.8×10^{-5}	0.030	UP00077_2
11	**CG(G/C)G(G/A)GG(C/A)GG(G/A)GC(T/G/C)**[b]	$\mathbf{4.0 \times 10^{-9}}$	**15**	**48**	**Sp1**	$\mathbf{1.3 \times 10^{-8}}$	$\mathbf{1.6 \times 10^{-11}}$	$\mathbf{2.5 \times 10^{-8}}$	**M00933**
12	(G/A)TGGTGGC(G/T)CA(C/T)(G/A)CC	1.0×10^{-5}	15	14	Jundm2_secondary	1.025	0.001	0.285	UP00103_2

Analysis of motifs enriched in the upstream sequences of the 48 early G1 genes was performed with MEME. Identified motifs were analyzed by TOMTOM by comparison against known motifs included in three databases, JASPARE CORE, TRANSFAC and UNIPROBE.

[a] "Sites" indicates the number of early G1 genes that contain each motif. Occurrences of these motifs among all upstream sequences of genes in the mouse genome were explored, and the motifs that were specifically observed in upstream sequences of early G1 genes were indicated in the list (Fisher' test, $p < 0.01$).

[b] A motif similar to a transcription factor known to regulate the early G1 genes is indicated in bold-faced type.

genomic regions, we carefully analyzed the order and the genomic position of the genes that were expressed at the early G1 phase. For this purpose, we mapped the genes expressed from very early at the beginning of the G1 phase. Interestingly, there were distinct regions where genes located in the neighborhood of early G1 genes were simultaneously up-regulated at the G1 phase. For example, regions within 100 kb from *Surf4*, *Psmd4*, *Tmem28*, *11034A24Rik* were remarkably simultaneously up-regulated as compared to regions within 100 kb from the genes that were not up-regulated at early G1 (e.g. *Coro1b*) (Fig. 4A and B, Supplementary Tables 3 and 4).

Next we tested whether the phenomena applies to a large proportion of neighboring regions of the early G1 genes, compared with the entire genome. We defined up-regulated genes at the G1 phase as genes that were up-regulated at two time points after release, between 1.5 h and 3.0 h. Then we counted each number of "up-regulated genes at the G1 phase" among the genes located within all the genome and the neighboring regions of the early G1 genes, respectively (Fig. 4C, Table 2). In the case of the whole genome that contained 18767 genes analyzed by microarray, 2625 genes were up-regulated at the G1 phase (14%). On the other hand, 83 genes out of 303 neighboring genes located within 100 kb of the early G1 genes were up-regulated (27%) ($p = 1.68 \times 10^{-11}$, Fisher's test). Neighboring genes of randomly selected genes were not significantly up-regulated at the G1 phase ($p = 0.76$, average of 1000 trials, Table 2). These data suggest that neighboring genes of early G1 genes are frequently up-regulated at the G1 phase.

4. Discussion

4.1. Identification of early G1 genes using nascent mRNA

Although early G1 genes are strictly regulated, few early G1 genes have been identified to date. We reasoned that comprehensive

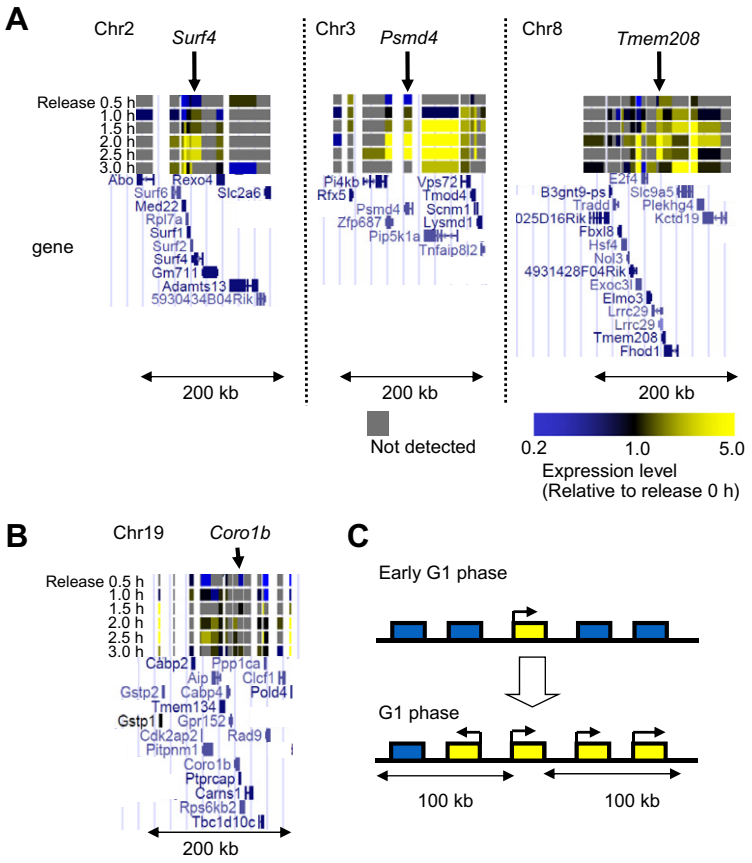

Fig. 4. Neighboring genes of early G1 genes are frequently up-regulated at the G1 phase. (A) An example of genomic regions where neighboring genes of early G1 genes were frequently co-up-regulated at the G1 phase. The UCSC genome browser was used for mapping of expression profiles. Gray box means that a gene's expression was not observed. (B) An example of genomic regions located within 100 kb from the genes that were not co-up-regulated at early G1. *Coro1b* was randomly selected. (C) Schematic diagram of the genomic regions that were chosen for the statistical test described in Table 2.

Table 2
Statistical analysis of transcription of neighboring genes of the early G1 genes.

	Analyzed genes	Up-regulated	Not up-regulated	*p*-Value	Average of *p*-Value	Minimum of *p*-Value
Within 100 kb from TSS	Neighbor of the early G1 genes	83	220	1.68×10^{-11}	–	–
	Neighbor of randomly selected genes[b]	–	–	–	0.76	4.6×10^{-6}
	All genes[a]	2625	16142	–	–	–

Each of the up-regulated genes, located either within the entire genome or located within 100 kb from the TSS of the early G1 genes, were counted. Up-regulated genes at the G1 phase were defined as those genes that were up-regulated for at least two time points after release from arrest, between 1.5 h and 3.0 h. The *p*-Value for the difference between both rates was calculated by one-sided Fisher's test. The same analysis was performed for the neighboring genes of randomly selected genes.

[a] "All genes" represents genes analyzed by microarray.

[b] For random sampling, 48 genes were randomly selected from among all genes. Random sampling was performed for 1000 trials, and the minimum *p*-Value was used as the *p*-Value for the random sampling.

identification of early G1 genes would be the first key step for understanding the regulatory mechanisms of transcription in the early G1 phase. We analyzed the genome-wide expression profile of the early G1 phase and globally identified the early G1 genes based on nascent mRNA analysis.

We hypothesized that small changes in the amounts of nascent mRNAs at the early G1 phase would not reflect changes in the amounts of total mRNAs. Microarray analysis of nascent mRNA accurately detected many genes that are up-regulated at the G1 phase, while total mRNA detected few, thus supporting our hypothesis.

Although some known early G1 genes, *c-Myc* and *Hsp90ab1*, were upregulated at the early G1 phase, the set of the early G1 genes identified in this study were significantly different from a previous microarray study of total mRNA. Gene Ontology analysis revealed that housekeeping genes were enriched among the early G1 genes, whereas Ras protein signal transduction and cell morphogenesis were enriched in a previously study using total mRNA [13]. A possible cause of this discrepancy might be the difference of experimental conditions. In the previous study, microarray analysis of total mRNA derived from cells that were collected from mitotic shake off release, and the genes that were up-regulated at various time points between release at 0 h and 2.0 h were identified as the early G1 genes. We identified the early G1 genes more strictly by analyzing nascent mRNAs and defining the early G1 genes as genes up-regulated at 1 h after release from nocodazole arrest. Thus, we consider our analysis to have more precisely identified the early G1 genes.

4.2. Motif analysis of up-stream sequences of early G1 genes

Sixteen motifs were enriched in the upstream sequences of early G1 genes, and some motifs were highly similar to the binding motifs of known transcription factors. Among the transcription factors, Sp1, which is known as C_2H_2 zinc finger proteins, rebind to DNA at the early G1 phase and reactivate transcription at the early G1 phase [19]. SRF remains associated with chromatin during mitosis [22]. As these factors included in list of predicted transcription factors for transcription of early G1 genes, it is possible that other factors, FOXA1, PITX2, and PAX6, in the list might be involved in transcription of early G1 genes.

4.3. Neighboring genes are up-regulated at the G1 phase

Our discovery that genes located in neighborhood of early G1 genes were frequently up-regulated at the G1 phase subsequent to transcription of the early G1 genes suggests that mechanisms for efficient transcription of the genes might exist in the M/G1 transition of daughter cells.

We discuss three possible mechanisms. Firstly, chromatin relaxation during mitosis might be important. For example, H3K4 trimethylation, H3 acetylation and H4 acetylation, which are markers of transcriptionally active chromatin, might be maintained during mitosis. H3.3 and H2A.Z are also known to be markers of active chromatin, and might be maintained at or near the TSS of early G1 genes. In some genomic regions of known early G1 genes, these histone modifications or variants were observed [6,11,12,23]. Secondly, the factors such as sequence-specific DNA binding transcriptional factors, transcriptional co-activators, and mediators might be important. For example, BRD4, a transcriptional co-activator, maintains binding to the transcription start sites of known M/G1 genes throughout mitosis [24]. This binding contributes to the recruitment of positive transcription elongation factor (P-TEFb) and transcriptional reactivation of these genes at the end of mitosis. These factors might be involved in efficient transcriptional reactivation. Thirdly, chromatin conformation might be significant. Chromatin looping mediates appropriate transcriptional regulation through interaction between regulatory elements, such as promoters, enhancers and insulators [25].

4.4. Conclusion, perspective

In this study, we have comprehensively identified the early G1 genes, and the information of these early G1 genes enabled us to discover the biological attributes of the early G1 genes, the candidate transcription factors for the early G1 gene activation and the phenomenon that neighboring genes of the early G1 genes were frequently transcribed at the G1 phase. Further research by use of the list and the common properties of the early G1 genes will be clue for understanding regulatory mechanisms of the early G1 genes. Recently, it was reported that in hematopoietic cells specific early G1 genes were regulated by mitotic gene bookmarking through the binding of hematopoietic transcription factor GATA1 [26]. Analysis of other cell lines by our method will enable the identification of common or cell-specific early G1 genes.

Acknowledgment

This work has been supported by the grants supplied by the Ministry of Education, Culture, Sports, Science and Technology, the Japan Science and Technology Agency.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2012.12.048.

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