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Cell growth- and differentiation-dependent regulation of RNA polymerase III transcription

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RNA polymerase III transcribes small untranslated RNAs that fulfill essential cellular functions in regulating transcription, RNA processing, translation and protein translocation. RNA polymerase III transcription activity is tightly regulated during the cell cycle and coupled to growth control mechanisms. Furthermore, there are reports of changes in RNA polymerase III transcription activity during cellular differentiation, including the discovery of a novel isoform of human RNA polymerase III that has been shown to be specifically expressed in undifferentiated human H1 embryonic stem cells. Here, we review major regulatory mechanisms of RNA polymerase III transcription during the cell cycle, cell growth and cell differentiation.

Eukaryotes contain three distinct DNA-dependent RNA polymerases (Pol I, Pol II and Pol III)[1] that share the task of transcribing the information contained in genes into mobile RNA entities. In humans, Pol I transcribes the precursor of the large ribosomal 45S RNA, Pol II transcribes all messenger RNAs, most snRNAs, snoRNAs and micro RNAs and Pol III transcribes a diverse group of small untranslated RNAs that participate in the regulation of transcription, splicing and translation. After transcription, Pol III transcripts are either directly degraded or modified for participation in the regulation and execution of processes in the nucleus and cytoplasm (transcription regulation; RNA processing; ribosome assembly; translation) that ultimately lead to protein synthesis. In the past few years, in part due to the discovery of novel classes of regulatory RNAs such as micro (mi) RNAs and small interfering (si)RNAs, it has become clear that the three classical eukaryotic RNA polymerases have acquired additional layers of complexity during evolution from unicellular to multicellular eukaryotes. For instance, derivatives of Pol II that fulfill specific functions in transcription of siRNAs (Pol IV) or of noncoding RNAs at target loci (Pol V) have been found in Arabidopsis.[2,3] More recently, an isoform of human Pol III has been described that is specifically expressed in embryonic stem cells and in certain tumor cell lines. This isoform of Pol III is able to contribute to cell transformation under tissue culture conditions.[4] In this review, we will describe our current understanding of how Pol III transcription is regulated during growth and differentiation, with emphasis on the mammalian Pol III system where appropriate.

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Introduction to Pol III Transcription

Promoters. Three types of promoters are recognized by RNA polymerase III in higher eukaryotes (**Fig. 1**). Type 1 and type 2 promoters are internal to the gene, whereas type 3 promoters are located entirely upstream of the transcription initiation site.[5] Type 1 (5S ribosomal RNA gene) and type 2 promoters [e.g., those in tRNA, VA1 RNA and VA2 RNA genes and in short interspersed nuclear elements (SINEs)] are composed of A- and C- or A- and B-boxes, respectively (**Fig. 1**). Transcription of type 1 and 2 genes is initiated about 8 to 50 nucleotides upstream of the 5'-end of Box A and terminates as soon as Pol III encounters four or more consecutive thymidines. Type 3 promoters (U6 RNA, 7SK RNA, RNAse P RNA, RNAse MRP RNA and Y RNA genes) are comprised of a distal sequence element (DSE) that is typically located about 200–250 nt upstream of the transcription initiation site, a proximal sequence element (PSE) at around -50 and a TATA box at -30. Type 3 promoters arose during evolution from unicellular to multicellular eukaryotes and are found in plants and animals, but not in yeast, which instead utilize a type 2 promoter for transcription of the U6 gene. Pol III-transcribed genes that contain both gene-internal and gene-external promoter elements have also been described and include the 7SL RNA, vault RNA, BC1 RNA, BC200 RNA, EBER1 RNA and EBER2 RNA genes.[5]

Transcription factors. The yeast and human transcription factors that recognize these promoters have been identified by genetic or biochemical means and their cognate subunits have been cloned (**Fig. 1**). The primary DNA-binding transcription factors that are required for the recognition of the evolutionary conserved type 1 and type 2 promoters have likewise been conserved from yeast to human. Type 2 genes are directly recognized by the six subunit transcription factor TFIIIC.[6,7] The type 1 promoter of the 5S gene requires prior binding of TFIIIA, the prototype gene-specific transcriptional activator in eukaryotes,[8] for recruitment of TFIIIC to the gene.[6,9] The type 3 promoters of

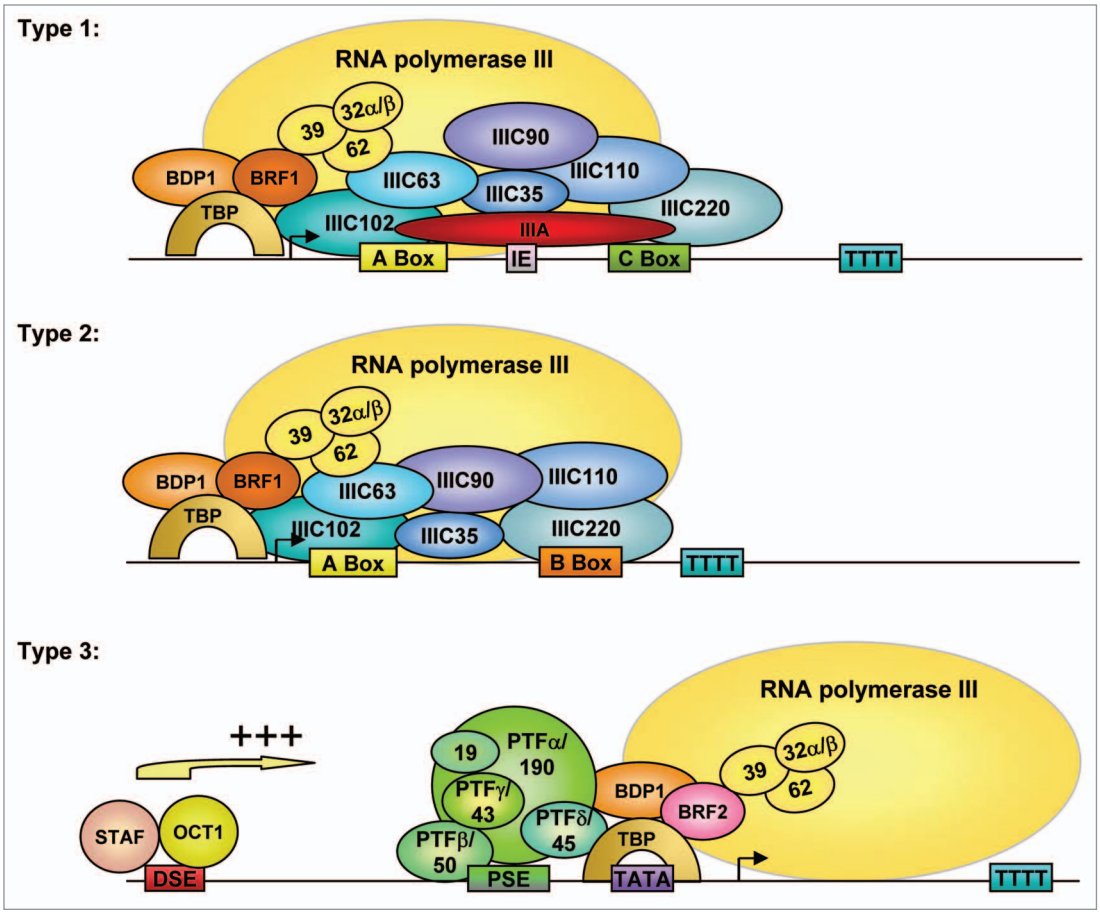

Figure 1. Mammalian RNA Polymerase III promoters and transcription factors. Promoter types 1–3. IIIA = TFIIIA. TFIIIB subunits are TBP, BDP1, BRF1 and BRF2; TFIIIC subunits are indicated as C35, C63, C90, C102, C110 and C220. PTFα, β, γ and δ subunits are also denoted according to the molecular weight of the respective SNAPc subunits (190, 50, 43 and 45). In addition, SNAP19 is shown, which has not been described in PTF. The ternary complexes composed of RPC39, RPC62 and RPC32α or RPC32β are high lightened within the symbolic representation of RNA polymerase III.

U6 and 7SK genes appeared during the evolution of multicellular eukaryotes, along with transcription factors required for their expression. Type 3 promoters are directly bound by the multisubunit PSE-binding transcription factor (PTF; also referred to as SNAPc or PBP),[10-12] for which no ortholog has been identified in yeast. The interaction of PTF/SNAPc/PBP with the PSE is reinforced by DSE binding proteins such as Oct-1,[13-16] and Staf (ZNF143).[17] For transcription activation of type 3 promoter-containing genes, DSE and PSE sequences may be juxtaposed by a positioned nucleosome.[18,19]

In the model of a stepwise assembly of preinitiation complexes (PIC) on Pol III promoters, the DNA-binding proteins, once bound to their promoters, recruit the initiation factor TFIIIB to their respective genes. After its recruitment to the promoter, TFIIIB alone is able to direct multiple rounds of transcription in the absence of TFIIIC and TFIIIA,[20] demonstrating that interactions of Pol III with TFIIIC and TFIIIA are not essential for transcription initiation, at least in vitro, but rather serve for the recruitment of TFIIIB. Only a single isoform of TFIIIB has been described in yeast.[6] In contrast, human cells contain two isoforms of TFIIIB (TFIIIB-α and TFIIIB-β)[21] that are specifically recruited either to gene-internal type 1 and 2 (TFIIIB-β) promoters or to type 3 promoters (TFIIIB-α). As for the evolution of PTF/SNAPc/PBP, the appearance of a second isoform of TFIIIB may again have been necessary for allowing promoter type- or gene-specific regulation of Pol III transcription in higher eukaryotes. Human TFIIIB-α and TFIIIB-β both contain TATA-binding protein (TBP) and BDP1 but differ with respect to the presence of the TFIIB-related factors BRF1 (TFIIIB-β) and BRF2 (TFIIIB-α).[22,23] Interestingly, it was demonstrated that purified *S. cerevisiae* BDP1 could replace its human ortholog in transcription of the human U6 gene reconstituted with human transcription factors, indicating that essential protein-protein-interactions with other components of the PIC at type 3 promoters could be established by *S. cerevisiae* BDP1.[24] An alternative model to the stepwise recruitment of the Pol III transcription machinery to promoters has been suggested by the discovery of an RNA polymerase III holoenzyme that contains TFIIIC and TFIIIB-β subunits in addition to Pol III.[25] This holoenzyme as an entity may directly recognize Pol III promoters and direct multiple rounds of transcription by mechanisms involving facilitated reinitiation of transcription.[26,27]

Accessory factors. A variety of proteins have been described that, while not necessarily essential, are highly stimulatory for

Pol III transcription in vitro. Complementation assays coupled with purification of factors from HeLa nuclear extracts showed that topoisomerase 1 and positive cofactor 4 (PC4) co-fractionate with TFIIIC (holo-TFIIIC) and that they activate Pol III transcription in a system reconstituted with highly purified components.[28] Similarly, NF1 was found to stimulate Pol III transcription from type 2 promoters and to extend the TFIIIC footprint over the transcription termination site.[29] A function similar to that of human PC4 was recently demonstrated for the *S. cerevisiae* ortholog Sub1.[30,31] Although the mode of action for PC4 or Sub1 in Pol III transcription has remained a puzzle owing to the high (50–100 fold) molar excess of PC4 (relative to other Pol III transcription factors) required for in vitro transcription activation, it has been speculated that DNA-binding properties of PC4 may help to structure DNA for facilitating Pol III transcription in vitro. Furthermore, the transcription termination and recycling factor La[32] co-purified with holo-TFIIIC preparations.[28] Although not absolutely required for in vitro transcription,[33] La was shown to associate with Pol III promoters in yeast[34] and human cells.[35] Moreover, the HMG-box-containing proteins NHP6A and NHP6B have been implicated in the activation of Pol III transcription in *S. cerevisiae*.[36,37] Up to now, there has been no identification of a mammalian NHP6A or NHP6B ortholog that might fulfill a similar function Pol III transcription.

RNA polymerase III. Along with the DNA-binding transcription factors, the distinct isoforms of human TFIIIB are necessary and sufficient to recruit Pol III to the transcription initiation site. Pol III is highly conserved from yeast to humans and is composed of 17 subunits (**Table 1**). Of these subunits, five (RPB5/POLR2E, RPB6/POLR2F, RPB8/POLR2H, RPB10/POLR2L and RPB12/POLR2K) are common to all three polymerases, two (RPAC40/POLR1C and RPAC19/POLR1D) are shared by Pol I and Pol III (with paralogous subunits in Pol II) and five (RPC1/POLR3A, RPC2/POLR3B, RPC8/POLR3H, RPC9 and RPC11/POLR3K) are paralogous to subunits found in Pol I and Pol II. The remaining five subunits (RPC5/POLR3E, RPC4/BN51/POLR3D, RPC3/RPC62/POLR3C, RPC6/RPC39/POLR3F and RPC7/RPC32/POLR3G) are specific to RNA polymerase III and no structural or functional counterparts have been identified in Pol I or Pol II.[38,39] However, it has been suggested that some of these subunits may share structural homologies to basal transcription factors of the Pol II system.[40,41]

Three of the five Pol III-specific subunits (POLR3C, POLR3F, POLR3G) form a stable subcomplex (**Fig. 1**). Thus, it was shown in the yeast *S. cerevisiae* (Sc) that the ScRPC31, ScRPC34 and ScRPC82 subunits (orthologous to human (Hs) RPC32, HsRPC39 and HsRPC62, respectively) could be separated from the other subunits of Pol III by native gel electrophoresis.[42] In addition, a mutation in the zinc-binding domain of the largest subunit of Pol III (ScRPC160) led to an increased dissociation of subunits ScRPC31, ScRPC34 and ScRPC82 from the remainder of the enzyme,[43] indicating that ScRPC31, ScRPC34 and ScRPC82 may form a Pol III sub-complex that is less stably associated with the residual enzyme. The association of this sub-complex with the rest of Pol III may involve a direct ScRPC160-ScRPC31-interaction, since overexpression of ScRPC160 is able to suppress a conditional growth phenotype of a mutation in the C-terminal part of ScRPC31.[44] It was further shown that ScRPC31, ScRPC34 and ScRPC82 interact with each other in two hybrid assays.[45] The latter and subsequent experiments also revealed an interaction between ScRPC34 and ScBRF1.[45,46] Altogether these results indicate that this subcomplex serves as a bridge between the enzymatic core of Pol III and its initiation factors. As a consequence, in pre-initiation complex formation, this subcomplex likely acts in a central position close to the transcription initiation site. Such a role was also supported by cross-linking experiments that projected ScRPC34 and ScRPC31 upstream of, and ScRPC82 also downstream of, the transcription initiation site.[47] By using the short distance crosslinker 4-S-dTMP, Bartholomew and colleagues[47] further showed that photoaffinity labeling of ScRPC82 and ScRPC31 by 4-S-dTMP, but not by the 9 Å-crosslinker N_3RdUMP, occurs in transcription bubbles of initiation complexes and stalled elongation complexes, indicating that these two subunits of Pol III may be in contact with single-stranded DNA.

Complementary data supporting a model in which HsRPC62, HsRPC39 and HsRPC32 likewise form a ternary complex were obtained with human Pol III. It was shown that the ternary complex can be removed from the other 14 subunits of Pol III by ultracentrifugation or by treatment with mild denaturants (2 M urea).[48] Human Pol III that was stripped of HsRPC32, HsRPC39 and HsRPC62 was capable of transcription elongation (following non-specific initiation), but was incapable of specifically initiating transcription from Pol III promoters, again indicating that this ternary sub-complex may be especially important for polymerase-transcription factor interactions during initiation. However, the residual elongation activity of the 14-subunit

Table 1. The subunits of human RNA polymerase III

Gene symbol	Protein name	Calculated mass [kDa]	Amino acids
POLR3A	RPC160	155.641	1390
POLR3B	RPC128	127.785	1133
POLR3C	RPC62	60.612	534
POLR3D	RPC53	44.396	398
POLR3E	RPC80	79.898	708
POLR3F	RPC39	35.684	316
POLR3G	RPC32α	25.914	223
POLR3GL	RPC32β	25.334	218
POLR3H	RPC25	22.918	204
-	RPC17	16.871	148
POLR3K	RPC11	12.336	108
POLR1C	RPAC40	39.250	346
POLR1D	RPAC19	15.237	133
POLR2E	RPB5	24.551	210
POLR2F	RPB6	14.478	127
POLR2H	RPB8	17.143	150
POLR2L	RPB10	7.645	67
POLR2K	RPB12	7.004	58

core Pol III complex, while significant, was nonetheless reduced, suggesting that the ternary complex may also function during transcription elongation.[48] Studies with recombinant proteins further showed that HsTFIIIC63 and HsRPC62, HsTFIIIC90 and HsRPC62 as well as HsTFIIIC90 and HsRPC39 interact in vitro,[49,50] reinforcing the hypothesis that the ternary sub-complex of RNA polymerase III fulfils important functions for establishing protein-protein-contacts with transcription factors on the one hand and with Pol III on the other.

Purification of Pol III from mouse myeloma cells (MOPC 315) led to the identification of two chromatographically distinct enzymes (Pol IIIA and Pol IIIB) that were both active in transcription of class III genes.[51] Determination of the subunit compositions of these enzymes revealed that they are highly related and differ only in the presence of either a 32 kDa (IIIA) or a 33 kDa (IIIB) polypeptide.[52] Recently, we have been able to isolate two distinct isoforms of Pol III from human cells. The major physical difference in between these two isozymes is the presence of either HsRPC32α/POLR3G in Pol IIIα or of HsRPC32β/POLR3GL in Pol IIIβ.[4] Taking into account the migration of these two subunits on SDS-PAGE, it is very likely that the two isoforms isolated from human cells are orthologous to the previously reported isoforms of Pol III in mouse myeloma cells.

Regulation of Pol III Transcription—Lessons Learned from Yeast

Many factors and mechanisms that underlie the regulation of RNA polymerase III transcription have been identified by studying yeast cells. These unicellular organisms adapt their gene expression programs by all three RNA polymerases to environmental conditions. Favorable growth conditions lead to higher rates of transcription, whereas deprivation in nutrients results in the repression of transcription. Importantly, transcription of components of the translational apparatus, including rRNAs, tRNAs and mRNAs encoding ribosomal proteins consume about 75–80% of cellular nucleotides, mainly through transcription by Pols I and III,[53,54] and this high energetic cost is restricted under unfavorable growth conditions.[55] Multiple pathways have been implicated in the regulation of Pol III transcription in *S. cerevisiae*. These include the secretory signaling pathway,[54] the TOR pathway,[56-58] the DNA damage pathway[59] and the PKA pathway (as a downstream effector of RAS).[60] Defects in the secretory pathway lead to the repression of 5S RNA and tRNA transcription. Temperature-sensitive mutations in two genes that function either in endoplasmic reticulum (ER) to Golgi complex transport (*YPT6*) or in protein and vesicle trafficking between ER and Golgi (*SLY1*) lead to repression of Pol III transcription at the non-permissive temperature. This repression can be partially rescued by deletion of protein kinase C (*PKC1*), the central effector kinase of the cell integrity pathway. Furthermore, deletions of either *WSC1* or *WSC2* genes, the farthest upstream components of the cell integrity pathway, also strongly reduce repression of Pol III transcription that is induced by secretory mutations.[54,55] Deletion of MAF1 blocks the repression of Pol III transcription caused by defects in the secretory pathway,[59] possibly placing MAF1 as a downstream effector of PKC. Likewise, MAF1 was identified as a downstream effector of the repression of Pol III transcription by TOR,[61] suggesting that many, if not all, repressive signals for Pol III transcription in yeast converge on MAF1.

MAF1 was originally identified in a genetic screen that decreased the nonsense suppressor efficiency of SUP11 tRNA[62] and the link to Pol III transcription was established by the isolation of fragments of the largest subunit of Pol III as multisuppressor copies of the conditional growth phenotype of the *maf1*-1 mutation.[63,64] MAF1 was shown to inhibit *S. cerevisiae* Pol III transcription as a downstream effector of several nutrition and stress signaling pathways. Starvation, rapamycin treatment and oxidative or endoplasmic reticulum stress were shown to be dependent on MAF1 for the repression of Pol III transcription.[61] Under repressive growth conditions, MAF1 is dephosphorylated by protein phosphatase 2A (PP2A), leading to its translocation into the nucleus where it inhibits Pol III transcription mainly through interactions with BRF1 and Pol III itself.[65,66] Favorable growth conditions lead to phosphorylation of MAF1 by SCH9 and PKA kinases, resulting in its retention in the cytoplasm.[60,67-69] Repression of Pol III transcription by MAF1, MAF1 regulation by phosphorylation and MAF1 interactions with BRF1 and Pol III have been conserved from yeast to humans.[70-72] It was demonstrated that facilitated recycling of Pol III transcription prevents repression by MAF1 in HeLa cell extracts, suggesting that the regulation of Pol III recruitment to preinitiation complexes represents an important mechanistic component of MAF1 function.[27] Interestingly, overexpression of MAF1 in human glioblastoma cells led to the inhibition of colony formation in soft agar assays, thus demonstrating functional aspects that are usually attributed to tumor suppressor proteins.[73] Possibly, direct inhibition of TATA-binding protein expression and its effects on Pol I and Pol III transcription may contribute to tumor-suppressive activities of MAF1.[73] However, no MAF1 mutation causative for the development of tumors has hitherto been described in higher eukaryotes.

Regulation of Pol III Transcription in Higher Eukaryotes

Gene-specific cellular factor TFIIIA. The prototypical example of Pol III-mediated transcriptional regulation in vertebrates is the regulation of 5S RNA transcription by TFIIIA during *Xenopus laevis* development. TFIIIA was the first eukaryotic transcription factor to be identified and purified to homogeneity,[8] allowing molecular cloning of the cognate cDNA encoding TFIIIA[74] and deduction of zinc-finger motifs.[75] It was shown that TFIIIA regulates 5S RNA transcription through site-specific binding to the 5S gene promoter[8] and that it also binds to 5S RNA, forming a 7S ribonucleoprotein storage particle.[76] Two types of 5S RNA genes have been described in *X. laevis*, an oocyte-specific gene that is present in about 20,000 copies per haploid genome and a somatic gene present in about 400 copies per haploid genome.[77] The somatic 5S gene is expressed in both oocytes and in adult animals, whereas expression of the oocyte-specific 5S genes decreases dramatically after oogenesis. The reduction of oocyte 5S gene transcription has been attributed to multiple mechanisms

involving both chromatin modifications[78,79] and regulation of the expression of TFIIIA itself.[74,77,80] Regarding the latter mechanism, there are high levels of TFIIIA mRNA and protein per cell during early oogenesis but dramatically reduced levels per cell during embryogenesis. Thus, the expression pattern of *X. laevis* TFIIIA suggests a regulatory role for TFIIIA in the developmental changes in 5S gene transcription. Differential expression of TFIIIA in oocyte and somatic cells has been attributed to the usage of distinct promoters. Interestingly, it has been reported that Pol III initiates transcription within the oocyte-specific promoter of TFIIIA, suggesting a Pol III-mediated downregulation of the oocyte-specific TFIIIA promoter in *Xenopus laevis* somatic cells.[81]

Viral proteins. In the late seventies and the eighties of the last millennium, after the discovery and partial characterization of general transcription initiation factors for Pol III,[82] Pol II,[83] and Pol I,[84] the focus of transcription research advanced to the identification of mechanisms that contribute to the regulation of the three transcription systems. The contribution of viral proteins in the process of transcription regulation was explored and, in particular, viral proteins with oncogenic functions were analyzed for their ability to enhance or repress transcription. We will restrict the description in this review to the regulation of mammalian Pol III transcription and refer to excellent publications that review the regulation of RNA polymerases I and II.[85-87] Major breakthrough discoveries with respect to the regulation of Pol III transcription by viral proteins were obtained with the adenovirus E1A protein that activates transcription of immediate early viral genes. Transfection of cDNAs encoding E1A stimulated transcription of co-transfected VA1 and tRNA genes.[88-90] The activation was attributed to indirect mechanisms that acted on the activity of TFIIIC, since depletion of E1A from HEK cell extracts did not abolish transcription activation.[91] The molecular cloning of TFIIIC110[92] showed that its expression could be regulated by transfection of adenoviral E1A or by serum stimulation of HeLa cells. However, it was also shown that recombinant E1A that was produced in baculoviral expression systems could likewise stimulate Pol III transcription,[93] pointing to the possibility that E1A may exert its function through alternative mechanisms. In addition to the regulation of Pol III transcription by E1A, it was demonstrated that the SV40 small t antigen also stimulates Pol III transcription.[94] The hepatitis B virus X (Hep B X) protein also was shown to activate transcription by Pol III.[95] It later was shown that the Hep B X protein acts, at least in part, through enhanced expression of the TATA-binding protein.[96]

Link to cell cycle control. Important mechanistic aspects of Pol III transcription regulation by viral proteins were revealed by the identification of cellular proteins that are regulated by these viral proteins. In particular, it was demonstrated that adenoviral E1A and E1B proteins, papillomaviral E6 and E7 proteins and SV40 large T antigen interacted with and inactivated p53 and pRb, thereby severely impacting on the regulation of the host cell's cell cycle.[97,98] These findings led subsequently to the discoveries that major tumor suppressor proteins, such as pRb,[99,100] p53,[101,102] ARF,[103] PTEN[104] and BRCA1,[105] negatively regulate Pol III transcription. For Rb it was demonstrated that only hypophosphorylated Rb was able to efficiently repress Pol III transcription.[99] The regulation of Pol III transcription by tumor suppressor proteins was shown to be exerted either through direct interactions with TFIIIB[102,106] or PTF/SNAPc/PBP[107] subunits or by the activation of signal transduction cascades that ultimately lead to the phosphorylation and inactivation of TFIIIB subunits.[104] However, indirect effects of p53 on the stability of BRF1 have also been described. In this case, it was necessary to maintain ectopic expression of p53 in $p53^{-/-}$ Li-Fraumeni cells for at least 4 days in order to reveal an inhibitory effect on Pol III transcription activity; and this effect proved to be mediated by the disappearance of a hyperphosphorylated form of BRF1, which was degraded in a proteasome-dependent manner.[108] Moreover, pRb family members p107 and p130 were also reported to repress Pol III transcription through direct interaction with BRF1.[109,110]

It was further reported that Pol III transcription is repressed in mitosis and that the repression is conferred by a kinase that phosphorylates subunits of TFIIIB. In *X. laevis* it was shown that a 92 kDa protein in fractions with TFIIIB activity becomes phosphorylated by $p34^{cdc2}$ (CDK1).[111,112] In HeLa cells, TBP-associated subunits of TFIIIB (presumably corresponding to BRF1 or BRF1 and BDP1) that were purified from cycling cells were shown to reconstitute transcription in mitotic extracts, suggesting that these components represent the target proteins of repression.[113] Subsequently, it was shown that BRF1 is phosphorylated and inactivated during mitosis by a kinase different from CDK1.[114] In addition, BDP1 within TFIIIB-α was shown to be phosphorylated by CK2 during mitosis, leading to the repression of Pol III transcription.[115] Apart from this inhibitory role of CK2, it was also reported that CK2 is able to stimulate transcription of the human U6 gene via phosphorylation of Pol III.[116] Regulatory roles for CK2 in Pol III transcription were also reported in the yeast *S. cerevisiae*.[117,118] The phosphorylation of BRF1 and of BDP1 during mitosis has been confirmed by quantitative analysis of protein phosphorylation in HeLa cells.[119] This report also showed that subunits of Pol III (POLR3C, POLR3E and POLR3G), TFIIIB-α (BRF2), TFIIIC (TFIIIC220, TFIIIC110) and PTF (PTFα/SNAPc190) are likewise phosphorylated during mitosis, which could possibly contribute to mitotic repression of Pol III transcription in human cells. Repression of PTFα/SNAPc190 activity was shown to be mediated by CK2,[120] but it remains to be shown whether CK2 or another kinase is responsible for PTFα/SNAPc190 phosphorylation during mitosis.

Link to growth control. In contrast to the repression exerted by tumor suppressor proteins, the proto-oncogene c-MYC[121] and components of the MAP kinase signal transduction pathway (ERK; JNK1)[122,123] were found to activate Pol III transcription. c-Myc, ERK and JNK1, respectively, were shown to function through recruitment of TFIIIB to Pol III promoters (c-Myc), through phosphorylation of the BRF1 subunit of TFIIIB (ERK) or through enhanced expression of BRF1 (JNK1). Subsequently, it was shown that c-Myc induces the association of GCN5 and TRRAP with Pol III promoters ($tRNA^{Leu}$; 5S), resulting in acetylation of histone H3.[124] The association of c-Myc with TRRAP and GCN5, as well as Pol III transcription activation is negatively

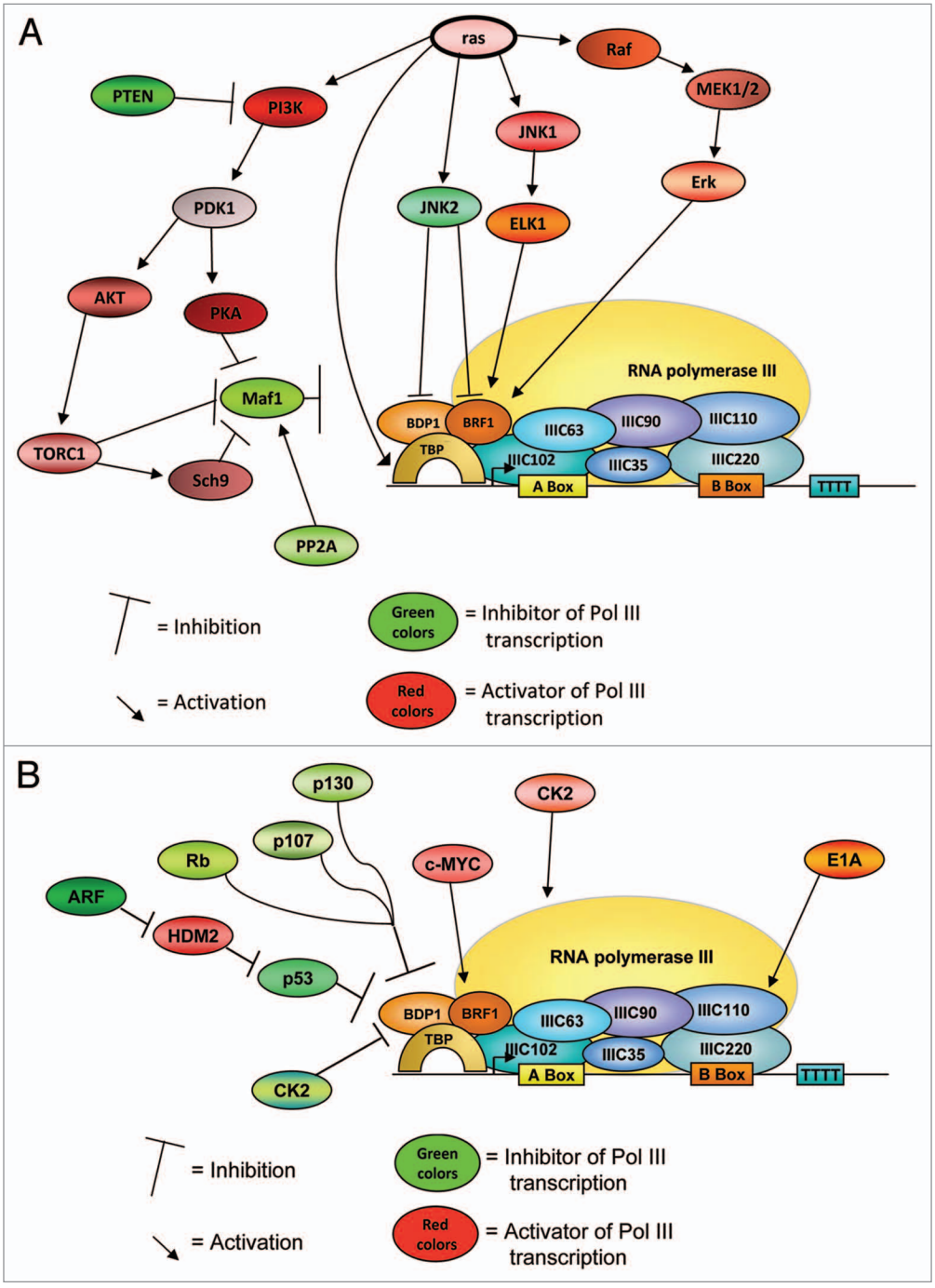

Figure 2. (A) Schematic representation of several regulatory pathways of mammalian RNA polymerase III transcription: Ras-dependent pathways. (B) Schematic representation of several regulatory pathways of mammalian RNA polymerase III transcription: Regulation of Pol III transcription by tumor suppressor and oncogene proteins.

regulated upon nucleolar stress (induced by actinomycin D or serum starvation) by the ribosomal protein L11.[125] Myc functions in regulating Pol III transcription were demonstrated to be independent of its heterodimerization partner Max in *Drosophila melanogaster*.[126] Moreover, in an independent link of Myc to the Pol III transcription apparatus, it was shown that c-Myc activates transcription of the RPC53 (BN51) gene,[127] which encodes a Pol III subunit that has been reported to suppress the temperature-sensitive G_1 cell cycle arrest in the hamster BHK-21 cell line.[128,129] Interestingly, mutation of the gene encoding RPC53 in yeast also induced cell cycle arrest predominantly in G_1, although no Myc ortholog has been described in this organism.[130] Collectively, these results strongly indicate that the regulation of growth and cell cycle control are intimately connected to the activity of Pol III transcription. Some of the regulatory mechanisms have been summarized in **Figures 2A and 2B**.

Link to tumor development. The above described discoveries that linked Pol III transcription to cellular processes such as cell cycle or growth suggested that Pol III transcription may be deregulated during cell transformation. In addition it was shown that the expression of five TFIIIC subunits (the sixth was not yet identified) is increased in ovarian carcinomas.[131] Importantly, the samples analyzed in this study were obtained from patients in clinics and not from cell lines grown under tissue culture conditions, demonstrating that the expression of Pol III transcription components is deregulated in tumors that have not been produced by experimental manipulations. It was nevertheless a surprise that the inducible overexpression of the BRF1 subunit of TFIIIB or of the $tRNA_i^{Met}$ gene in mouse 3T3 fibroblasts was sufficient for transformation of these cells.[132] These data suggested that enhanced transcription from type 3 promoters was not required for tumor formation, but that only transcription by BRF1-containing TFIIIB-β, and in particular that of the $tRNA_i^{Met}$ gene, was crucial in this process. However, overexpression of BRF1 or $tRNA_i^{Met}$ in rat1a fibroblasts proved insufficient for cellular transformation, indicating that cell type-specific differences may exist between these two model systems.[133] The analysis in rat1a cells has further shown that enhanced Pol III transcription is required for oncogenic transformation by c-Myc.[133] In summary, and even if the model of BRF1- or $tRNA_i^{Met}$-mediated cell transformation may not be applicable to all types of cells, these two studies clearly demonstrate the importance of Pol III transcription for cell transformation.

Regulation of Pol III Transcription during Cellular Differentiation

In addition to the mechanisms that coordinate the regulation of growth and Pol III transcription activity, multicellular organisms must have evolved the means to regulate transcription during differentiation in order to ensure that cells with high protein synthesis rates are capable of producing the components necessary for translation (i.e., ribosomal RNAs and proteins, as well as tRNAs)—even if they are resting and thus in the G_0 phase of the cell cycle. Some tissues such as the exocrine[134] or endocrine[135] pancreas probably circumvent this problem in part by balancing cell growth and apoptosis, resulting in stable cell numbers whilst allowing cell growth and division. In these tissues, the required protein synthesis and thus active Pol III transcription, may presumably occur predominantly in dividing cells, although the presence of high amounts of endoplasmic reticulum suggests high protein synthesis rates in both dividing and resting cells. Other cells, including Schwann cells that induce myelin gene transcription after cell cycle exit,[136] require transcription of ribosomal components after entering the G_0 phase of the cell cycle.

Only one study addresses the regulation of Pol III transcription in cells that have entered the G_0 phase of the cell cycle. The model system for this study is the hypertrophic growth of cardiomyocytes that is induced by serum, endothelin-1 or phenylephrine. Even if these cells are in the G_0 phase of the cell cycle, they are still able to increase cell mass (hypertrophy) upon serum stimulation and to a lesser extent by endothelin-1 or phenylephrine stimulation. Induction of hypertrophy is accompanied by enhanced BRF1 and c-Myc expression and by elevated rates of phosphorylated ERK, as well as phosphorylated Rb.[137] As a result, Pol III transcription is enhanced in cardiomyocytes by these stimuli. Except for this particular case, there is no detailed information on how mammalian Pol III transcription is regulated during differentiation and in terminally differentiated cells and tissues.

Little is known about the regulation of Pol III transcription during differentiation of mammalian cells. In particular, analyses of Pol III transcription at the level of protein expression and/or modification during early steps of differentiation (e.g., in undifferentiated embryonic stem cells and in the course of their differentiation) are limited by the amounts of cells and extracts that can be derived from these cells. To overcome these limits, embryonic carcinoma (EC) cells have been employed for analyzing the regulation of Pol III transcription during early steps of differentiation. Mouse F9 or human NTERA2 EC cells are tumor cell lines with certain stem cell-like features.[138] Suspension cultures of F9 EC cells can be differentiated into embryoid bodies by the addition of retinoic acid and monolayer cultures of F9 cells differentiate into parietal entoderm (PE) upon the addition of retinoic acid and cAMP (**Fig. 3**). This cell system has been employed for analyzing the activity of the Pol III transcription system during differentiation. It was shown that Pol III activity decreased for transcription of gene-internal promoters as well as of type 3 promoters. The reduced transcriptional activity at gene-internal promoters was attributed to altered TFIIIB activity[139] or to a decrease in TFIIIC1 activity.[140] The decrease in TFIIIB activity was shown to result from the combined reduction of the abundance of TFIIIB subunits (TBP, BRF1 and BDP1).[141,142] Furthermore, the protein levels of c-MYC were also dramatically downregulated during differentiation of EC into PE cells, which may account in parts for the reduction of Pol III transcription.[142] Impaired transcription of type 3 genes was correlated with a decrease in binding of PTF/SNAPc/PBP to the PSE[143] (**Fig. 3**).

These results, indicating that TFIIIB-, TFIIIC1- and PTF/SNAPs/PBP-activities are regulated during differentiation of F9 EC cells could be functionally linked to each other by the finding that the TFIIIB subunit BDP1 is essential for TFIIIC1-activity.[144] Originally, TFIIIC was separated by B-Box-based affinity purification or by chromatography over Mono Q into the TFIIIC1 and DNA-binding TFIIIC2 components, which were both required for Pol III transcription.[145,146] TFIIIC1 was shown to stimulate binding of the six-subunit TFIIIC2 complex to gene-internal type 2 promoters,[145] as well as PTF/SNAPc/PBP binding to the PSE.[147] Extensive purification of TFIIIC1 in conjunction with analyses of recombinant TFIIIB150 (corresponding to amino acids 1–846 of BDP1) revealed that BDP1 and TFIIIC1 were functionally replaceable in complementation assays of transcription with extracts that were derived from differentiated F9 cells (and thus contained limiting amounts of TFIIIC1) or in transcription systems that were reconstituted with partially purified transcription factors.[144] Together, these data indicate that the activity of BDP1 is negatively regulated during differentiation of F9 teratocarcinoma cells.

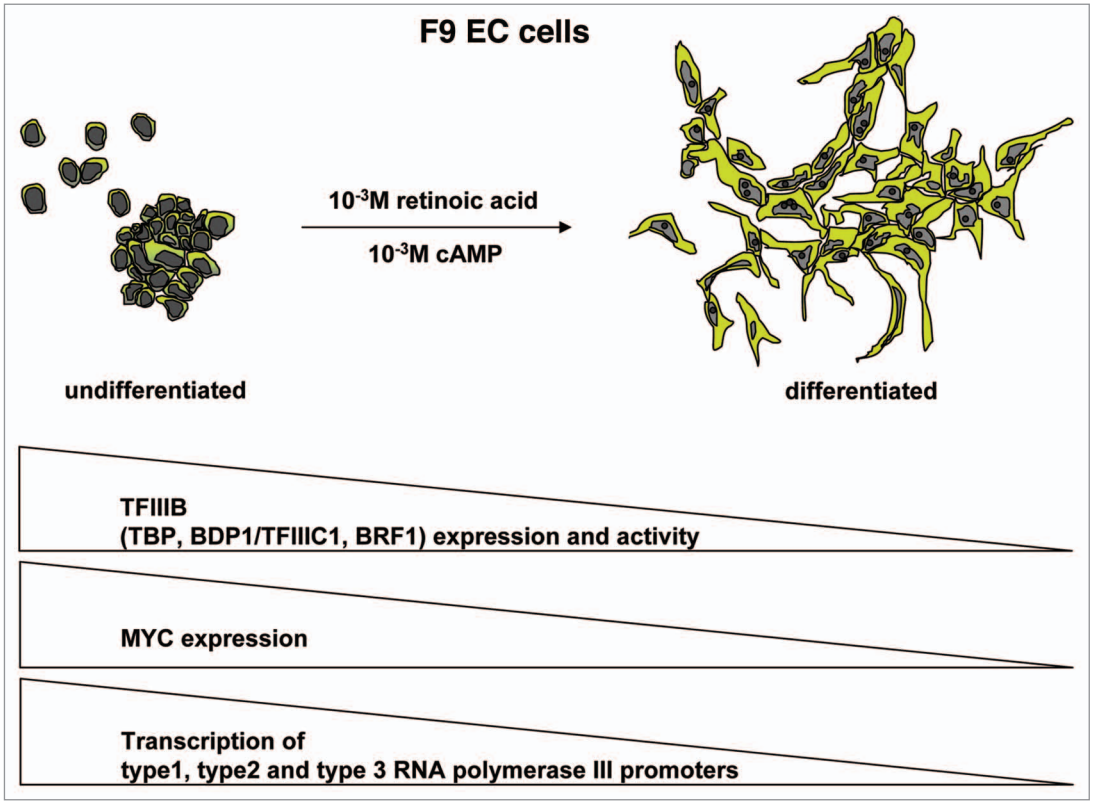

Figure 3. Regulation of RNA polymerase III transcription during differentiation of mouse F9 embryonic carcinoma cells.

The importance of Pol III transcription for proliferation and differentiation and thus for organ development, was further demonstrated in *Danio rerio*. Expression of a splice mutant of the second largest subunit of Pol III (POLR3B Δ239-279; *slim jim*) in zebrafish led to disruption of the development of digestive organs and to size reductions in the exocrine pancreas, liver, retina and terminal branchial arches. Although the strongest expression of POLR3B was reported in the nervous system 24 hours post fertilization, no neuronal phenotype other than that of the retina was reported for the *slim jim* mutant.[148] These data suggest that normal Pol III transcription rates may be crucial for the development of rapidly growing cells. In support of this notion, it was proposed that tissue-specific expression of tRNAs may be coordinated with the codon usage of individual cells, which may in turn be crucial for tissue or cell type-specific translation regulation.[149]

Recent data indicate that expression of a subunit of Pol III itself is also subject to regulation during the process of differentiation. It was shown that RPC32α mRNA expression is negatively regulated during differentiation of human H1 embryonic stem cells and that RPC32α mRNA could not be detected in RNA blots from differentiated tissues (**Fig. 4**). In addition, RPC32α mRNA and protein expression were found to increase during transformation of human embryonic lung IMR90 fibroblasts by defined genetic elements.[4] These data collectively suggested that RPC32α mRNA and protein expression is negatively regulated during differentiation and upregulated during the malignant transformation of human cells. Furthermore, by employing siRNAs that specifically suppress RPC32α-expression, it was demonstrated that RPC32α is important for anchorage-independent growth of a HeLa S3 carcinoma cell line. Most importantly, overexpression of RPC32α in IMR90 human embryonic lung fibroblasts with altered functions of p53 and pRb (through the expression of papillomaviral E6 and E7 proteins) led to full transformation and immortalization of these cells. Altogether, these data indicated that the changes in expression of RPC32α were not only coincident with differentiation or cell transformation, but that RPC32α may play an active role in these processes.[4]

In view of these results it is relevant to ask why studies that examined Pol III transcription during the differentiation of F9 teratocarcinoma cells did not identify the stem cell-specific isoform of RNA polymerase III. A possible explanation is that the genes analyzed in these studies were the well-known Pol III genes (transfer-, 5S-, U6- or VA1-RNA genes), that can be transcribed in vitro either by Pol IIIα or by Pol IIIβ.[4] As a consequence, the expression of these genes presumably does not change during the process of stem cell differentiation. If this supposition holds true, the downregulation of RPC32α during differentiation may affect the transcription of genes other than the 5S and tRNA genes—and these hypothetical yet-to-be-identified genes may turn out to be important for maintaining cells in an undifferentiated state. The possible existence of such Pol IIIα-specific genes also implies that the phenotypes observed in the zebrafish (which according to BLAST analyses contains orthologs of RPC32α and RPC32β) expressing the *slim jim* mutant may, at least in part, be attributable to a dysfunction of Pol IIIα. Thus, the identification of genes that are specifically transcribed by Pol

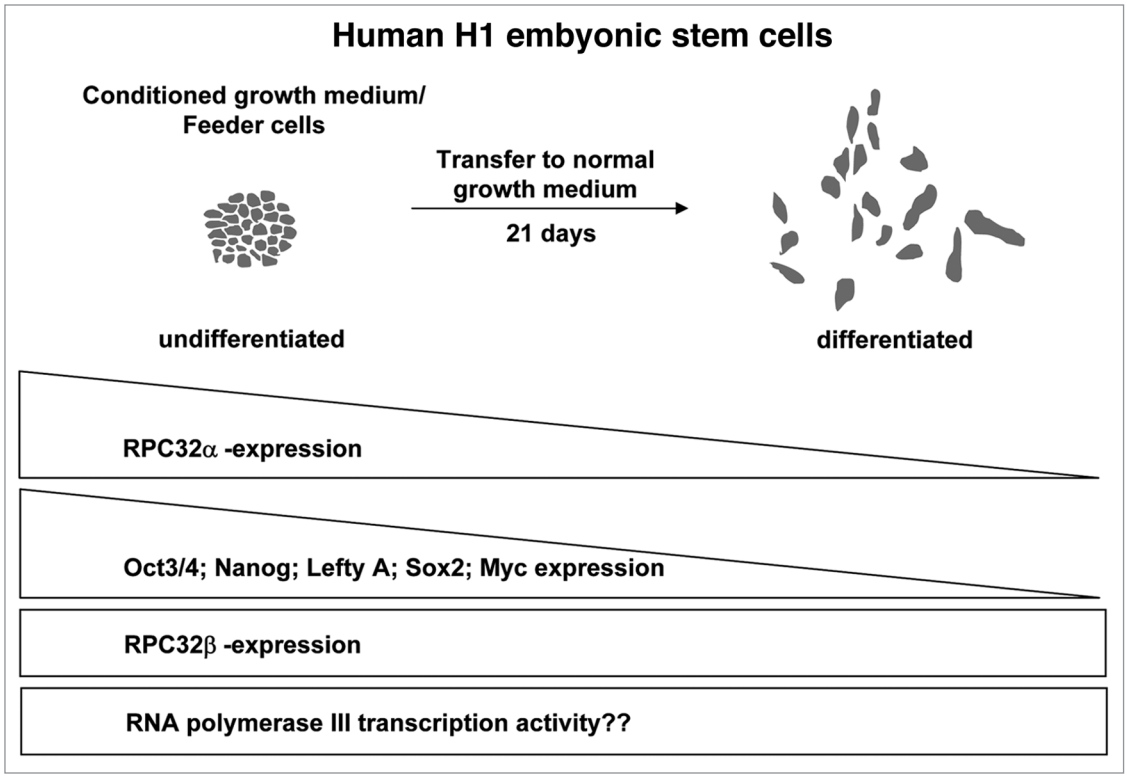

Figure 4. Regulation of RNA polymerase III transcription during differentiation of human H1 embryonic stem cells.

IIIα and that cannot be transcribed by Pol IIIβ will be important for understanding the roles of Pol IIIα and Pol IIIβ in growth and development. A first step towards the identification of such genes that may fulfil important functions in growth and differentiation has been made by establishing a genome-wide map of RNA polymerase III DNA interactions.

The Human Pol III Transcriptome

Recently, the results from five independent genome-wide chromatin immunoprecipitation (ChIP) sequencing projects in human cells have been published.[150-154] Antibodies against several distinct subunits of Pol III (RPC155/POLR3A; RPC53/POLR3D; RPC32/POLR3G) and its transcription factors (BRF1; BRF2; BDP1; TFIIIC220; TFIIIC110; TFIIIC63; PTFδ/SNAPc2/SNAP45) were employed for determining the genes that are in contact with these proteins and presumably transcribed in a variety of untransformed, immortalized or transformed cell lines (IMR90 fibroblasts/TERT; human foreskin fibroblasts/TERT; Jurkat; HEK; HeLa; K562; $CD4^+$ cells). As expected, at least one copy of each multicopy gene (individual tRNA, 5S, 7SL and U6 genes) is associated with Pol III and BRF1 (TFIIIB-β) or BRF2 (TFIIIB-α).[151-154] Single-copy Pol III-transcribed genes include the 7SK, RNAse MRP, RNAse P, BC200, U6atac and vault-1, -2 and -3 genes). Of these, the 7SK, U6atac, RNAse MRP, RNAse P and vault genes were reported to be associated with Pol III in each of the studies. BC200 was crosslinked to Pol III and identified in the ChIP-seq (K562 cells)[152] and microarray (HeLa cells)[153] analyses, but was not identified by the other studies. The differential detection of the BC200 gene in individual studies may be attributable to distinct cut-off values that were used to distinguish positive and negative results and/or a cell type-specific expression pattern of the BC200 gene.[155] A greater discrepancy between the different studies and distinct cell types was observed with respect to the occupancy of tRNA genes by Pol III and/or subunits of TFIIIC and TFIIIB. This variation may be attributable to the copy number of individual tRNA genes and cell type-specific nuclear organization of the genome. In general, the ChIP-sequencing results do not support earlier reports[156,157] indicating that micro RNAs may be transcribed by Pol III. In fact, the only miRNA loci that were found to be associated with Pol III are hsa-mir565 (a tRNA fragment),[150] hsa-mir-1975 (overlaps with the hy5 gene)[151,152] and hsa-mir-886 (overlaps with a vault gene).[151-154] Thus, all these micro RNA genes overlap genes that possess classical Pol III promoters. One single microRNA gene (has-mir-498) has been described to associate with Pol III in $CD4^+$ cells but not in HeLa cells.[150] The number of novel Pol III genes is difficult to assess, although tens to hundreds of candidate genes, depending on the study, have been identified. These genes include SINEs, snaR loci, sn/snoRNA loci and unannotated genes.

Interestingly, two of the five studies employed antibodies directed against RPC32α for ChIPs.[153,154] Some of the genes identified in these studies may represent Pol IIIα-specific genes, although the specificity of the antibodies for Pol IIIα versus Pol IIIβ in immunoprecipitation assays remains to be proven. At present, it cannot be excluded that the genomic loci

identified in these studies also contain Pol IIIβ-transcribed genes, such that Pol IIIα-specific genes remain unequivocally to be determined.

Pol III, Chromatin and Higher Order Genome Organization

Chromatin modifications found near Pol III-bound genes share features with the histone modifications found at actively transcribed Pol II genes, including histone H3K4me3 or H3K9Ac.[150,152,153] However, other positively acting histone modifications described at Pol II transcribed genes, namely the RPB1 CTD-dependent, Set2-mediated H3K36me3 or H3K79me2 were absent at transcribed Pol III genes. Furthermore, H3K27me3 was rarely found at actively transcribed Pol III promoters.[150]

In addition to the discovery of novel genes that may be transcribed by Pol III, two of the publications also described sites within the genome that are occupied by TFIIIC, but not by Pol III (extra TFIIIC [ETC] loci).[152,153] These sites are often found in close vicinity to genes transcribed by Pol II and may represent boundary or insulator elements, similar to what was reported in yeast.[158] TFIIIC may bind to ETCs via a novel DNA recognition sequence[152] and might also directly recruit histone modifying factors.[159] CCCTC-binding factor (CTFC) also was detected at these ETC sites[152] and at a subset of tDNAs with the highest enrichment of Pol III.[153] The association of the cohesin-interacting protein CTCF with TFIIIC-bound ETCs or tDNA genes is reminiscent of a situation described in yeast wherein tDNAs and Pol III-associated proteins have been reported to contribute to the establishment of sister chromatid cohesion at the HMR locus.[160]

c-Myc was crosslinked close to Pol III promoters, in support of a role for c-Myc in activating Pol III transcription.[154] Surprisingly, in addition to associations with Pol III transcription factors, c-Myc and Pol III itself, many of the transcribed Pol III genes were also in close proximity to Pol II transcription activators such as Fos and Jun[154] or Ets1 and STAT1.[153] Moreover, basal Pol II transcription factors and the cyclin T1 subunit of elongation factor PTEFb could be crosslinked close to sites occupied by Pol III.[150] Most importantly, Pol II was similarly enriched at Pol III-transcribed genes,[151-154] often upstream of the transcription initiation site and sometimes attributable to the presence of Pol II promoters within a distance of 2 kb.[153] Notably, in about two-thirds of the cases these Pol II promoters directed transcription by Pol II in the opposite direction of that of Pol III. The co-occupation of these sites by Pol II and Pol III has been interpreted as being advantageous for Pol III-mediated transcription as a result of Pol II-dependent chromatin modifications. However, this assumption has not been experimentally validated and alternative scenarios can be envisaged. In favor of direct interactions of Pol III components with chromatin-modifying enzymes, it has been shown that Pol III transcription of a chromatin template is facilitated by a direct TFIIIC-mediated recruitment of the histone acetyl transferase p300,[159] which could contribute to the histone acetylation[161] observed at these promoters in cells.

In addition to local chromatin modifications that are important for Pol III transcription, tRNA-induced and condensin-mediated organization of chromatin domains results in the recruitment of tRNA genes to the nucleolus in *S. cerevisiae*.[162,163] This could result in the co-recruitment of Pol II genes to these sites and placement of the tRNA genes into a chromatin context that may be favorable for their expression or repression. Moreover, perinucleolar domains (PNC) have been shown to form in tumor cells in a Pol III-dependent manner[164] and may represent sites that are favorable for gene expression. With respect to PNCs, it remains to be established whether Pol IIIα contributes to the formation of these subcellular structures. If so, the ability of Pol IIIα to contribute to cell transformation may be attributable to repositioning Pol II genes involved in cell transformation or tumor suppression into actively transcribed or repressed domains, respectively. In summary, the genome-wide determination of Pol III-DNA associations provides important information about the genes that are in contact with Pol III in several distinct cell lines and a closer analysis of these genes may reveal the ones that contribute to essential functions of Pol III in cell growth and differentiation.

Conclusion

Research in recent years has contributed to an improved understanding of how RNA polymerase III-mediated transcription is regulated in yeast and mammals. There has been considerable progress with respect to an understanding of the molecular mechanisms that link cell growth and cell cycle control to Pol III transcription in lower and higher eukaryotes. This understanding has also allowed an appreciation of the importance of Pol III transcription for cell transformation and for sustaining tumor growth. Recent data have linked Pol III-mediated transcription to the differentiation of EC and of ES cells, indicating that the transcription of small untranslated RNAs by Pol III is essential not only for the regulation of growth, but also for the regulation of differentiation. Future research will provide a more detailed understanding of how Pol III contributes to these processes, including the specific functions of the two Pol III isoforms.

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