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Review

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Alternative isoforms of RNA polymerase III impact the non-coding RNA transcriptome, viability, proliferation and differentiation of prostate cancer cells

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Abstract

RNA polymerase III (pol III) synthesizes short noncoding RNA (ncRNA) exclusively and is unique in having alternative paralogues of one of its subunits, POLR3G and POLR3GL. Although most pol III target loci can be transcribed by either isoform, exceptions have been found. For example, depletion of POLR3G curtails the production of BC200 and snaR ncRNAs that are implicated in cancer progression. Furthermore, POLR3G may protect pol III against repression by MAF1, a key physiological regulator. Expression of POLR3G is promoted selectively by MYC, NANOG and OCT4A, master regulators of stem cell pluripotency, resulting in its preferential accumulation in undifferentiated cells. Indeed, differentiation of prostate cancer cells is suppressed by a positive feedback mechanism between POLR3G and NANOG, involving the control of NANOG mRNA degradation by ncRNAs. Specific knockdown of POLR3G inhibits proliferation and induces differentiation of prostate cancer cells, but this response is not seen following comparable depletion of its POLR3GL paralogue. ML-60218 is a cell-permeable small molecule pol III inhibitor that triggers the replacement of POLR3G with POLR3GL. Proliferation and viability of primary prostate cancer cells are suppressed by ML-60218, whereas differentiation is induced, effects that mimic POLR3G depletion. Transient exposure to ML-60218 reduced tumour initiating activity in a xenograft model. Untransformed prostate cells are much less sensitive to these treatments, raising the possibility of therapeutic benefit.

Keywords: Prostate cancer, POLR3G, SINEs, RNA Polymerase III, MAF1, ncRNA, NANOG

POLR3G AND POLR3GL IN RNA POLYMERASE III TRANSCRIPTION

RNA polymerase III (pol III) is a 17-subunit complex required exclusively for the synthesis of untranslated RNAs, many of which have key roles in protein synthesis and RNA processing[1]. The most abundant pol III products are the tRNAs, 5S rRNA and the 7SL RNA scaffold of the signal recognition particle, but an eclectic variety of other short noncoding RNAs (ncRNAs) are also produced[1]. Mammalian cells contain two pol III isoforms that differ only in the presence of one essential subunit, either POLR3G or POLR3GL, which arose from a gene duplication event and share 49% protein sequence identity[2,3]. Expression of POLR3G is selectively promoted by several oncogenes that do not induce POLR3GL, including MYC[2,4,5]. Accordingly, the ratio of POLR3G to POLR3GL is significantly elevated compared to patient-matched controls in a variety of cancer types, such as lung and colorectal adenocarcinomas[5]. High POLR3G levels correlate with a worse prognosis for patients with lung adenocarcinomas, oesophageal, bladder urothelial and transitional cell carcinomas[5,6]. Furthermore, overexpression of POLR3G can have oncogenic effects both in cultured cells[2,3] and in mice[7]. Knockout of mouse POLR3G is lethal during early embryogenesis, whereas mice without POLR3GL survive until three weeks after birth, when they die with only half the body weight of their wild-type siblings[8]. For both knockouts, compensatory increases were seen in the expression of the remaining paralogue[8]. POLR3G levels are elevated in human or mouse embryonic stem cells (ESC) due to direct induction by pluripotency factors MYC, NANOG and OCT4A, but decrease strongly during differentiation[8-10]. Knockdown of POLR3G causes a loss of stem cell markers and induces differentiation of human ESC[11]. Overexpression of POLR3GL can rescue the defective differentiation of mouse ESC after knockout of POLR3G[8], but it is uncertain if this redundancy is physiological.

INDUCED DIFFERENTIATION OF PROSTATE CANCER CELLS BY TARGETING POLR3G

The pluripotency protection provided by POLR3G in ESC prompted tests for a similar role in the PC-3 cell line, which was isolated from a prostate cancer metastasis[12,13]. As well-differentiated tumours are generally associated with better survival prospects, suppression of pluripotency might prove to be beneficial. RNAi-mediated depletion of POLR3G in PC-3 cells was found to cause a significant decrease in NANOG expression and induction of neuroendocrine (NE) markers, whereas markers of luminal and basal prostate epithelial cells were unchanged[13]. Proliferation also slowed significantly[13]. These observations suggest that POLR3G depletion promotes directional differentiation towards a specific cell type. In contrast, comparable knockdown of POLR3GL did not slow proliferation or induce differentiation, despite a similar decrease in pol III activity, as measured by $tRNA^{Tyr}$ synthesis[13]. Thus, POLR3G is implicated specifically in maintaining an undifferentiated proliferative state in PC-3 prostate cancer cells, as seen previously in ESC.

ML-60218 is a specific cell-permeable small molecule inhibitor of pol III[14,15]. It has been shown to induce differentiation of preadipocytes[16]. When PC-3 cells were treated with this inhibitor, proliferation was slowed, NANOG expression suppressed and NE markers induced, demonstrating a similar differentiation response as when POLR3G is depleted[13]. This can be explained by the observation that treatment with ML-60218 provokes loss of POLR3G from the pol III complex and its replacement by POLR3GL[13]. The viability of PC-3 cells and their ability to invade matrigel were also compromised by ML-60218[13]. In contrast, the PNT2C2 line of immortalized healthy prostate epithelial cells shows little or no change in viability, proliferation and differentiation when exposed to ML-60218, despite comparable pol III inhibition to that seen in the PC-3 model[13]. This differential responsiveness may reflect the higher levels of POLR3G found in PC-3 cancer cells[13].

POLR3G INFLUENCES THE EXPRESSION OF THE PLURIPOTENCY FACTOR NANOG

Short interspersed nuclear elements (SINEs) are found in large numbers throughout mammalian chromosomes and are weakly transcribed by pol III[17]. However, transcription by pol II can also occur if a SINE is located within a longer protein-coding gene, as is often the case due to their random integration through retrotransposition[17]. DR2 SINEs are a subset of the Alu family, and their transcripts are processed by DICER to produce small repeat-induced RNAs (riRNAs), which can target specific mRNA transcripts for degradation[18]. Such targets of DR2-derived riRNAs include the master regulators of cell stemness and pluripotency NANOG and OCT4; thus, overexpression of DR2 Alu in ESC reduces levels of NANOG and OCT4 mRNA and inhibits stem cell regeneration, whereas depletion of these Alu transcripts suppresses ESC differentiation[18,19]. In PC-3 cells, DR2 Alu expression is unaffected by depletion of POLR3GL, but RNAi-mediated knockdown of POLR3G increases levels of DR2 Alu transcripts, causing elevated riRNA and degradation of its NANOG mRNA target[13,18,19]. The specific response of DR2 Alu transcription and hence NANOG expression to knockdown of POLR3G but not POLR3GL provides some explanation as to the selective effect of POLR3G on pluripotency.

NANOG-Alu-Sx is a member of the DR2 Alu family, which lies ~6 kb upstream of the *NANOG* gene; transcription of this specific SINE produces riRNAs that are complementary to the 3'-UTR of NANOG mRNA, causing its specific degradation[18]. Whereas depletion of POLR3GL has minimal effect, knockdown of POLR3G increases expression of NANOG-Alu-Sx in PC-3 cells[13]. Transfection of PC-3 cells with a 33 nt synthetic RNA fragment corresponding to the NANOG-Alu-Sx riRNA suppresses proliferation and NANOG expression and induces NE differentiation markers[13]. This is consistent with previous evidence that synthetic RNAs corresponding to the DR2 Alu consensus sequence can suppress NANOG in ESC[18]. Therefore, maintenance of PC-3 proliferation and self-renewal by POLR3G can be explained at least in part by the selective repression of NANOG-Alu-Sx transcription, which allows accumulation of NANOG, a key driver of pluripotency.

Although Alu SINEs can be transcribed by pol III, expression of NANOG-Alu-Sx increases in response to the pol III inhibitor ML-60218[13]. This counterintuitive observation may be explained by the fact that pol III transcription of Alu is usually inefficient, but expression can be boosted by pol II in some cases[17]. As proliferation slows and differentiation commences in response to ML-60218, epigenetic changes might favour more active transcription by pol II. Further analysis will be necessary to establish the mechanistic details of this transition. Nevertheless, the available data show that treatment with ML-60218 allows more efficient transcription of NANOG-Alu-Sx by pol II, generating riRNA that targets NANOG mRNA for degradation, thereby favouring differentiation [Figure 1].

RESPONSES OF PRIMARY PROSTATE CELLS TO ML-60218

The positive feedback loop between NANOG and POLR3G expression, which maintains pluripotency and self-renewal of PC-3 cells, might indicate a novel target for therapeutic intervention. To test if human cancers respond in a similar way to the cell line, Gleason grade 7 prostate tumours were excised from four patients and cultured with 20 μM ML-60218 for 48 h, which was sufficient to reduce pol III transcription by ~36%[13]. For two of the tumours, DR2 Alu SINEs, including NANOG-Alu-Sx, were induced by ML-60218 treatment and this was accompanied by depletion of NANOG mRNA[13,20]. All four tumours displayed induction of differentiated epithelial markers, but cell fate determination varied, with three tumours favouring an NE lineage, as seen with PC-3 cells, but one differentiating towards a luminal phenotype[13]. The reasons for this mixed behaviour are uncertain and highlight the complexity of predicting patient responses[21].

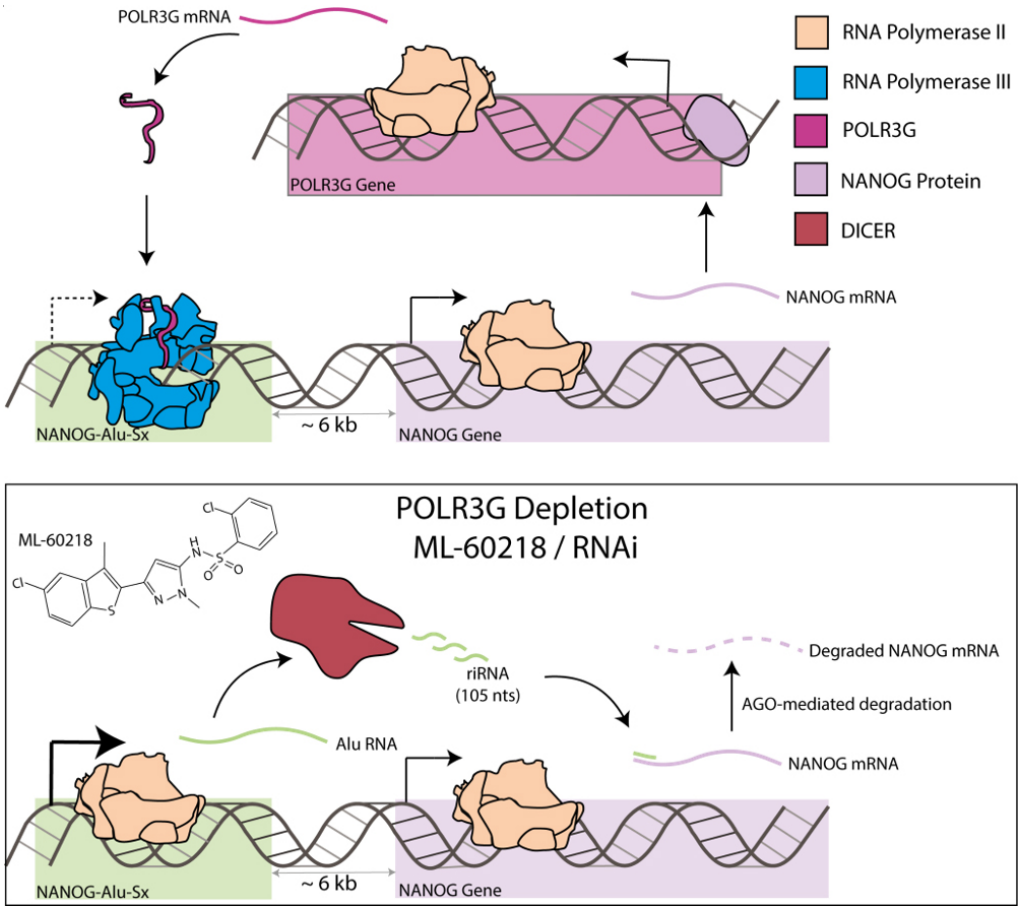

Figure 1. Model of NANOG regulation by DR2 Alu and the effect of POLR3G depletion. NANOG-Alu-Sx is a member of the DR2 family of Alu SINEs that lies approximately 6 kb upstream of the *NANOG* gene. A positive feedback loop exists between the expression of NANOG and the POLR3G subunit of pol III. Undifferentiated prostate cancer cells express NANOG, which binds the promoter of the *POLR3G* gene and stimulates its transcription by pol II. The POLR3G protein is incorporated into pol III, which binds to DR2 Alu SINEs, such as NANOG-Alu-Sx, but supports relatively inefficient transcription. POLR3G depletion by small molecule ML-60218 or RNAi allows replacement of pol III by pol II at DR2 Alu and increases transcription of these SINEs. DR2 Alu RNA is processed by DICER to generate small (~105 nts) repeat-induced RNAs (riRNA) with complementary sequence to the NANOG mRNA; this results in AGO-mediated degradation of NANOG mRNA, inhibiting self-renewal and allowing differentiation.

Identical treatment of healthy prostate tissue from the same four patients resulted in minimal effects on expression of DR2 Alu, NANOG, basal or luminal markers and only weak induction of NE markers, despite similar levels of pol III inhibition by ML-60218, as determined by comparing pre-tRNA^{Tyr} levels[13]. Proliferation was slowed in both healthy and tumour cells, but the latter were significantly more sensitive[13]. Furthermore, 48 h of 20 μM ML-60218 treatment reduced tumour cell viability by ~25%, whereas normal prostate cells remained fully viable[13]. A higher dose (50 μM) of the pol III inhibitor did decrease the viability of the normal cells, but they were still more tolerant of the cytotoxic effects than the cancer cells, which saw viability fall to ~40%[13].

The cancer stem cell (CSC) hypothesis places small clusters of pluripotent stem cells within tumours that are able to survive radiation and chemotherapy, and have the ability to self-renew and differentiate once the selective pressure of treatment has been removed, allowing recurrence of disease, often more aggressive than before[21,22]. Engrafting into mice extreme limiting dilutions of a heterogeneous cell population derived from tumours allows the frequency of tumour initiating CSC cells to be determined[23]. Androgen-

independent tumour cells derived from a patient with castration-resistant prostate cancer were treated in culture for 48 h with 20 μM ML-60218, which induced NE differentiation markers and NANOG-Alu-Sx and reduced cell viability by ~25%[13]. Extreme limiting dilution analysis with equal numbers of viable treated or untreated cells revealed that pre-exposure to 20 μM ML-60218 for 48 h prior to engraftment delayed the subsequent onset of tumourigenesis by 25 days (100 days total) compared to untreated cells, which had a mean latency period of 75 days[13]. Furthermore, the ML-60218 pretreatment caused a significant four-fold reduction in the percentage of cells forming tumours[13]. Thus, transient exposure to ML-60218 can have enduring impact on tumour initiating activity, consistent with CSC depletion through differentiation and/or death. Therefore, a mechanism to target the CSC population in prostate cancer might include finding effective methods of inhibiting POLR3G-dependent transcription by pol III.

SELECTIVE TARGETING OF SPECIFIC NCRNA GENES BY POL III CONTAINING POLR3G

Small NF90-associated RNAs (snaRs) are ncRNAs of ~117 nucleotides encoded by a family of pol III-transcribed tandemly repeated genes[24]. Elevated expression of snaR ncRNA has been observed in tumours and/or plasma of patients with liver, breast and ovarian cancer and can promote proliferation or metastasis[25-27]. ChIP-seq of human monocytes revealed that *snaR* genes are targets for pol III when it incorporates POLR3G, but not when bound by POLR3GL[5]. When monocytes differentiate, POLR3G is down-regulated and pol III disappears from *snaR* genes, which become silent; although POLR3GL levels remain stable, it seems unable to substitute for POLR3G at these loci[5]. Similar effects are seen following treatment with ML-60218, with specific loss of POLR3G and silencing of *snaR* genes[5].

The gene for BC200 ncRNA was also found to be targeted selectively by pol III containing POLR3G, relative to POLR3GL[5]. BC200 (BCYRN1) is a 200 nucleotide ncRNA that is found at elevated levels in several types of malignancy, including breast and oesophageal carcinomas, where high expression correlates with poor prognosis[28-31]. Manipulation of BC200 revealed an oncogenic role through alternative splicing of Bcl-x mRNA to inhibit apoptosis[30].

POLR3G may release pol III from a principle restraining influence

Pol III output is controlled in part through direct interaction with MAF1, a repressor that was first discovered in *Saccharomyces cerevisiae* and later shown to be conserved from yeast to humans[32-35]. The binding of MAF1 prevents pol III from being recruited to its target genes[36,37]. Such transcriptional restraint helps ensure that pol III output is sensitive to signalling through the mTOR pathway in response to growth factors, as MAF1 is a direct target for phosphorylation by mTOR[38]. This explains, at least in part, the elevated activity of pol III observed in prostate cancer cells following the loss of PTEN, a tumour suppressor that counteracts mTOR signalling[39]. Recent cryo-EM analysis revealed a striking difference in the interaction of the POLR3G and POLR3GL paralogues with the core of pol III, which greatly impacts binding and repression by MAF1[40]. It appears that POLR3G interacts more stably than POLR3GL with the pol III core and may therefore block the specific site which MAF1 would occupy[40]. This model predicts that pol III can evade one of its physiological restraints by utilizing POLR3G [Figure 2]. Thus, an ancient control mechanism may be bypassed in vertebrates through the evolution of a resistant form of pol III. This adaptation could have severely detrimental effects on cancers that overexpress POLR3G.

CONCLUSION

Pol III is a highly specialized RNA polymerase dedicated to the production of short ncRNAs. It is unique in having evolved a paralogue of one of its subunits that confers distinct properties. Whereas the canonical form of pol III containing the ancestral paralogue POLR3GL is repressed by MAF1 under conditions that are unfavourable to cell growth, this control may be compromised by POLR3G[40]. Not only is this likely to

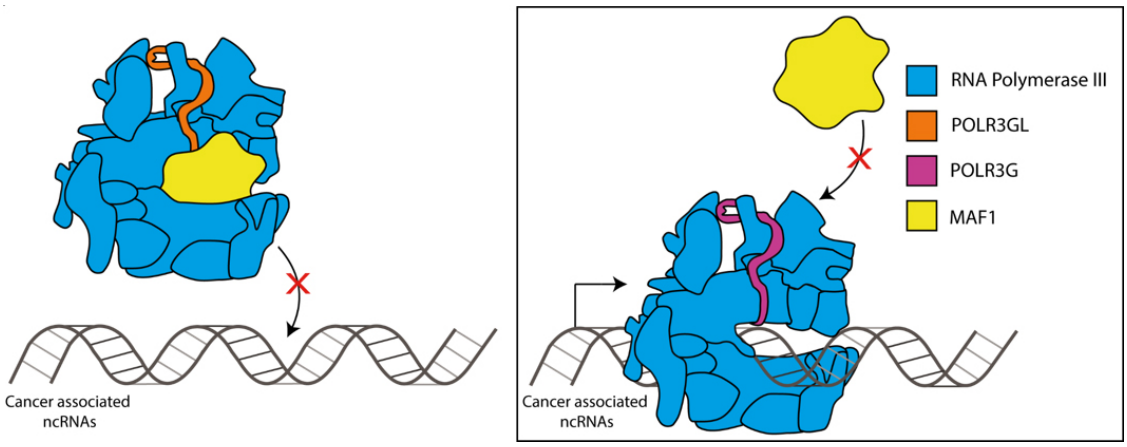

Figure 2. MAF1 regulation of pol III may depend on subunit composition. POLR3GL (orange) is the ancestral paralogue and is expressed ubiquitously; it allows repression of pol III by MAF1. POLR3G (purple) is enriched in stem and cancer cells; its incorporation may make pol III more resistant to MAF1 and thereby contribute to unregulated transcription and selective induction of ncRNAs such as BC200 and snaR. ncRNAs: Noncoding RNAs.

have quantitative effects on overall pol III output, but it may also promote the selective synthesis of ncRNAs that promote cancer progression, such as snaR and BC200 ncRNAs[5]. POLR3G can also suppress differentiation through a positive feedback loop involving the pluripotency factor NANOG. Accordingly, poor prognosis in several cancer types correlates with elevated POLR3G[5,6]. Knockdown experiments in the PC-3 model of metastatic prostate cancer provide evidence that targeting POLR3G can slow proliferation and promote differentiation[13]. This effect can be mimicked pharmacologically using the small molecule pol III inhibitor ML-60218, which triggers the replacement of POLR3G by POLR3GL, potentially restoring the sensitivity of pol III to MAF1-mediated control[13]. This inhibitor reduces viability, proliferation and invasion of PC-3 cells and stimulates their differentiation[13]. The response to ML-60218 of primary cells from prostate tumours is similar to that of PC-3 cells, whereas healthy prostate from surrounding tissue is significantly more resistant[13]. Although these features can be considered beneficial, an undesirable direction of differentiation was triggered in PC-3 cells and three of the four tumours exposed to ML-60218 assumed NE features that are linked with low survival[13,41]. However, the tumour from one patient differentiated towards a luminal phenotype without induction of NE markers[13], suggesting a more favourable outcome. It is possible that this reflects a subgroup of cancers that would respond well to therapeutic targeting of POLR3G, perhaps using PROTAC technology. Potentially the most important finding is that transient exposure *ex vivo* to ML-60218 can significantly reduce tumour initiation frequency of castration-resistant prostate cancer cells from a patient undergoing palliative care for advanced metastatic disease[13]. It was estimated through limiting dilution that 0.04% of the cells in this tumour were capable of seeding a new tumour in mouse xenografts, but this subpopulation with cancer stem cell properties was depleted ~4-fold by ML-60218, most likely through differentiation[13]. Pol III may therefore be worth considering as a novel therapeutic target.

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Authors' contributions

Writing original draft: Malcolm JR

Conceptualization, review and editing: White RJ

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