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The third (III) road to cell transformation

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Oncogenic cell transformation is a multistep process that ultimately leads normal cells to become cancer cells. The road to tumorigenesis involves several changes at the cellular, genetic and epigenetic levels to finally confer an abnormal cell division phenotype to normally dividing cells. Several lab protocols have been published to infuse replicative immortality and anchorage-independent growth to normal cells in order to make them capable of forming *in vivo* tumor, to invade and ultimately metastasize: all hallmarks of tumoral transformation [1]. As cell division is tightly associated with cell growth, it has become increasingly clear that RNA polymerase (pol) III (one of the three nuclear RNA polymerases), responsible with its cognate transcription factors for transcription of a large number of non- protein coding RNAs (ncRNAs) acting at the core of protein homeostasis might become deregulated thereby playing an important role in the transformation process [2]. However, thus far only little was known about the different levels at which such a dysregulation might take place. In particular, while considerable effort has been put in dissecting the regulation of recruitment of the pol III machinery to target genes in response to cancer-related signaling pathways [3,4], the contributions to cancer of subtle changes in pol III transcriptome and epigenome are still unexplored.

Durrieu-Gaillard and colleagues [5] have been taking advantage of a previously published protocol [6] that they modified to implement a step-wise process of cell transformation of human fetal lung fibroblasts (IMR90) with defined genetic elements [5]. By expressing papilloma virus E6 and E7, SV40 small t-antigen, constitutive active RAS (RAS-G12V) and the catalytic subunit of the telomerase (TERT) they created 16 different cell lines which represent transformation intermediates of which 6 were chosen by the study as major representatives of the transformation process steps [5]. By employing transcript and protein level measurements the authors investigate the concentration changes for both components of the pol III machinery and selected pol III transcripts across the different steps of cell transformation. They report that albeit during cell transformation cellular levels of the major pol III transcripts did not change dramatically, the levels of several subunits of the pol III enzyme and its cognate transcription factors (namely TFIIIB, TFIIIC and PTF/SNAPc) significantly increased over the transformation process [5]. Therefore, the study for the first time provides an in-depth view on quantitative changes of the pol III machinery during the transformation process and identify potential targets for more precise cancer treatment in order to diminish the oncogenic potential of tumorigenic cells.

Importantly, the study also opens a new world of possible explorations with the creation of intermediate steps of cell transformation that, given their validation as a new experimental model for pol III dysregulation studies, can be potent tools to dissect genome-wide all the pol III-related transcriptome and epigenome changes involved in the initiation and maintenance of the oncogenic phenotype. Such a new tool is welcome, as recent work suggests that the pol III-dependent ways to cell transformation and cancer might be more numerous and diverse than previously thought. For instance, a recent study suggested a new role of specific tRNA-derived fragments (tRF) as a major source of pol II transcriptome regulation to favor a more or less metastatic phenotype [7]. By extensively mapping the pol III transcriptome, including tRFs, in parallel with the pol III machinery abundance and genome occupancy at each stage of the transformation process would allow to comprehensively characterize the molecular framework within which these tRFs ultimately might lead to a more aggressive phenotype. An even more fascinating scenario could be that changes in the pol III occupancy mirror those to favor expression of tRNAs harboring anticodons that complement codons more represented in cancer-associated transcripts [8]. Targeting transformation stage-specific tRNAs or tRFs might therefore help to set up and tune more precise clinical intervention.

Although the study by Durrieu-Gaillard et al. did not address one of the major pol III target in the human genome, namely Alu elements, it would be of extreme general interest to address how Alu transcription is affected during tumorigenesis, as several studies suggest a compelling and not marginal role of repetitive elements during the transformation process [9,10]. Moreover, some of the pol III-associated factors have been associated with extra-transcriptional functions. TFIIIC, a six multisubunit complex

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involved in pol III recruitment, has also been described as one of the few mammalian boundary-binding factors known so far [11]. It is tempting to speculate that perhaps changes in the levels of TFIIIC might also reflect in changes in 3D genome organization during the transformation process.

In conclusion, the study by Durrieu-Gaillard and colleagues [5] is a promising entry point into an extremely complicated phenomenon whose molecular elucidation will require further studies, and it represents a general benchmark in approaching an intricate cellular process such as oncogenic transformation. Most interestingly, this study discloses several future possible genomic investigations on the regulation of a nutrient-sensing machinery (such as pol III) that might ultimately enlighten our understanding of how normal cells become tumorigenic and consequently expand the roads of therapeutic interventions.

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