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Editorial

A Potential New Target Gene of the Master-Regulator Microphthalmia-Associated Transcription Factor in Melanoma

Suhu Liu, MD, PhD

Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

I read with great interest the recent manuscript by Ren et al[1] because their experience has many parallels with that of other research groups, including our own, that are currently examining the critical role of transcriptional factors and their target genes in cancer. I am particularly interested in and excited by the findings reported in this paper because progestagen-associated endometrial protein (PAEP) has not been previously identified as a downstream target gene for microphthalmia-associated transcription factor (MITF), a known master-regulator—determining the identity and properties of the melanocyte lineage—for melanoma.

As we all know, patients diagnosed with metastatic melanoma have a very poor prognosis because of multidrug resistance and novel molecular pathways that researchers are just beginning to fully understand. The development of melanoma begins with the malignant transformation of normal human epidermal melanocytes located within the skin's basement membrane. The basic helix-loop-helix MITF has been rightfully described as the master-regulator gene. It is a lineage-specific oncogene with a critical role in the pathogenesis of melanoma. As a transcriptional factor, MITF has the capacity to control melanocyte growth, survival, and differentiation by controlling the transcription of numerous other genes. Thus, the identification of target genes that are regulated by MITF is absolutely essential for understanding the mechanisms of melanoma oncogenesis.

Since the first description of MITF 16 years ago, more than 40 MITF-target genes have been reported.[2] Chromatin immunoprecipitation coupled to high-throughput sequencing (ChIP-seq) has become an important tool to further characterize the global binding sites and identify novel target genes of transcriptional factors. Most recently, Strub et al[3] have used this method and identified a novel set of genes regulated by MITF that are important for DNA replication, repair, and mitosis in melanoma.

Here, Ren et al[1] provide exciting new findings for a potential MITF-target gene, identified as the PAEP gene. From their original gene expression microarray data that analyze freshly procured, snap-frozen melanoma tissue, the researchers found that PAEP was one of the few genes highly expressed in advanced (metastatic) melanoma samples compared to early-stage (primary) melanomas. This finding has led to the explanation that significant differences exist in the gene expression levels of PAEP, strongly correlating with MITF transcript levels in these same tissue samples. To eliminate the influence of other cell types in tissue samples on gene expression, they used a series of short-term passaged melanoma cell lines derived from human melanoma tissue to validate the expression of PAEP and MITF, providing compelling corroborative results that strongly support the correlation between these two genes. Lastly, the knocking-down of MITF significantly reduced the mRNA and protein levels of PAEP, but the silencing of PAEP had no effects on MITF, further suggesting that PAEP is regulated by MITF.

What makes this work particularly unique and exciting is that the observed correlation between PAEP and MITF was derived directly from human melanoma tissue samples, making this finding readily relevant for translation into the clinical setting. Another unique feature of this work is the utilization of short-term in vitro passaged melanoma cells derived from surgical specimens instead of the standard melanoma cell lines that have been in cell culture for longer time periods. It would be interesting to see if this PAEP/MITF correlation can also be observed in those well-known, standard melanoma cell lines such as the A375, Lox, WM (Wistar melanoma), and SK-MEL cell lines that are often maintained in cell culture long term. If this PAEP/MITF correlation can only be observed in short-term cultured cell lines but not in long-term passaged melanoma cells lines, this difference will highlight the issue of biological correlations existing in vivo that may be lost after long-term in vitro cell culture. If this is the case, then the usage of melanoma cells freshly derived from tumor tissue will become particularly crucial in investigating these types of biological questions.

At this point, it is still uncertain whether MITF directly or indirectly regulates PAEP expression. Ren and colleagues[1] pointed out consensus-binding sequences within the PAEP promoter region. Thus, further experiments will need to be performed, such as chromatin immunoprecipitation, to determine whether MITF directly binds to the PAEP gene promoter or regulatory region. Nevertheless, the functional significance of PAEP gene overexpression in human melanoma has been strongly implicated in this study, with the silencing of PAEP expression resulting in the significant inhibition of melanoma cell migration, to an extent similar to that of MITF knock-down. Overall, this study adds to the developing drama of further defining and understanding melanoma progression and metastasis, with much more work needed to better understand the function and regulation of the PAEP in human melanoma.

REFERENCES

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