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Dear Dr. \_\_\_\_\_\_\_\_\_\_,

We are submitting a manuscript for your consideration titled:

**MYC oncogene promotes tissue-specific dedifferentiation gene expression changes in tumorigenesis**

Authors: **Delaney K. Sullivan, Anja Deutzmann, Maya S. Krishnan, Arvin M. Gouw, David I. Bellovin, Stacey J. Adam, Daniel F. Liefwalker, Renumathy Dhanasekaran, and Dean W. Felsher**

The MYC oncogene is frequently deregulated in cancer. To investigate how MYC drives tumorigenesis, our lab has developed multiple transgenic mouse models whereby MYC is overexpressed in a specific tissue of interest. We have previously shown that tumorigenesis can result whether MYC is overexpressed in liver tissue, kidney tissue, lung tissue, or lymphoid tissue. How a single oncogene can cause neoplastic transformation of such diverse tissue types is a question our lab has been highly interested in addressing. Here, we perform a thorough investigation of the gene expression changes which accompany MYC-driven tumorigenesis across multiple different tissue types.

Although many studies have identified MYC-regulated cancer pathways, it remains unclear whether MYC drives tumorigenesis through a common or tissue-specific set of genes. Approaches to identifying genes involved in MYC-driven tumorigenesis have been focused on one or two experimental cancer models even though MYC-regulated genes may be highly cell type-dependent. Here, we provide comprehensive evidence that, in tumorigenesis, the MYC oncogene primarily regulates gene expression in a tissue-specific manner. However, despite the tissue-specificity of MYC’s effect on gene expression, we found a common pattern that emerges. Specifically, MYC appears to drive gene expression changes that resemble tissue dedifferentiation. Our results provide novel mechanistic insight into the transcriptional changes involved in MYC-driven tumorigenesis.

Leveraging transcriptomic data from five transgenic MYC-induced autochthonous mouse tumor models, we analyzed genes differentially in tumorigenesis (comparing tumor vs. normal tissue). We discovered that MYC-driven tumors upregulate embryonic stem cell-like genes, especially ribosomal biogenesis genes, and downregulate genes abundantly expressed in the respective tissue-of-origin. Furthermore, analysis of histone modifications reveals epigenetic alterations in promoters and enhancers that are consistent with the gene expression changes in MYC-induced tumorigenesis. These epigenetic changes may, in part, facilitate a tissue state that allows these tissue-specific dedifferentiation gene expression changes to occur. We therefore propose a general model whereby MYC overexpression causes a new tissue state to form which puts the brakes on the normal tissue’s gene expression program while ramping up the expression of embryonic stem cell genes.

As part of our efforts to comprehensively characterize tissue-specific effects on gene expression in MYC-driven tumorigenesis, we generated novel microarray data in tumor tissue from MYC-driven autochthonous transgenic mouse models and have deposited the data in the Gene Expression Omnibus (GEO accession number: GSE143254; reviewer access token: qhybegamzzwjpar).

Potential reviewers include:

Dr. Chi Dang MYC biology and gene signatures

Dr. Bruno Amati MYC biology and functional genomics

Dr. Rosalie Sears MYC biology and signaling

Dr. Carla Grandori MYC biology and functional genomics

Sincerely



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