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Translational Implications of *GATA4* mutation and deletion in liver cancer

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Abstract: *MYC* is an ancient coordinator of cell growth and division and the most frequently amplified gene in cancer. This oncogenic role is well-established also in liver cancer, the 3rd leading cause of world-wide cancer deaths. Indeed, liver cancer in mice resolves when Myc is antagonized by genetic methods. However, MYC is also antagonized normally**:** explosive MYC-mediated proliferation of normal liver and other progenitors is effectively and predictably terminated by differentiation-related antagonists of MYC function. This suggests that liver cancer cells must not only activate MYC, but also suppress these physiologic MYC-antagonists. The pathways of such suppression are unknown. One possible pathway to suppression is genetic alteration of a key early-differentiation driving transcription factor, since with one such genetic event, multiple downstream proliferation-terminating differentiation genes can be simultaneously repressed by epigenetic means. In a collaboration between National Cancer Center Singapore and Cleveland Clinic/Case Western Reserve University, we discovered that *GATA4*, a transcription factor essential for hepatocyte maturation, is recurrently mutated (V267M) and deleted in 56% of liver cancers analyzed. Introduction of wild-type *GATA4* but not mutant *GATA4* into GATA4-deficient liver cancer cells restored expression of hundreds of liver differentiation genes, antagonized MYC function, and induced cell cycle exit even though p53 and p16/CDKN2A (master apoptosis mediators) were missing. Importantly, we were able to identify specific and drugable chromatin regulators that connect GATA4 loss to this reversible epigenetic repression of proliferation-terminating genes. In this way, a scientific rationale has been generated for evaluation and optimal application of specific chromatin regulator inhibitors, out of the many tens in development, for non-cytotoxic, p53-independent, treatment of HCC.

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