MYC and Metastasis

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Abstract

Aggressive primary tumors express transcriptional signatures that correlate with their metastatic propensity. A number of these signatures have been deployed in the clinic as risk stratification tools. However, the molecular basis of these clinically useful prognostic signatures has remained largely unresolved. We recently found that many prognostic signatures reflect the activity of the MYC oncogene, which in turn regulates tumor metastasis through specific effects on cancer cell invasion and migration. These findings offer a general framework for understanding the molecular basis of clinically useful transcriptional signatures and suggest potentially new avenues for studying metastasis.
expression of specific downstream programs. For example, MYC can regulate the epithelial-to-mesenchymal transition (EMT) that is necessary for cellular invasion and migration in some contexts. MYC does this by promoting TGFβ-mediated activation of the SNAIL transcription factor, both directly and indirectly through a microRNA network involving a LIN28B/let-7/HMGA2 cascade (Fig. 1; refs. 16–22). Importantly, however, we found that RNA interference (RNAi)–mediated MYC knockdown in highly metastatic MDA-MB-231 breast cancer cells disrupts cellular invasion, migration, and metastasis in vivo, independent of effects on EMT. This suggests that MYC may also regulate metastasis-promoting mechanisms beyond EMT (5). Consistent with this idea, MYC can regulate cell–cell–matrix interactions through transcriptional activation of LGALS1, which is a β-galactosidase–binding protein that promotes cell migration and invasion (23). Similarly, OPN is a MYC-regulated integrin-binding ligand that has been widely implicated in stimulating cancer cell migration and invasion (24, 25). MYC also cooperates with SKP2 to recruit MIZ1 and p300 into a transcriptional complex that activates RhoA, which is necessary for migration, invasion, and lung metastasis in vivo (26). In addition, MYC repression of ID2 inhibits expression of the secreted protein SEMA3F, which has been found to increase cell migration and invasion through RhoA activation and modulation of the actin cytoskeleton (Fig. 1; refs. 27–29). Clearly, more work is needed to comprehensively understand all MYC transcriptional targets that can directly contribute to metastasis.

Although MYC is necessary for the invasive and metastatic behavior of cancer cells, it seems to be insufficient (5, 26). Furthermore, MYC promotes but, paradoxically, can also retard migration depending on cell type (30). These and other
observations suggest that MYC likely cooperates with other genes (particularly RAS pathway components) to promote both the early (e.g., invasion and migration) and late (e.g., seeding) phases of metastatic progression (15, 31–33). Systematic and unbiased approaches should increasingly reveal the spectrum of cellular and molecular contexts in which MYC promotes distant metastasis. Furthermore, MYC-driven primary tumors seem to remain dependent on this oncogene even after becoming established (34). If MYC-driven metastatic tumors also remain dependent (currently, an unanswered question), then strategies to target MYC in cancer patients with advanced disease may prove to be clinically useful.

Beyond direct transcriptional regulation of metastasis-relevant target genes, MYC may also play a more global role in regulating the metastatic phenotype. MYC is a powerful cellular reprogramming factor that determines normal and cancer cell differentiation (35). Presumably, cancer cells in an undifferentiated, more stem cell–like state might more easily migrate to and seed distant sites. Along these lines, MYC regulates the expression of different stem cell–associated transcriptional profiles (5, 33). How MYC regulates cellular differentiation is still not completely clear. However, genome-wide chromatin immunoprecipitation (ChIP) profiling studies have recently shown that MYC binds widely across the human genome (36). Other recent studies also suggest that MYC-directed transcriptional complexes containing histone-modifying enzymes may, in part, promote cellular reprogramming by uniquely inducing genome-wide changes in chromatin conformation (36–39). These findings suggest a fascinating but still speculative model. Perhaps MYC contributes to metastasis by globally altering the epigenomic landscape of cancer cells, thus providing a permissive molecular context in which additional, cooperative molecular alterations can specifically promote different aspects of the metastatic phenotype. If this speculative model proves to be correct, a deeper understanding of MYC complexes that promote metastasis in this way may provide new opportunities to target this important but currently “undruggable” cancer pathway. Further work will be required to fully explore this model.

Disclosure of Potential Conflicts of Interest

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