restabilization of IκBα after NF-κB activation, apparently through recruiting the protein to the CSN-associated deubiquitylating enzyme USP15. Whether this mechanism is also at play in CSN-mediated Snail stabilization remains to be investigated (Figure 1). Likewise, future work will be required to clarify the role, if any, of CSN-mediated cullin deneddylation in Snail stabilization. For example, one wonders whether the Snail stabilizing activity of CSN5 depends on the integrity of its JAMM metalloprotease domain. The finding that CAND1 is required for CSN2-induced Snail accumulation is intriguing in this regard, but difficult to reconcile with other reports demonstrating that, in vivo, CAND1 behaves as an activator of CRLs (Zheng et al., 2002), although this has not been established for $SCF^{\beta\text{-}TRCP}$. Based on the data available to date, it appears that preventing Snail phosphorylation is the primary role of the CSN in Snail stabilization.

Regardless of the exact mechanism, the current study deepens the link between inflammation and metastasis and introduces the CSN as a further player in these processes. The new findings also provide initial mechanistic insight into the emerging connection between CSN activation and tumorigenesis (Adler et al., 2008).

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YB-1 Translational Control of Epithelial-Mesenchyme Transition

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Transitions between epithelial and mesenchmal phenotypes play critical roles in normal development and cancer progression. In this issue of *Cancer Cell*, Evdokimova et al. demonstrate that YB-1 regulates epithelial-mesenchyme transition (EMT) by inducing cap-independent translation of mRNAs encoding EMT-promoting factors and suppressing cap-dependent translation of mRNAs encoding growth-promoting factors.

Metastasis is a multistep process that mediates the spread of cancer cells from primary tumors to distant sites. This process relies on structural and phenotypic changes that enable tumor cells to dissociate from the tumor mass, invade the surrounding tissue, intravasate into vascular or lymphatic vessels, and extravasate and proliferate at a secondary site. An increasing number of reports provide evidence that epithelial cancer cells adopt embryonic transcription programs during the invasive phase of metastasis, which allow them to suspend some or all of their epithelial properties and acquire those of mesenchymal cells (Thiery and Sleeman, 2006; Yilmaz and Christofori, 2009). This epithelial-to-mesenchymal transition (EMT) is associated with changes in cell-cell adhesion, remodeling of cell-matrix adhesion, and enhanced migratory activity. Several transcription factors have been implicated in this transition, including Snail, Slug, Zeb1, and Twist. The canonical Ras pathway has also been shown to play a crucial role in EMT in certain contexts. Ras activity, however, is not sufficient to induce EMT; other factors collaborate with Ras to orchestrate this process (Thiery, 2003). The relevance of EMT as an integral and obligate phase of cancer cell invasion/metastasis in vivo is controversial; in fact, several cancer cell types are able to invade by adopting modes of migration that don't involve an EMT, such as collective or amoeboid (Friedl et al., 2004). Nevertheless, an increasing body of evidence demonstrates the occurrence of EMT in tumor cell subpopulations during the progression of certain types of cancers (Yilmaz and Christofori, 2009; Polyak and Weinberg, 2009), and a recent study

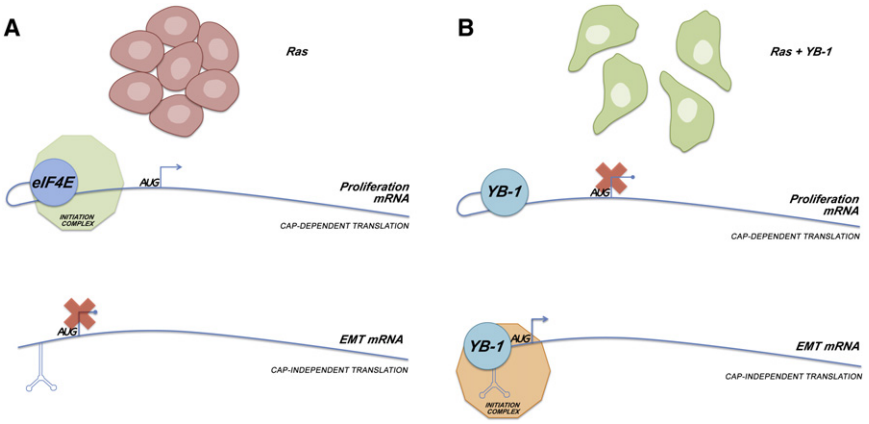

Figure 1. Model for EMT Translational Control by YB-1
EMT in Ras-transformed cells is dependent on two events.
(A) Transcription of genes that induce EMT and promote proliferation.
(B) YB-1 suppression of the translation of proliferation genes (suppression of cap-dependent translation) and induction of the translation of EMT genes (induction of cap-independent translation).

shows that EMT in vivo might be particularly important for a subset of tumors, especially for those with basal phenotype (Sarrio et al., 2008).

In this issue of *Cancer Cell*, Evdokimova, Sorensen, and colleagues identify YB-1 (Y-box binding protein-1) as a new player in the regulation of EMT through a novel mechanism involving translation of cap-independent mRNAs encoding Snail and other EMT regulators in Ras-transformed cells (Evdokimova et al., 2009). YB-1, a DNA/RNA-binding protein with a conserved cold-shock domain, has been implicated in tumor progression; however, the exact role of YB-1 in this process is ambiguous since it has been described as both a tumor suppressor and an oncogene. YB-1's activity as a transcriptional activator in the nucleus has been reported to be protumorigenic: YB-1 induces proliferation by activating progrowth genes through binding to the Y-box elements in their promoter region (Evdokimova et al., 2006). In contrast, in the cytoplasm, YB-1 can silence translation through binding to the 5′ terminus of mRNAs with extensive 5′ UTR secondary structures, thus outcompeting the eIF4E initiation complex (Evdokimova et al., 2006). Many of these YB-1-silenced mRNAs encode growth-related proteins and are dependent on 5′ cap-binding proteins for initiation of translation. Hence, YB-1 can suppress growth and proliferation and has been described to possess tumor suppressor properties (Evdokimova et al., 2006).

In this issue's report, YB-1 is described as a crucial factor in the initiation of the translation of a set of cap-independent mRNA transcripts. Microarray analysis of translationally active and inactive mRNAs identified several known EMT-regulatory factors, including the transcription factors Snail1 and Twist, that were differentially translated in Ras-transformed cells. The authors further demonstrated that YB-1 overexpression could increase Snail1 protein expression and induce subsequent EMT. The 5′ UTR of Snail1 mRNA is predicted to form highly stable stem-loop structures with conserved nucleotides, resembling the structure of internal ribosome entry sites (IRES), which mediate cap-independent translation initiation directly activated by YB-1 binding. In parallel, YB-1 overexpression in Ras-transformed human breast epithelial cells suppressed translation of transcripts involved in cell proliferation and induced proliferation arrest. Hence, YB-1 plays a dichotomous role in translational regulation: it suppresses the cap-dependent translation initiation of progrowth mRNAs and promotes the cap-independent translation initiation of EMT-inducing mRNAs, the transcription of which is induced by sustained Ras-Erk activation.

Therefore, EMT induction in Ras-transformed cells involves two steps: (1) Ras induces the transcription of EMT-mediating factors (including Snail 1 and Twist) and (2) YB-1 induces the translation of these factors concomitant with the suppression of the expression of growth related transcripts (Figure 1). While the studies in this report involved analysis of tumor cells expressing an H-Ras oncogene, it is predicted that YB-1 could collaborate with other genes that promote transcription of EMT-regulatory mRNAs.

These studies highlight the critical role of YB-1 in the coordinated induction of both EMT and proliferation arrest. Interestingly, an invasion "signature," derived by analysis of mRNAs from invading cells associated with mouse and rat tumors, exhibited an increase in the expression levels of genes that induce migration and suppress proliferation and apoptosis and a decrease in the expression levels of genes that promote proliferation (Condeelis et al., 2005); this change in gene expression is consistent with a coordination of invasive behavior and proliferation arrest. The dormancy of invading cells, moreover, could contribute to the failure of most tumor cells to expand at secondary sites. YB-1 expression could arrest proliferation of metastatic cells through silencing of translation of mRNAs required for proliferation. If such a mechanism takes place, release from dormancy may involve inactivation of YB-1 translational regulation. Akt phosphorylation of YB-1 has been shown to inhibit YB-1 binding to the 5′UTR cap (Evdokimova et al., 2006). Thus, this phosphorylation event is predicted to promote proliferation by releasing the YB-1 imposed block on the translation of growth-regulatory genes. Interestingly, it has been suggested that the escape from dormancy at metastatic sites is contingent on the reversal of EMT in a mesenchymal-to-epithelial transition (MET) (Chaffer et al., 2007; Polyak and Weinberg, 2009).

Another interesting finding in this report is that YB-1 regulates expression of several progenitor cell markers (upregulation of p63, CD44, and CD10, and downregulation of CD24). This is consistent with recent studies that indicate a link between EMT and acquisition of stem/progenitor cell properties (Polyak and Weinberg, 2009). Together, these studies support the notion that tumor cells undergo dedifferentiation through EMT. During metastatic progression, this dedifferentiated mesenchymal state could revert back to an epithelial state (MET) upon expansion at secondary tumor sites. According to this scenario, cancer cells that metastasize could be derived from primary site

epithelial tumor cells that underwent a transient dedifferentiation associated with EMT rather than cancer stem cells that pre-exist as a subpopulation of the primary tumor. YB-1 gain or loss of translational control could potentially be involved in the regulation of both EMT and MET, respectively.

These studies raise the question: is YB-1 a target for therapeutic intervention in metastasis? As the authors point out, direct targeting of YB-1 might prove to be futile or even counterproductive since YB-1 could be an important factor in keeping cells dormant after they metastasize.

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Agonizing Integrin Antagonists?

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A recent study published in *Nature Medicine* reports that low-dose treatment with RGD-mimetic integrin inhibitors may paradoxically enhance angiogenesis and tumor growth. This work implies that delivery of these agents should be redesigned in order to avoid nanomolar plasma concentrations and to improve their efficacy to treat human cancers.

Integrins mediate cell-cell and cell-matrix interactions to "integrate" extracellular cues with intracellular signaling pathways and to promote a wide array of biological responses. During development, tissue remodeling, and in various disease conditions, integrin-mediated cell migration/invasion occurs via transient binding and release of the extracellular matrix (ECM). Thus, local microenvironments containing substrate and soluble protein fragments provide situational cues to integrins which guide cell behavior. Several integrins, including $\alpha v\beta 3$ and $\alpha v\beta 5$, recognize the arginine-glycine-aspartic acid (RGD) sequence shared by a number of extracellular matrix ligands. Accordingly, RGD-mimetic peptides or small molecules bind to these integrins on the surface of cells to block specific αv integrin-mediated signaling pathways and act as anticancer and antiangiogenic agents.

Reynolds and colleagues recently reported in *Nature Medicine* that low nanomolar concentrations of RGD mimetics may actually stimulate tumor growth and angiogenesis (Reynolds et al., 2009). These conclusions were drawn from examination of B16F0 melanoma or LLC lung carcinoma cells grown on the flanks of syngeneic C57BL6 mice treated systemically with a cyclic RGD peptide (cilengitide) or a small molecule RGD mimetic (S 36578). Since the RGD mimetics did not increase tumor growth or vascularization in integrin $\beta 3/\beta 5$ double knockout mice, the authors concluded that low doses of integrin antagonists promoted tumor growth by acting on host endothelial cells. While these findings may seem surprising, several independent groups reported in the early 1990s that nanomolar concentrations of soluble ECM proteins could induce chemotaxis (Aznavoorian et al., 1990) and that the chemotaxis induced specifically by RGD-containing fibronectin fragments could be overcome by millimolar concentrations of RGD-containing peptides (Odekon et al., 1991). As a rationale for their experiments, Reynolds et al. also pointed to work by Legler and coworkers who found that cyclic RGD-peptides have a biphasic effect on $\alpha v\beta 3$, with an antagonistic phase at high concentrations and an agonistic phase at low concentrations (Legler et al., 2001). Thus, it has been known for years that low concentrations of soluble antagonists will agonize or "superactivate" (Legler et al., 2001) integrins (Figure 1). Nonetheless, in their new study, Reynolds et al. have extended these previous findings to confirm that integrin activation by low-dose antagonists does occur in endothelial cells and may be relevant for angiogenesis among subcutaneously growing tumors.

The authors commented in the paper that integrin antagonism as an antiangiogenic therapy has been largely unsuccessful in man and that any observed efficacy is probably due to direct action on tumor cells. While it is generally true that many antiangiogenic strategies for cancers have performed below