expression in cancer may be yet another possibility. For example, IL-11 is known to be regulated by STAT3, oncogenic insults, and hypoxia that are constantly present in the tumor microenvironment, thereby allowing prolonged IL-11 production, whereas IL-6 production by immune cells may be more tightly and spatially regulated. A recent study suggests that CAC tumorigenicity depends on IL-6R produced by epithelium in mice with altered colonic microbiota (Hu et al., 2013). Adding to the mix, there are other STAT3-activating cytokines beyond IL-6 and IL-11, such as IL-22, that also can regulate CAC and CRC development (Huber et al., 2012).

The work by Putoczki et al. (2013) expands our understanding of the role that cytokine-induced signaling plays in cancer and warrants further examination of the modalities of IL-11 inhibition in various solid tumors. Given that another recent study identified the IL-11/STAT3 pathway as a critical regulator of human CRC invasion and metastasis (Calon et al., 2012), it is safe to conclude that IL-11 constitutes an important component of the tumor microenvironment, influencing every step of tumorigenesis and representing an attractive target for preventive and therapeutic approaches.

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HSF1 in Translation

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The master regulator of the classical cytoprotective "heat shock" response, heat shock factor 1 (HSF1), is increasingly implicated in cancer pathogenesis, but the mechanisms remain poorly understood. A recent study connects increased protein translation to activation of HSF1 in malignant cells and demonstrates the therapeutic benefit of targeting this link.

It is fast becoming clear that the stress-activated transcription factor heat shock factor 1 (HSF1) is not only the master regulator of the classical heat shock response and "guardian of the proteome," but is also a key player in aging and oncogenesis (Anckar and Sistonen, 2011). The well-known activation of HSF1 by elevated temperature or other acute proteotoxic stressors leads to increased transcription of genes involved in protein quality control, thereby allowing cells to survive the stress. The emerging role of HSF1 in oncogenesis is best exemplified by *Hsf1*-knockout mice having reduced susceptibility to tumorigenesis driven by oncogenic Ras or mutant p53 (Dai et al., 2007). Accumulation and activation of nuclear HSF1 is triggered by diverse cellular or environmental stresses associated with cancer. These include proteotoxic stress or oncogenic stress (Dai et al., 2012a, 2012b).

Recent research unexpectedly revealed an HSF1 gene expression program in cancer cells distinct from, though overlapping with, the transcriptional profile in the classical heat shock response (Mendillo et al., 2012). The HSF1 cancer program comprises not only genes encoding proteins mediating proteostasis and survival, but also those facilitating invasion and metastasis, cellular proliferation, protein synthesis, and glucose metabolism. Importantly, the HSF1 cancer gene signature correlates strongly with metastasis and survival in breast, colon, and lung cancer patients.

Despite recent progress, the precise molecular details of how HSF1 is activated in cancer are poorly understood.

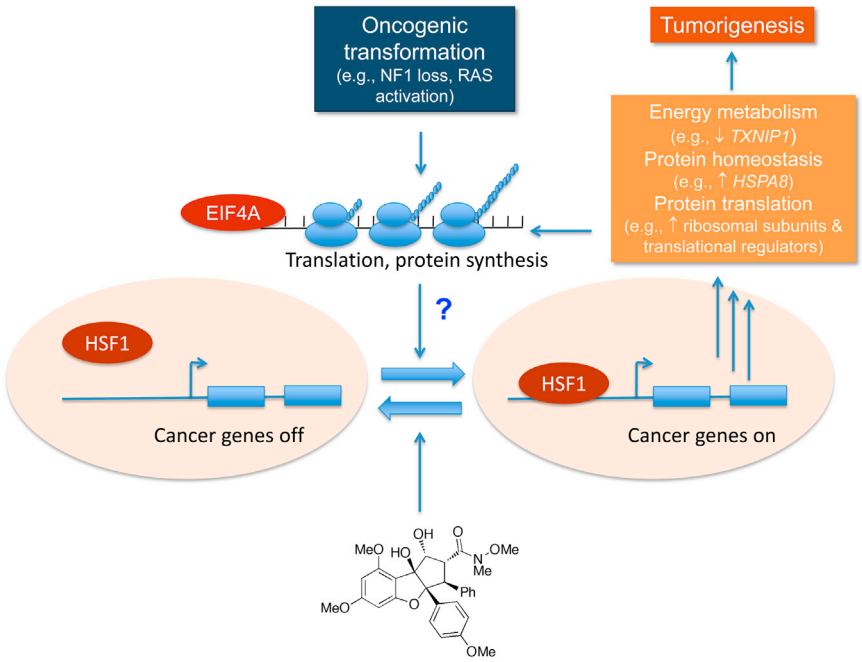

Figure 1. Linking Protein Translation to the HSF1 Transcriptional Response

Oncogenesis, such as that induced by the loss of NF1 or activation of RAS, induces protein synthesis by increasing the activity of the translation machinery. This boost in protein synthesis induces, by a currently unknown molecular mechanism (indicated by the blue "?"), the binding of HSF1 to the promoter of the cognate cancer-associated genes, thereby altering the transcription of these genes. The HSF1 cancer program includes genes involved in energy metabolism, protein homeostasis, and protein translation. Blocking translational initiation, exemplified by inhibition of EIF4A using rohibitin, reverts HSF1 activation and switches off the HSF1 cancer program, resulting in the inhibition of the growth of cancer cells in vitro and tumors in vivo.

Now, Santagata et al. (2013) report the important discovery that regulation of HSF1 transcriptional activity is tightly linked to protein translation rate and suggest a model in which HSF1 responds to the enhanced protein production in cancer by remodeling the transcriptional program to support the anabolic malignant state. Furthermore, they provide proof of concept for reversing this process with small-molecule inhibitors of protein translation for potential therapeutic application (Figure 1).

Santagata et al. (2013) used an interesting chemical-genetic approach. First, they conducted gene expression profiling of breast cancer cells exposed to translation elongation inhibitors. The most enriched mRNAs corresponded to genes with promoters containing HSF1-binding motifs, which were validated by promoter occupancy analysis and include both those associated with classical heat shock and those in the HSF1 cancer program. Thus, protein translation is linked to HSF-1-mediated transcription and oncogenesis.

Next, the researchers determined a gene signature of HSF1 silencing and looked for close matches in a public database. Best negative correlations were with expression profiles for proteasome and HSP90 inhibitors, validating the approach because both activate HSF1. Significantly, they also found the HSF1 knockdown gene signature to be positively correlated with the expression profile of cells treated with protein translation inhibitors and PI3K/mTOR inhibitors, which are known to block translation. Moreover, the most enriched gene ontology classes seen are ribosomal subunit proteins, translation initiation factors, and aminoacyl tRNA synthetases. The results provide independent confirmation of the connection between translational flux and HSF1 function in cancer.

Santagata et al. (2013) then screened a compound library looking for small molecules that inhibited a cell-based HSF1 reporter selectively. The most potent and selective hit identified was rocaglamide A, a natural product of the flavagline class that includes silvestrol. Silvestrol binds to the EIF4A RNA helicase, trapping it in a complex with RNA and thereby impairing the early stage of protein synthesis initiation mediated by the EIF4F complex (Sadlish et al., 2013). By screening analogs, Santagata et al. (2013) identified an even more potent synthetic inhibitor, rohibitin. They showed that rohibitin does not affect HSF1 levels, but blocks both HSF1 binding to DNA and the HSF1-regulated gene expression program across histologically diverse human cancer cell lines, with lesser effects in non-tumorigenic cells. Genes affected by rohibitin include both classical heat shock genes and genes specific to the HSF1 cancer program, but not two control housekeeping genes. These results identify rohibitin as an upstream inhibitor of HSF1 activity and once more confirm the connection between HSF1 regulation and protein translation in cancer.

Santagata et al. (2013) proceeded to demonstrate that rohibitin inhibits glucose uptake and reverts the cancer-associated aerobic glycolysis ("Warburg effect") characteristic of cancers, which is already associated with HSF1. These metabolic changes were attributed to the transcriptional modulation of HSF1-regulated genes directly known to control energy metabolism.

Seeking more defined therapeutic contexts, Santagata et al. (2013) assessed the sensitivity to rohibitin using isogenic models with different oncogenic lesions. They found rohibitin to be more active in mouse embryo fibroblasts lacking the NF1 tumor suppressor compared with wild-type counterparts. Consistent with HSF1 function in regulating survival through increased chaperone expression in aneuploid cancer cells (Kim et al., 2009), they found rohibitin to be more potent against aneuploid cells compared to near-diploid cancer cells and healthy cells. Interestingly, inhibiting translation initiation with rohibitin proved more "cancer-selective" than blocking translation elongation with cycloheximide in these models. Cancer selectivity was confirmed in broader cell panel profiling. Finally, Santagata et al. (2013) demonstrated impressive antitumor activity for rohibitin in vivo by using a sensitive acute myeloid leukemia cell line growing as a tumor xenograft in immunocompromised mice. Modulation of HSF1-regulated genes and glucose

uptake again supported an HSF1-mediated mechanism and represented potential biomarkers for future translational studies.

Overall, Santagata et al. (2013) have established an important regulatory link between the translation pathway and HSF1 that allows cancer cells to reprogram the cancer transcriptome to accommodate the essential increase in protein production, including the switch to aerobic glycolysis required to meet the biosynthetic needs of malignant growth, especially the massive energy demands of translation. Furthermore, targeting translation initiation with rocaglates blocks HSF1 activation via EIF4 inhibition and thereby reverses malignant transcriptional reprogramming, disables the glycolytic switch, removes cytoprotective chaperones, and inhibits tumor growth.

So what is next? There remain many unanswered questions. What is the precise molecular mechanism that links protein translation to HSF1 activation? Does it involve the translation of a factor required for HSF1 activity? Might it involve the production of a key protein involved in one of the many posttranslational modifications regulating HSF1? Does blocking the translation of oncogenic mRNAs with long highly structured 5′UTRs that require EIF4A-dependent unwinding contribute to the anticancer effects seen? Intriguingly, the results obtained here for cancer cells contrast those in yeast where the HSF1-mediated stress response is activated by the translational stress resulting from stalled rather than enhanced protein synthesis (Brandman et al., 2012). Coordinating the malignant proteome and transcriptome likely involves a highly complex network of interactions of which HSF1 is but one—albeit very important—regulatory element. It would be fascinating to know how the reported effects connect with another critical proteostasis pathway hijacked in cancer: the unfolded protein response in which inadequate protein folding leads to the beneficial reprogramming of translation and transcription to promote survival. Other key questions include: why does inhibition of protein initiation deliver a more selective anticancer effect than blockade of protein elongation? How might cancer cells develop resistance to EIF4A inhibition? Global proteomic analysis could be used alongside transcriptome profiling to ask whether a subset of proteins is regulated as opposed to a global effect.

Although inhibiting translational initiation appears to be a promising approach, it is clear that the effects will be very pleiotropic. Ongoing research will continue to reveal the proximal regulators of the multifaceted and megalomaniac functions of HSF1 in cancer. This could help us to develop a range of yet more selective inhibitors of HSF1 function. Given the widespread resistance seen with drugs targeting single oncogene addiction and synthetic lethality (Al-Lazikani et al., 2012), new therapeutics selectively targeting such essential regulators of core malignancy programs like HSF1 are urgently needed.

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