

Structurally Diverse Chemicals Produced by Microorganisms and Plants

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Description

Natural products are a group of bioactive structurally diverse chemicals produced by microorganisms and plants. These molecules and their derivatives have contributed to over a third of the therapeutic drugs produced in the last century. However, over the last few decades traditional drug discovery pipelines from natural products have become far less productive and far more expensive. One recent development with promise to combat this trend is the application of synthetic biology to therapeutic natural product biosynthesis. Synthetic biology is a young discipline with roots in systems biology, genetic engineering, and metabolic engineering. In this review, we discuss the use of synthetic biology to engineer improved yields of existing therapeutic natural products. We further describe the use of synthetic biology to combine and express natural product biosynthetic genes in unprecedented ways, and how this holds promise for opening up completely new avenues for drug discovery and production.

Head and Neck Cancers Encompass

Head and neck cancers encompass a heterogeneous group of tumors in the upper aerodigestive tract; the main type is oral squamous cell carcinomas (OSCCs), which arise primarily in the oral cavity. OSCC has a propensity to metastasize through lymphatics to regional lymph nodes. Cancer cells establish a myriad of interactions with components of their microenvironment, including vascular endothelial cells, infiltrating immune cells, and fibroblasts. The tumor microenvironment (TME) greatly influences cancer cell growth and invasion, immunogenicity, and even drug resistance. Via a complex network that includes secreted growth factors/cytokines and the extracellular matrix, cancer cells modify their stromal neighbors, which in turn impact tumor growth, metastasis, and response to therapy. Changes in the TME and immune surveillance represent a crucial hallmark of various types of cancer including OSCC. Understanding how cancer cells produce factors that exert autocrine and paracrine effects on cancer progression is important for the development of targeted therapies.

Tumor-associated macrophages are abundant tumor-infiltrating immune cells in the TME and contribute to lymph node metastases and poor prognosis of OSCC. We first examined whether DDX3 modulates macrophage differentiation of human monocytic THP-1 cells. SAS cell CM induced the expression of macrophage marker genes (IL1B, IL23A, MAF, and VEGFA) in THP-1 cells; knockdown of DDX3 or AREG reduced this activity by ~50–80% (CM/shD and CM/shAREG). However, the observation that rAREG was insufficient to induce macrophage gene expression indicated that AREG-induced factors in SAS cells rather than AREG itself promoted macrophage differentiation. Because M2-polarized tumor-associated macrophages in general promote tumorigenesis, we evaluated whether the DDX3-AREG pathway promotes M2 differentiation. We first observed that SAS cell CM could induce M2 marker (CD163, IL10, and MRC1) expression in phorbol ester-primed THP-1 cells in a DDX3-dependent manner. On the other hand, phorbol ester-primed THP-1 cells expressed a higher level of M1 markers (HLADR, IL12B, and IL18) in DDX3 knockdown SAS CM than that of control CM. Because M2 macrophages have angiogenic potential, we then functionally examined whether SAS CM-primed THP-1 cells could induce angiogenesis. Indeed, CM of the aforementioned primed THP-1 cells efficiently induced tubularization of EA.hy926 cells, whereas the CM of THP-1 that had been cultured in DDX3-depleted SAS CM was incapable of doing so. This result implied that the DDX3-AREG axis can potentiate THP-1 differentiation into M2 macrophages.

Translation of AREG

The above result that DDX3 may regulate the translation of AREG via 3' UTR-mediated translation control prompted us to identify its interacting partners that participate in the expression of secreted proteins. We performed immunoprecipitation of endogenous DDX3 from SAS cells and analyzed the coprecipitates using mass spectrometry. After RNase digestion, coprecipitates were fractionated by electrophoresis. Thirteen visible bands were subjected to mass spectrometry analysis. In total, 444 proteins were identified, and the 10 non-redundant proteins with the highest scores for each band are listed in Table S2. Gene

Ontology analysis revealed enrichment of DDX3-interacting proteins in translation initiation and SRP-dependent cotranslational protein targeting to the membrane. Using the technique “stable isotope labeling by amino acids in cell culture” followed by Gene Ontology analysis, we identified a similar set of DDX3-interacting partners. We knocked down 22 candidate genes that are involved in mRNA processing and translation using shRNA and observed that depletion of SRP components (SRP9 and 68) reduced the translation of the AREG 5'+3' UTR reporter to a level comparable to that of DDX3 knockdown. Further examination revealed that depletion of either SRP component compromised the translation but not mRNA level of the 3' UTR reporter, whereas it had no effect on the 5' UTR reporter.

All these SRPs were also required for the expression of endogenous AREG. We deduced that DDX3 acts in conjunction with the SRP in 3' UTR-mediated translation control.

Many of the cancer-associated mutations of DDX3, however, result in altered protein function rather than a loss of function. In TCGA PanCancer Atlas database, six missense mutations of DDX3 were identified among 523 HNSCC samples. Interestingly, three mutations exclusive to OSCC tumors occur at the negatively charged amino acids around the C-terminal region of the RNA helicase domain, including D521H, D558H, and E572Q.