tissue-exudative EV (Te-EV) from patient samples ex vivo to quantify the differences in their role. Here, Ikeda and colleagues use proteomics to characterize the cargoes of these EV and identify 25 novel fusion products among the human and canine samples. Though the fusions were themselves non-recurrent, they co-occurred alongside recurrent mutations in TP53, PIK3CA, PIK3R1, and NRAS, suggesting that genomic instability induced by these mutations may play a role in the genomic complexity of the disease. Further, the novel fusions were uniformly associated with increased angiogenic signaling, indicating that diverse genomic events in AS likely converge on the activation of a specific transcriptional program. Taken together, the data nominate a host of new molecular targets for investigation and clarify a unifying role for diverse genomic events in the pathogenesis of AS.

**CAT1+ EVs Promote Angiogenesis in CRC**

Ikeda et al. | Page 834

Extracellular vesicles (EV) have emerged as a key mediator of intercellular signaling and have been linked to the pathogenesis of cancer. EV are loaded with different "cargo" depending on their source, and the characterization of these cargoes is important to understanding and contextualizing their role. Here, Ikeda and colleagues use proteomics to quantitatively probe the differences between EV from cancerous versus normal colon. Employing an ex vivo method for harvesting tissue-exudative EV (Te-EV) from patient samples, the authors find that the amino acid transporter CAT1 is enriched in Te-EV from colorectal cancer (CRC). CAT1-positive EV were found at higher abundance in the plasma of CRC patients. Though the fusions were themselves non-recurrent, they co-occurred alongside recurrent mutations in TP53, PIK3CA, PIK3R1, and NRAS, suggesting that genomic instability induced by these mutations may play a role in the genomic complexity of the disease. Further, the novel fusions were uniformly associated with increased angiogenic signaling, indicating that diverse genomic events in AS likely converge on the activation of a specific transcriptional program. Taken together, the data nominate a host of new molecular targets for investigation and clarify a unifying role for diverse genomic events in the pathogenesis of AS.

**IAPP Is Required for Oncogene-Induced Senescence**

Garnett et al. | Page 874

Oncogene signaling is a potent driver of tumorigenesis and progression, but cells inherently resist oncogenic transformation via feedback loops leading to cellular senescence. Understanding how oncogene-induced senescence (OIS) is subverted by tumors is critical to the development of new methods to clinically manage cancers driven by BRAF- and RAS-activating mutations. Here, Garnett and colleagues employ a genetic screen to identify mediators of OIS in the context of BRAF activation. The authors found that Amylin, a 37-amino acid peptide that promotes glycolysis, is a key mediator of OIS. Amylin-ablated cells underwent a series of metabolic and epigenetic changes that circumvented senescence. Understanding how oncogene-induced senescence (OIS) is subverted by tumors is critical to the development of new methods to clinically manage cancers driven by BRAF- and RAS-activating mutations. Here, Garnett and colleagues employ a genetic screen to identify mediators of OIS in the context of BRAF activation. The authors found that Amylin, a 37-amino acid peptide that promotes glycolysis, is a key mediator of OIS. Amylin-ablated cells underwent a series of metabolic and epigenetic changes that circumvented senescence. Understanding how oncogene-induced senescence (OIS) is subverted by tumors is critical to the development of new methods to clinically manage cancers driven by BRAF- and RAS-activating mutations. Here, Garnett and colleagues employ a genetic screen to identify mediators of OIS in the context of BRAF activation. The authors found that Amylin, a 37-amino acid peptide that promotes glycolysis, is a key mediator of OIS. Amylin-ablated cells underwent a series of metabolic and epigenetic changes that circumvented senescence. Understanding how oncogene-induced senescence (OIS) is subverted by tumors is critical to the development of new methods to clinically manage cancers driven by BRAF- and RAS-activating mutations. Here, Garnett and colleagues employ a genetic screen to identify mediators of OIS in the context of BRAF activation. The authors found that Amylin, a 37-amino acid peptide that promotes glycolysis, is a key mediator of OIS. Amylin-ablated cells underwent a series of metabolic and epigenetic changes that circumvented senescence.

**ERBB2 and BCL2 Inhibition in MDS and AML Cells**

Kam et al. | Page 886

Acute myeloid leukemia (AML) is a genetically diverse cancer with over ten different molecular subtypes characterized by specific genomic events. EGFR pathway signaling has also been described in AML cells, but most AML cells paradoxically do not express any EGFR family members on the cell surface. In this study, Kam and colleagues address this discrepancy and identify intracellular expression of truncated ERBB2 isoforms in AML cells and myelodysplastic syndrome, an AML precursor lesion. These ERBB2 isoforms—which are also known to be pathogenic in breast cancer—mediated active signaling via classical EGFR-related pathways and were sensitive to inhibition with ERBB2 tyrosine kinase inhibitors. While ERBB2 inhibition was effective as a single agent, combination of the ERBB2 inhibitor lapatinib with the BCL-2 inhibitor venetoclax resulted in marked synergism at all tested doses. These observations nominate ERBB2 inhibitors for further investigation to complement the growing arsenal of therapeutic options for AML patients.