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The dichotomy of the TGF-β pathway in inflammation, tumor suppression or metastases remains elusive. We analyzed TGF-β pathway across all 33 TCGA (The Cancer Genome Atlas) tumor types and 9125 samples to address this question. Our studies provide new insight into how this pathway is regulated across multiple cancer types in TCGA. We comprehensively catalogued 140 TGF-β pathway-related genes that are involved in cancer. We found that 41% of all samples have at least one genomic alteration in the TGF-β pathway predominantly as mutations. Genome wide mutation and CNV analysis suggests that most of those aberrations are due to mutations rather than CNVs. Gastrointestinal cancers have the highest alteration frequencies and are enriched for mutational hotspots, whereas renal and brain cancers show fewer aberrations. We found hotspots in six genes, including the newly identified hotspots on TGFBR2, AVCR2A and BMP5. mRNA transcriptomic analyses revealed three clusters of expression, increased, decreased or not altered in multiple cancers, with altered expression conferring significantly decreased survival in some cancers. Epigenetic and miRNA analyses showed that although both the first two clusters (altered levels of the pathway members) play key roles in regulating the pathway, the balance of power between them these is highly dependent on tumor type. We also determined correlation between TGF-β pathway and other oncogenic pathways and observed strong positive correlation with DNA damage repair and EMT pathways and a strong negative correlation with cell cycle pathway. This multidimensional study provides the genomic landscape of TGF-β signaling in both individual disease and PanCancer settings to guide future functional and therapeutic studies of this key remarkable cancer pathway.