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Hitting where it hurts: Exploiting cancer cell 'addiction' may lead to new therapies

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A new study uncovers a gene expression signature that reliably identifies cancer cells whose survival is dependent on a common signaling pathway, even when the cells contain multiple other genetic abnormalities. The research, published by Cell Press in the June 2nd issue of the journal *Cancer Cell*, identifies critical molecular vulnerabilities, thereby revealing promising therapeutic targets for a common and notoriously treatment resistant cancer.

Although previous work has identified K-Ras as a frequently mutated oncogene in solid tumors, development of clinically effective cancer therapies that target K-Ras has proven challenging and has been largely unsuccessful. "There remains a pressing need to identify pharmacologically tractable components of K-Ras-driven tumorigenesis," says senior study author Dr. Jeff Settleman from Massachusetts General Hospital Cancer Center and Harvard Medical School.

Dr. Settleman and colleagues undertook a series of studies to identify characteristics that define "K-Ras addiction". Oncogene addiction refers to the requirement of a tumor for the sustained expression of a single aberrantly activated gene, even in the presence of other mutations. Settleman's group identified two classes of cancer cells: K-Ras mutant dependent and K-Ras-independent. "We established a gene expression signature that distinguishes these two groups and identified genes that are specifically upregulated in K-Ras-dependent cells and required for their viability," says Dr. Settleman.

The researchers went on to show that several of the genes associated with K-Ras-dependent cancer cells were required to maintain a state of cell differentiation. Furthermore, oncogene dependency (and therefore cancer cell viability) was strongly linked with the differentiation state. "The notion that poorly differentiated tumors are generally more drug resistant and are associated with poorer prognosis has been widely recognized in clinical oncology, and our findings might provide some mechanistic insight into this observation," offers Dr. Settleman.

The authors conclude that comparing gene expression profiles between cancer cell lines on the basis of oncogene addiction is likely to provide a broadly useful strategy for context-specific drug target discovery. In this study, one particular gene, ITGB6, was strongly associated with differentiated K-Ras driven tumors. "Efforts to target the activity of ITGB6 are currently underway," says Dr. Settleman.

Source: Cell Press (news : web)