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Non-canonical p53 signaling to promote invasion

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Commentary to: Grugan KD, Vega ME, Wong GS, Diehl JA, Bass AJ, Wong KK, Nakagawa H, Rustgi AK. A common p53 mutation (R175H) activates c-Met receptor tyrosine kinase to enhance tumor cell invasion. Cancer Biol Ther 2013; In press; PMID:23792586

It has been known for a number of years that mutated "inactive" p53 proteins still capable of binding to DNA per se, can bind to DNA sequences that are non-canonical for p53, with for example, a resultant increase in the transcription and expression of growth factor receptors such as ERBB1,[1,2] i.e., mutation of p53 not merely results in "no p53 function" but in fact results in "oncogenic p53 function". And in agreement with this postulate transduction of p53 null cells with mutant p53 can cause transformation.[3] In prior studies the authors of the present manuscript had demonstrated that expression of p53 (R175H) and ERBB1 could transform immortalized primary esophageal cells, in parallel with increased migratory ability.[4] These present studies have defined why those transformed cells became invasive: increased c-Met activity.[5]

In the present study the authors demonstrated that mutant p53 (R175H) stimulated c-Met activity that was mutant p53 specific and that this receptor activation was not due to the extracellular actions of the receptor's ligand, HGF. The phosphorylation of c-Met was not dependent on trans-phosphorylation by ERBB1 and was blocked by a c-Met kinase domain inhibitor; whether the FDA approved c-Met inhibitor crizotinib also could block c-Met phosphorylation and/or tumor cell invasion was not determined. The authors of the present manuscript did not determine precisely the mechanisms by which c-Met phosphorylation was increased. In a prior study the authors showed that ERBB1 and p53 (R175H) expression increased c-Met tyrosine phosphorylation but did not alter c-Met protein levels; but while c-Met phosphorylation was increased that of ERBB1 was not. One mechanism by which receptor tyrosine kinases can be activated is by inactivation of the tyrosine phosphatases that dephosphorylate them. For example, increased reactive oxygen species levels inhibit tyrosine phosphatases resulting in increased ERBB1 tyrosine phosphorylation.[6,7] Clearly, as c-Met, but not ERBB1, phosphorylation is altered this cannot be the explanation. Another possibility is that the tyrosine phosphatase(s) that regulate ERBB1 and c-Met phosphorylation are different, with the phosphatase that dephosphorylates c-Met being downregulated by p53 (K175H). In this regard the phosphatase that targets ERBB1, SHP2, is different from the phosphatase that targets c-Met, receptor protein tyrosine phosphatase β.[8,9] There is no literature as to whether RPTP-β expression and/or function is altered by p53 (K175H). Finally, it is possible that non-receptor tyrosine kinases play a role in the increase in c-Met tyrosine phosphorylation, which is a mechanism that will likely be investigated by the authors in the future.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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