p53 mutation and TGFβ signaling culminate in cancer invasiveness via GEP100-Arf6-AMAP1 pathway

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Mutation of p53 tumor suppressor protein is very frequent in cancer, and often gains oncogenic activities, rather than simply abrogating its tumor suppressive functions. Identification of genes whose expression is altered as a result of p53 mutation and hence elicit tumor malignancy is the major goal of current cancer research. This may be a difficult task, however, because like wt p53 cellular functions of oncogenic p53s appear to be highly contextual, and the final readouts of the mutant p53s may not be simply determined only by biochemical properties by their own. On the other hand, another aspect towards the substantial understanding of mutant p53-driven cancer malignancy would be to identify molecular machineries that actually accomplish invasive and metastatic phenotypes in response to mutant p53s.

TGFβ1 is produced mostly upon inflammation and wounding. Among different signaling pathways, TGFβ signaling was found to be most frequent in inducing invasive and mesenchymal properties, as well as generating cancer stem cell-like cell properties of human primary breast cancers. A series of our studies have shown that GEP100-Arf6-AMAP1 signaling pathway is frequently upregulated in many breast cancers and contributes to invasiveness and cancerous EMT, by promoting the recycling of β1 integrins, such as α3β1, and the downregulation of E-cadherin. Here, we describe this signaling pathway, as well as detailed mechanisms by which it works in invasion and metastasis. We also show that TGFβ1 signaling activates this GEP100-Arf6-AMAP1 pathway, and provide lines of evidence that mutant p53s, like R280K, are essential for this activation.