We obtained mass spectrometry proteomic data for 4956 proteins found in MDA-MB-231 from [25892236]. Of the 12087 genes with RNA data, 4717 had protein data.

MRs are nodes in the network (genes, proteins, or complexes) that regulate, simultaneously, the TFs in our network. We will identify MRs by mapping pathways in which the identified TFs participate. To integrate proteomic data of the studied tumor, we will use the Master Regulators with Context Genes with weights pipeline [29900117] with the manually curated TRANSPATH database [47]. The modified pipeline will use the proteomics expression data as the context to preferentially choose pathways enriched with abundant protein levels.

Using the manually curated Catalogue of Somatic Mutations in Cancer (COSMIC) database, we identified 150 somatic mutations, mapping to 81 genes in MDA-MB-231 [30371878]. RNA expression data is present for 48 of these genes of which 19 additionally have protein data. We used the Variant Effect Predictor (VEP) to annotate the SNVs with information regarding status in coding and non-coding regions, as well as protein translation effect (missense, splice-site variation, frameshift, deletion) [27268795]. For the nodes in our network, VEP identified one missense mutation of TP53 p.R280K. The TP53 R280K mutation is a known gain of function mutation in MDA-MB-231 that also acts as a driver mutation [22822097]. A literature search provided insight to the pathways affected by this gain-of-function mutant p53. One such pathway is the mevalonate pathway, whose increased activity promotes tumor cell survival [27562463]. Mutant p53 also activates the TGFβ pathway by binding to and inhibiting p63, which typically inhibits the pathway, leading to increased cell migration [19345189, 21263025]. Furthermore, mutant p53 also interacts functionally and physically with the vitamin D receptor to increase transcription of vitamin D response elements, transforming vitamin D into an antiapoptotic agent [20227041]. The increased vitamin D and TGFβ pathway signaling by Mutp53 causes a non-canonical wnt5a, leading to increased cell migration [21416313].

We predicted the effect of SNVs on kinase function using reKINect software [[26388441](https://www.ncbi.nlm.nih.gov/pubmed/26388441)]. ReKINect uses the amino acid sequence of a mutant protein to predict the functional impact of a mutation on various kinase and SH2 domains. The BRAF p.G464E mutation was identified to effect kinase activity. This mutation is known to increase protein kinase activity of BRAF and cell proliferation through activation of MEK and ERK [23680146, 29533785].

The identified mutated pathways will be added to the network manually, as they are not included in signaling databases, but can be found through literature curation.