Drug resistance in breast cancer remains a big challenge with many patients relapsing on endocrine therapies. To investigate growth dependent signalling pathways in cancer we have generated a novel, MCF-7 derived, long-term estrogen (E2) deprived cell line in serum-free conditions, called DH. DH cells are E2 hypersensitive, estrogen receptor alpha (ER) dependent and sensitive to endocrine treatment. To interrogate growth dependent signalling pathways DH cells were treated with 1nM E2 for 5 days followed by E2 withdrawal for 5 days. E2 stimulation triggers a slow up regulation of EGFR and a rapid reduction in ER levels. After initial stimulation EGFR expression is maintained despite E2 withdrawal indicating a stable epigenetic modification at the EGFR promoter. This was accompanied by activated MAPK signalling and resistance to tamoxifen demonstrating a surprising functional switch between the ER and EGFR survival pathways, triggered by E2. Expression microarray analysis, of E2 responsive genes, identified the transcription factor MYB as a potential link between these two pathways. Upon E2 treatment, ER binds to MYB intron 1 promoting MYB expression which then transiently binds upstream of the EGFR promoter. MYB depletion by siRNA abrogates E2 dependent EGFR expression showing a direct link between these two pathways. This data suggests that MYB activated EGFR signalling could be one mechanism of drug resistance to endocrine therapy and highlights MYB as a potential therapeutic target in breast cancer.