FRE3 is part of a family of nine homologous genes involved or predicted to be involved in iron uptake that can be roughly grouped into three classes based on sequence similarity and transcriptional regulation: FRE1 and FRE7; FRE2 through FRE6; and FRE8 and YGL160W. FRE2 through FRE6 are induced during iron depletion, with FRE2 and FRE3 being strongly induced and FRE4, FRE5, and FRE6 being moderately induced. Aft1p regulates transcription of FRE1 through FRE6 in response to iron levels.Fre1p and Fre2p are the major cell-surface iron reductases and together account for 90-98% of cell-surface reductase activity. This activity is directed against both free Feand Febound in siderophores, bacterially-secreted compounds that chelate Fefor direct uptake. Fre1p and Fre2p are homologous to the human gp91phox protein, the large subunit of human cytochrome b558, which reduces oxygen to bactericidal superoxideon the surface of phagocytic leukocytes. Deficiency of gp91phox causes X-linked chronic granulomatous disease.Fre3p and Fre4p can reduce Febound to specific siderophores. In an fre1 fre2 background, deletion of FRE3 ablates 73% of the residual ferrioxamine B-iron reductase activity. Fre3p, which is a plasma membrane protein, can also reduce iron bound to ferrichrome, triacetylfusarinine C, or rhodotorulic acid, but not enterobactin. Fre1p and Fre2p can reduce enterobactin-iron. Fre4p can reduce rhodotorulic acid-iron at high concentrations.