Extended Note 1: Cadaverine formation is not toxic to yeast cells

We chose to increase cadaverine concentrations intracellularly by making use of metabolic engineering. We cloned a bacterial (*E. coli*) lysine decarboxylase (*ldc*C) and expressed it in the WT strain, BY4741. In SM, the expression of *ldcC* increased cadaverine concentrations 93.9 times (Extended data Figure 8a). The expression of *ldcC* also affected the concentration of aminopropylcadaverine (APC), the cadaverine derived spermidine analogue, 5.5 times (Extended data Figure 8b). In typical growth media, the modification and the increased intracellular concentration of the alternative polyamines had no effect on yeast growth (Extended data Figure 8c). However, in lysine-rich media (250 μg/mL), the strain expressing *ldcC* exhibited a moderate growth defect (Extended data Figure 8c). In this condition, cadaverine was elevated 192 times and APC 18.6 times above WT levels (Extended data Figure 8a and 8b), concentrations that are unlikely to be reached under any physiological conditions in yeast. These results indicate that cadaverine and APC are well tolerated at the levels detected in cells and become only inhibitory to growth at extreme and non physiological concentrations.

Extended Note 2: Cadaverine can partially substitute for canonical polyamines, but only at non physiological high concentrations and certain pH

The putrescine-spermidine-spermine pathway is essential for yeast. The essentiality of Spe1p, Spe2p, Spe3p and Spe4p enzymes in SM can be rescued by adding their missing products (i.e. putrescine supplementation rescues a *SPE1* deletion, spermidine supplementation a *SPE1* and *SPE2* deletion, and so on). To test whether cadaverine or aminopropylcadaverine (APC) complement the function of the canonical polyamines, we depleted the Δ*spe1* strain of external spermidine. Upon passaging in minimal polyamine-free media, the strain lost viability. Cadaverine could only rescue growth at very high and non physiological conditions (250 mM) (Extended data Figure 9a). However, when Δ*spe1* strain was grown in the presence of 0.1 mM spermidine and 250 mM cadaverine, the growth rate of this strain improved compared to the one grown in the presence of spermidine (Extended data Figure 9b).

Eventually, we took advantage of the bacterial lysine decarboxylase LdcC to generate a strain that is incapable of producing the canonical polyamines putrescine, spermidine and spermidine but can form cadaverine and APC. This was achieved by deleting the ornithine decarboxylase *SPE1* and expressing *LdcC* (Δ*spe1 LdcC+*), in the presence of external spermidine, to prevent lethality. We inoculated the strain in minimal medium supplemented with lysine, to boost cadaverine production to high levels. The supplementation of lysine rescued Δ*spe1 LdcC+* strain, but fast growth rates were only obtained under acidic conditions, either in unbuffered synthetic minimal medium at a pH 5.0 or at 150 mM citrate/phosphate buffered minimal medium, also at pH 5.0. At neutral or alkaline pH, complementation was minimal (Extended data Figure 9c). One can derive two conclusions

from these experiments. First, our experiments strongly suggest that the alternative polyamine pathway is not functioning as a substitute for the canonical polyamine pathway. The concentrations we had to generate, to achieve a complementation under some of the conditions are not seen in *Saccharomyces in vivo*. However, at the same time, the alternative polyamines have chemical properties that are not fundamentally different to that of the canonical polyamines either, because under specific conditions a partial complementation was achieved. As the alternative polyamine pathway does not work as a substitution for polyamine function, we were wondering if it has other properties important for the H_2O_2 response of cells. First, we tested whether cadaverine supplementation could simply have a direct protective effect for H_2O_2 treated cells or in other stress situations. We could not find a condition in which the external presence of cadaverine, or the expression of lysine decarboxylase, would have significantly altered survival in several stress-tolerance experiments (Extended data Figure 9d; Extended data Table 1). Certainly, one can never test for all possible conditions, but as we could not find any protective effect in dozens of different stress tests conducted over several months, this is compelling evidence to indicate that it is not cadaverine that provides antioxidant protection.