5. SUMMARY

Optic atrophy 1 (OPA1) is a dynamin-related GTPase, which is imported into mitochondria. Mutations in *OPA1* cause autosomal dominant optic atrophy (adOA) and lead to blindness (Alexander et al., 2000). Haploinsufficiency was postulated as pathological mechanism for adOA, resulting in loss of retinal ganglion cells and degeneration of the optic nerve.

OPA1 was extensively studied in the last five years, and it was implicated in fusion of mitochondria. Fusion and fission of mitochondria are processes constantly happening in cells, making mitochondria not static, but dynamic organelles. They ensure that an equilibrium is kept between short and long forms of mitochondria and allow exchange of their contents.

Even with many excellent studies on OPA1 done in mammalian cells, the function of this protein is not yet clear. In order to study its physiological function *in vivo* and its role in the manifestation of autosomal dominant optic atrophy, the *OPA1* gene was disrupted by homologous recombination. OPA1-deficient heterozygous ($OPA1^{+/-}$) mice show reduced OPA1 protein levels, but are phenotypically indistinguishable from wild-type littermates. On the other hand, OPA1-deficient homozygous ($OPA1^{-/-}$) embryos are reduced in size and die during gastrulation. Mitochondria in $OPA1^{-/-}$ embryos are completely fragmented, loose their DNA and many cells show hallmarks of apoptosis.

Mouse embryonic fibroblasts (MEFs) derived from $OPA1^{-/-}$ embryos also contain completely fragmented mitochondria, which have lost their ability to undergo mitochondrial fusion. Their mitochondria are enlarged, with abnormal inner membrane morphology. They show complete respiration deficiency and mitochondrial membrane potential decrease. $OPA1^{-/-}$ fibroblasts are less sensitive to staurosporine-induced apoptosis and do not undergo cytochrome c release, opposite to what was seen in wild-type cells after the same treatment. Transfection of $OPA^{-/-}$ MEFs with wild-type *OPA1* isoform 1 restored respiratory chain activity, mitochondrial membrane potential, tubular morphology and fusion of the mitochondrial network. However, the sensitivity to staurosporine-induced apoptosis was not restored.

Results presented in this thesis show that functional mitochondrial networks are essential in early embryonic development and that OPA1 is required for cristae maintenance, activity of respiratory chain and tubulation of mitochondrial networks.

Therefore, OPA1 is absolutely necessary for early embryonic development and survival. Besides, reconstitution experiments showed that one particular OPA1 isoform, out of eight isoforms known, has special and distinct functions in mitochondria.