INDO SWISS JOINT RESEARCH PROGRAMME (ISJRP)

JOINT RESEARCH PROJECT

ABSTRACT

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THE ROLE OF ORGANELLES DURING CELL DEATH OF PLASMODIUM PARASITES

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PROJECT ABSTRACT

There is accumulating evidence that protozoan parasites can undergo an ordered form of cell death but little is known about the corresponding molecular mechanisms. In multicellular organisms mitochondria play a central role in cell death but it is not known whether mitochondria in protozoan parasites have an adequate function. The malaria parasite *Plasmodium* possesses two essential organelles, the mitochondrion and the apicoplast, which cannot be synthesized de novo and thus have to be distributed to daughter parasites during cytokinesis. We suggest investigating their role and behaviour during parasite cell death. Generally three forms of cell death can be distinguished: apoptosis, necrosis and autophagic cell death. For *Plasmodium* parasites morphological markers of all of them have been identified and we intend to analyse the role of organelles in cell death in two important life cycle stages of *Plasmodium* parasites, the liver and the blood stage. Results obtained in one parasite stage can be validated with complementary sets of experiments in the other stage resulting in a much faster understanding of molecular events during parasite cell death. We will initially focus on two classes of molecules potentially acting on organelles during cell death: proteases as well as dynamins and related proteins. Proteases are the main executors of cell death and are often organized in cascades. During apoptosis in cells of higher eukaryotes initiator caspases proteolytically process and activate effector caspases. This effect can be amplified via mitochondria: activation of initiator caspases initiate the release of cytochrome c and the formation of an apoptosome. Result of this protein complex formation is again the activation of effector caspases, which finally execute apoptosis. Although *Plasmodium* parasites do not possess typical caspases a similar scenario is still possible. In the parasite genome many protease genes have been identified and it has already been shown that, during parasite egress, some proteases act in cascades similar to what has been found for caspases. We have already identified a candidate protease of the parasite, which indeed is part of a protease cascade and is suspected to act on host cell mitochondria during parasite egress. There are indications that this protease may have an additional role during parasite death and we intend to analyse its role in this respect. We also identified and characterized organelle localized proteases that are also expected to

play key role in organelle development and may be important for cell death. Dynamins and related proteins are responsible for organelle fission and genes coding for dynamin homologues have been identified in the genome of all *Plasmodium* species investigated. Since in higher eukaryotes dynamins play also a role in autophagic events, it is envisaged to investigate their role in organelle development and organelle morphology during parasite cell death. Deciphering the molecular mechanisms of parasite cell death would open new avenues to interfere with parasite dissemination and thus might help to control one of the most important infectious diseases worldwide.