ABSTRACT

Interleukin-1α (IL-1α) is a pleiotropic cytokine and a key mediator of host immune response. It is synthesised as a 31-kDa precursor, that is cleaved by the cysteine protease calpain into the 17-kDa mature IL-1α and the 16-kDa N-terminal peptide of IL-1α (IL-1αNTP). Although IL-1α can be secreted, act on target cells through the surface receptor IL-1RI and trigger the signal transduction pathway, increasing evidence points toward the involvement of IL-1α in certain nuclear processes. IL-1αNTP is highly conserved among higher eukaryotes and contains a nuclear localisation sequence; indeed, both the precursor and IL-1αNTP are found in the cell nucleus. Previously, a genetic interaction of IL-1α with nuclear histone acetyltransferase (HAT) complexes has been reported from mammalian cells and, interestingly, also from the heterologous yeast model.

This thesis extends the research of the nuclear function of IL-1α and demonstrates that IL-1α physically associates with the HAT/Core module of yeast SAGA and ADA HAT complexes. Results of the HAT subunit gene knock-out experiments followed by a set of co-immunoprecipitations also suggest a novel model of the yeast SAGA complex assembly, in which ADA appears to represent only a partly functional HAT complex.

In its natural milieu of mammalian cells, IL-1α is demonstrated to co-localise with the tumour suppressor protein p53 within the cell nucleus. This interaction is further supported with a co-immunoprecipitation experiment where the IL-1α precursor binds p53. Moreover, it is shown that the subcellular localisation of IL-1αNTP can be modulated under different culturing conditions.

Finally, this thesis presents an analysis of *HOX* gene expression in immunophenotypically and genotypically defined subsets of paediatric patients with acute lymphoblastic leukaemia (ALL). The expression of 23 selected *HOX* genes in 61 ALL patients is studied and the results are compared with the levels of *HOX* gene transcription in sorted cell populations of B and T lymphocytes from healthy donors. Aberrant *HOX* gene expression patterns have been identified in the leukaemic cells compared to their closest physiological counterparts

Keywords: interleukin-1; interleukin-1α; histone acetyltransferase; SAGA; ADA; *HOX* genes; acute lymphoblastic leukaemia; heterologous expression; transcription