Genetic factors in lymphoproliferative malignancies. Focus on *CHEK2* gene in lymphomas with comparison to distinct solid tumors.

MUDr. Ondřej Havránek

Summary of PhD thesis:

Background: The checkpoint kinase 2 gene (*CHEK2*) codes for an important mediator of DNA damage response pathway that among others interacts with the p53 protein. Mutations in the *CHEK2* gene increase the risk of several cancer types, however, their role in non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) is not clear. The most frequent *TP53* gene R72P polymorphism was analyzed in several studies in NHL but not in HL. **Methods:** We have performed mutation analysis of the whole *CHEK2* gene coding sequence in 340 NHL patients and the segment coding for *CHEK2* forkhead-associated (FHA) domain in 298 HL patients and compared the results with our analyses of *CHEK2* in breast, colorectal and pancreatic cancers. The *TP53* R75P genotype was assessed in the same lymphoma populations. Both genes were analyzed using denaturing high-performance liquid chromatography. **Results:** The overall frequency of *CHEK2* alterations within FHA-coding region was significantly higher in NHL and HL patients (19/340 - 5.6%; 17/298 - 5.7%, respectively) compared to non-cancer controls (19/683 - 2.8%; p = 0.03 and 0.04, respectively). These alterations were associated with increased risk of lymphoma development (OR = 2.1; 95% CI 1.2-3.7; p = 0.01) and worse progression-free survival (PFS) in NHL patients (p = 0.008). Better overall survival in diffuse large B-cell lymphoma and PFS in all NHL patients was associated with *CHEK2* IVS1+43dupA alteration (p = 0.02 and 0.01, respectively). We have identified the association of *CHEK2* FHA alterations also with colorectal cancer risk (OR = 2.3; 95% CI 1.3-4.1; p = 0.003), but not with breast or pancreatic cancers. The *TP53* R72P polymorphism did not influence lymphoma risk or survival. **Conclusions:** Alterations in the *CHEK2* gene FHA coding region represent moderate genetic predisposition factor increasing the risk of lymphoma and together with IVS1+43dupA alteration may modify lymphoma disease course.