

To establish efficient expression of their genes, retroviruses integrate proviral copies into the genomes of the cells they have infected. Epigenetic events, however, silence expression of the integrated proviruses. This silencing protects host cells from harmful viral spread, but also creates a reservoir of latent proviruses that subsequently hinders the cure of retroviral (e.g., HIV-1) infections. Furthermore, the silencing of retrovirus-derived integrative vectors complicates their application in transgenesis and gene therapy. The goal of this thesis is to describe the interaction between retroviral expression and host (epi)genomic environment at the site of proviral integration.

To pursue the goal, we sought to define the (epi)genomic environment of the proviruses, which expression is not affected by the epigenetic silencing. Diverse retroviral vectors derived from avian sarcoma and leukemia virus (ASLV), murine leukemia virus (MLV), and human immunodeficiency virus type 1 (HIV-1) were used as model retroviral systems, and expression stability of the vectors in human cell lines was examined. In order to identify the features unique to integration sites of the active proviruses, we sorted the cells positive for the proviral expression, identified their proviral integration sites, and compared them to proviral integration sites from nonselected populations. *In silico* analytical methods were applied to define the genomic and epigenomic features associated with proviral integration sites. Despite marked differences in the attributes of the vectors used, we identified the features that are common to long-term expressed proviruses. The proviruses were strongly associated with transcription-regulating elements including enhancers and promoters of active genes. We propose that the loci closely associated with transcriptional start sites provide the strongest transcription permissive environment for retroviral expression.

In this thesis, we defined the chromatin environment permissive for the expression of retroviral genes. The results presented here show that the proviruses selected for stable proviral expression tend to be found in transcriptionally active chromatin and closely associated with regulatory sequences. This fact should be considered in approaches utilizing retroviral vectors.