“The Human Papillomavirus E7 oncoprotein regulates the activity of Oct4 in Cervical Cancer”

The stem cell-related transcription factor, Octamer binding transcription factor-4 (Oct4), has well-defined roles in Embryonic stem cells (ESCs) for maintaining self-renewal and pluripotency and has recently been implicated in carcinogenesis. However, the postnatal function of Oct4 is poorly understood. We and others have demonstrated that HPV-associated cervical cancers over-express Oct4. The upregulation of Oct4, as well as its proliferation-associated phenotypes in HPV (+) cervical cancers, are in part linked to an interaction between Oct4 and the E7 oncoprotein of HPV. To explore the molecular function of Oct4 and understand the differential Oct4-mediated phenotypes in HPV (+) and HPV (-) cervical cancers, we aimed to investigate the Oct4 interactome using parallel proteomics and bioinformatics approaches. Mass spectrometry and bioinformatics data have identified several members of the NuRD complex (Nucleosome Remodelling and Deacetylase complex) as relevant interactors of Oct4 in cervical cancer cells. We have validated these protein-protein interactions using co-immunoprecipitation approaches. Notably, using co-immunoprecipitation assays, we have found that different members of the NuRD complex interact with Oct4 in the presence and absence of E7. In HPV (-) C33A cells Oct4 interacts with the Mbd2-NuRD variant whereas in the context of E7 expression, Oct4 co-immunoprecipitated with components of the Mbd3-NuRD variant. To further investigate the biological role of Mbd2-NuRD variant in cervical cancer cells we used a pharmacological inhibitor targeting the function of Mbd2. The inhibition
of Mbd2 modified the Oct4-controlled transcriptional output and the Oct4-regulated proliferation phenotype only in cervical cancer cells where E7 was not expressed. The binding of Oct4 to distinct variants of the NuRD complex may explain the diverse functions of Oct4 in different cell contexts.