ABSTRACT

A GENOMIC INVESTIGATION OF MAREK'S DISEASE LYMPHOMAS

By

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Meq, a bZIP transcription factor and the viral oncogene for pathogenic strains of Marek's disease virus (MDV), is required to induce CD4 T cell lymphomas that characterize Marek's disease (MD) in chickens. However, Meq is not sufficient for neoplastic transformation as not all birds infected with pathogenic strains of MDV developed Marek's disease. We hypothesize that additional drivers or somatic mutations in the chicken genome are required for MDV-induced transformation. Using and integrating DNA and RNA genomic screens of Marek's disease tumors from genetically-defined experimental layers, our analyses reveal 0.3 somatic mutations per megabase consisting primarily of somatic single nucleotide variants (SNVs) and small insertions and deletions (Indels). Somatic deletions, insertions, and point mutations were enriched in *IKZF1* (Ikaros), the first driver gene of Marek's disease lymphomas. Ikaros, a Zn-finger transcription factor and the master regulator of lymphocyte development, is a known tumor suppressor in human and murine acute leukemias and lymphomas. In our surveyed Marek's disease tumors, 41% of the samples had somatic mutations in key N-terminal Zn-finger binding domains, strongly suggesting perturbed Ikaros function in its ability to bind DNA and regulate transcription. Somatic mutations in *IKZF1* were preferentially found in tumors of gonadal tissues as well as their metastatic clones. *IKZF1* mutant Marek's disease tumors revealed gene expression profiles indicative of Ikaros perturbation. In addition to *IKZF1*, other putative somatic mutations reside in *ZNF384, EFNA5, CLDND1*, *FOXD1, ROBO1, and ROBO2* and

warrant evaluation. Our results suggest MDV-induced tumors are driven by both Meq expression and *IKZF1* somatic mutations that in combination lead to unregulated proliferation, increased cell adhesion, increased migration, and dedifferentiation.