11 MOLECULAR CHARACTERIZATION OF NATURALLY OCCURRING COLORECTAL AND BREAST CANCER IN NON-HUMAN PRIMATES TO MODEL HUMAN IMMUNOTHERAPEUTIC AGENTS

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Background Non-human primates (NHP) with naturally occurring cancers (also called tumor-bearing monkeys or TBM) are a proposed model for translational cancer immunotherapy (CIT) research.[1] TBM spontaneously develop cancers with progression patterns similar to humans, potentially bridging the gap between preclinical models and cancers in patients. Interventional CIT trials recently conducted in colorectal (CRC) and breast cancer (BC)-bearing NHP, have generated relevant proof-of-mechanism evidence for three different CIT agents.[1–3] To further validate these animals as translational models for CIT, we conducted a deep molecular characterization of tumors at baseline and reverse translated biomarker assays employed in human patients.

Methods Our cohort (n=19) consisted of Indian-origin rhesus macaques (Macaca mulatta) with naturally occurring CRC (n=14, female=9, male=5) and BC (n=5, female=5). Clinical examination, imaging (contrast-enhanced CT, PET) and biopsy to confirm cancer histology were performed. Molecular characterization was done by IHC for CRC-associated mismatch repair (MMR) proteins MLH1, MSH2, MSH6, and PMS2 and BC markers ER, PR, and HER2. We assessed microsatellite instability (MSI) by PCR and electrophoresis, and for selected cases somatic tumor mutations and tumor mutational burden (TMB) by whole exome sequencing.

Results Deficiency in MMR proteins determines eligibility for PD-1 blockade therapy, is observed in approximately 15% of human CRCs, and surprisingly in 100% (14/14) of our NHP CRCs. The absence of MLH1 (14/14), MSH2 (1/14), MSH6 (0/14) and PMS2 (14/14) observed in NHP CRCs clearly exceeds the frequencies reported in human CRCs ranging from 2–15% for each individual MMR protein.[4 5] Moreover, we have documented MSI cases in some NHP CRCs, as described in human CRCs. We sequenced 3 CRCs and observed mutations in KRAS (G12D & A59T), WNT7A (V238M), IDH2 (R362Q), AKT3 (R388H), and TMB of 4.27, 22.95, and 29.3 mut/Mbp. Regarding breast, we found hormone receptor positive (Luminal A), HER2 positive, and TNBC, as in human BC patients. Sequencing of 2 BCs revealed mutations in PTEN (G251V), TGFBR2 (L162P), and ERBB4 (R1250Q), and TMB of 2.32 and 17.22 mut/Mbp.

Conclusions NHP cancers can be similarly characterized as human cancers, both macroscopically and molecularly. In this study we demonstrated an overrepresentation of MMR deficiency in NHP CRCs. Receptor expression in NHP BCs revealed similar subtypes as in human BCs. Cancer-associated mutations described in humans are also evident in TBM. This work highlights the possible translatability of naturally occurring NHP cancers for human cancer immunotherapy research, and can be further explored in future TBM trials.

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Ethics Approval Wake Forest University is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC) and registered with the United States Department of Agriculture (USDA) to conduct research in laboratory animals. The protocols and any subsequent amendments are reviewed and approved by the Wake Forest Institutional Animal Care and Use Committee (IACUC) and in compliance with the U.S. Animal Welfare Act, the *Guide for the Care and Use of Laboratory Animals*, the Office of Laboratory Animal Welfare, and public health service regulations.

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