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PRECLINICAL STUDY

Life stage differences in mammary gland gene expression profile in non-human primates

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Abstract Breast cancer (BC) is the most common malignancy of women in the developed world. To better understand its pathogenesis, knowledge of normal breast development is crucial, as BC is the result of disregulation of physiologic processes. The aim of this study was to investigate the impact of reproductive life stages on the transcriptional profile of the mammary gland in a primate model. Comparative transcriptomic analyses were carried out using breast tissues from 28 female cynomolgus macaques (*Macaca fascicularis*) at the following life stages: prepubertal ($n = 5$), adolescent ($n = 4$), adult luteal ($n = 5$), pregnant ($n = 6$), lactating ($n = 3$), and postmenopausal ($n = 5$). Mammary gland RNA was hybridized to Affymetrix GeneChip® Rhesus Macaque Genome Arrays. Differential gene expression was analyzed using ANOVA and cluster analysis. Hierarchical cluster analysis revealed distinct separation of life stage groups. More than 2,225 differentially expressed mRNAs were identified. Gene families or pathways that changed across life stages included those related to estrogen and androgen (ESR1, PGR, TFF1, GREB1, AR, 17HSDB2, 17HSDB7, STS, HSD11B1, AKR1C4), prolactin (PRLR, ELF5, STAT5, CSN1S1), insulin-like growth factor signaling (IGF1, IGFBP1, IGFBP5), extracellular matrix (POSTN, TGFB1, COL5A2, COL12A1, FOXC1, LAMC1, PDGFRA, TGFB2), and differentiation (CD24, CD29, CD44, CD61, ALDH1, BRCA1, FOXA1, POSTN, DICER1, LIG4, KLF4, NOTCH2, RIF1, BMPR1A, TGFB2). Pregnancy and lactation displayed distinct patterns of gene expression. ESR1 and IGF1 were significantly higher in the adolescent compared to the adult animals, whereas differentiation pathways were overrepresented in adult animals and pregnancy-associated life stages. Few individual genes were distinctly different in postmenopausal animals. Our data demonstrate characteristic patterns of gene expression during breast development. Several of the pathways activated during pubertal development have been implicated in cancer development and metastasis, supporting the idea that other developmental markers may have application as biomarkers for BC.

Keywords Breast development · Gene microarray · Breast cancer · Stem cell · Estrogen · Progesterone

Abbreviations

AKR1C4	Aldo-keto reductase family 1, member C4
AKT1	v-akt Murine thymoma viral oncogene homolog 1
ALDH1	Aldehyde dehydrogenase 1 family, member A1
AR	Androgen receptor
BC	Breast cancer

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