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From Metabolites to Mechanisms: Linking Tryptophan Metabolism and AhR Activation in Breast Cancer

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Introduction

Tryptophan (Trp), an essential amino acid, is metabolized through the kynurenine, indole, and serotonin pathways. Imbalances in Trp metabolism have been implicated in cancer progression. However, clinical trials targeting indoleamine-2,3-dioxygenase (IDO), a key enzyme in Trp catabolism, have yielded unsatisfactory results, prompting the exploration of alternative therapeutic targets within the Trp metabolic network. Emerging evidence discovers that several Trp-derived metabolites can bind to and activate the aryl hydrocarbon receptor (AhR), a ligand-dependent transcription factor that is essential in immune response and tumorigenesis. Although AhR is widely expressed in various breast cancer subtypes, its precise role in breast cancer development remains unclear, likely due to disease complexity and the diversity of AhR ligands. Thus, investigating Trp metabolism in relation to AhR activation may provide novel insights into the role of Trp-activated AhR pathway in breast cancer progression.

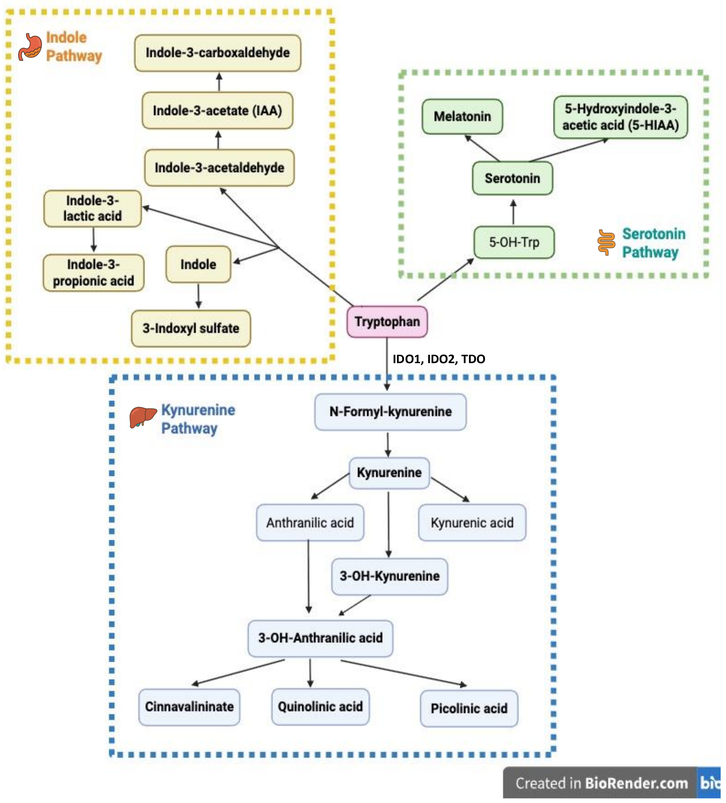


Figure 1: Tryptophan metabolism through indole, kynurenine and serotonin pathway

Methods

Clinical data and serum samples were collected from patients with breast cancer (n = 13) and age-matched individuals with breast fibroadenoma (n = 9). Eighteen Trp metabolites were quantified using Ultra-High Performance Liquid Chromatography (UHPLC). Metabolite levels were normalized using Z-score transformation and visualized via heatmap. Hierarchial clustering was performed to assess sample grouping. AhR mRNA expression levels were compared between primary breast cancer tissues (n = 1111) and benign tissues (n = 113) by retrieving RNA-sequencing data from The Cancer Genome Atlas (TCGA) Breast Invasive Carcinoma cohort.

Table 1: Characteristics of patients with breast cancer and fibroadenoma

	Fibroadenoma (n = 9)	Breast cancer (n = 13)
Age at initial diagnosis (years)	56.9 ± 7.4	56.0 ± 7.2
Hormone status of tumor		
HR+ (ER+ and/or PR+)	-	8 (61.5%)
HR - (HER2+ or triple negative)	-	5 (38.5%)

Ages were demonstrated as mean ± S.D. HR: hormone receptor; ER: estrogen receptor; PR: progesterone receptor; HER2: Human Epidermal Growth Factor Receptor 2.

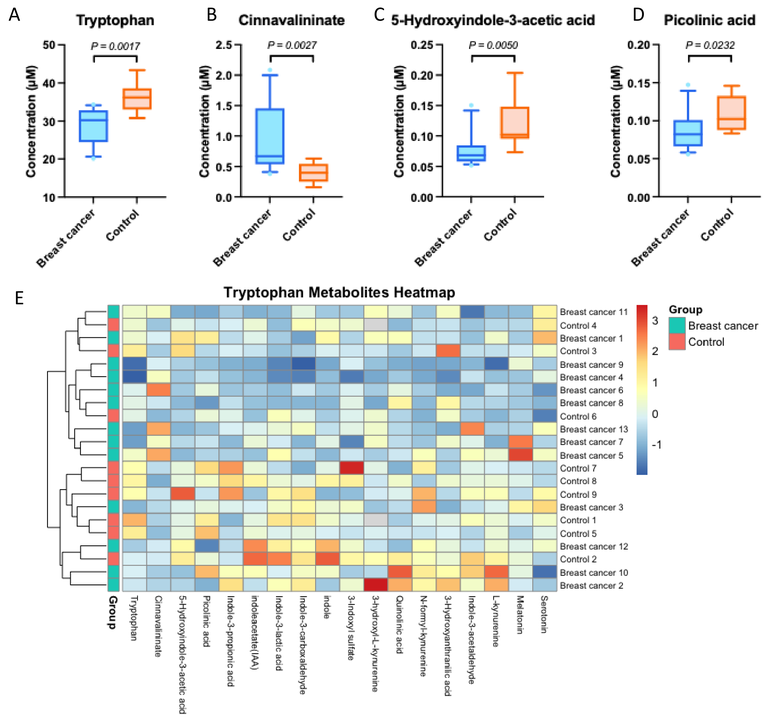


Figure 2: Tryptophan (Trp) metabolite levels in breast cancer vs. fibroma. Eighteen tryptophan metabolites were measured by UHPLC. Boxplots show significant differences in (A) tryptophan, (B) cinnavalininate, (C) 5-hydroxyindole-3-acetic acid, and (D) picolinic acid between breast cancer (n=13) and fibroadenoma (control, n=9). (E) Heatmap illustrates metabolite levels and clustering across samples. P values by Mann–Whitney U test.

Results

Differential levels of Trp metabolites were identified between breast cancer and fibroadenoma groups, with Trp, cinnavalininate, 5-hydroxyindole-3-acetic acid and picolinic acid showing the most significant differences. Heatmap visualization revealed distinct Trp metabolite profiles across all samples. Hierarchical clustering showed partial segregation between the breast cancer and fibroadenoma groups. Analysis of TCGA data demonstrated significantly reduced AhR mRNA expression in breast cancer tissues compared to benign tissues.

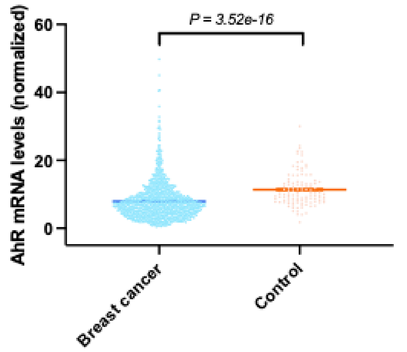


Figure 3: Comparison of AhR mRNA level in breast tumors vs. benign tumors. RNA-sequencing gene expression data (STAR-counts workflow) for breast cancer (n = 1111) and matched normal tissue samples (n = 113) were retrieved from The Cancer Genome Atlas Breast Invasive Carcinoma (TCGA-BRCA) cohort.

Conclusion

Trp metabolism is disrupted in breast cancer. The partial clustering of breast cancer and fibroadenoma samples reflects both the biological heterogeneity of breast cancer and the overlapping metabolic features between the two groups. The observed alterations in Trp metabolism, along with reduced AhR expression in breast cancer compared to benign tissues, suggest that impaired Trp-activated AhR signaling may play a critical role in breast cancer pathogenesis. These findings support further investigation into the Trp-activated AhR pathway as a potential therapeutic target in breast cancer management.

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