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MOLECULAR AND GENETIC DETERMINANTS OF SURGICAL OUTCOMES IN CANCER PATIENTS: A COMPREHENSIVE ANALYSIS OF BIOMARKERS, TUMOR BIOLOGY, AND POSTOPERATIVE PROGNOSIS

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ABSTRACT

Recurrence of prostate cancer after radical prostatectomy is a significant clinical issue, but little is known about the molecular programs involved in determining postoperative recurrence. Transcriptomic profiling provides a chance to discover biologically significant changes associated with the poor surgical outcome. The present work aimed to characterize transcriptomic differences associated with biochemical recurrence and to identify candidate genes and pathway-level programs linked to postoperative disease progression. A retrospective exploratory transcriptomic analysis was conducted using RNA-sequencing data from prostate tumor samples with and without biochemical recurrence. Following preprocessing, replicate consolidation, log2 transformation, low-expression filtering, and quality control, 15 samples were retained. Differential expression analysis was performed using Welch's t-test with Benjamini-Hochberg correction, and pathway-level alterations were examined using gene set enrichment analysis with Hallmark gene sets. The final cohort included 7 recurrence and 8 non-recurrence cases. Principal component analysis demonstrated partial separation between groups. No genes remained significant after multiple-testing correction, although several transcripts showed low nominal p-values and moderate fold changes. In contrast, pathway analysis identified 34 significantly enriched pathways, with recurrent tumors demonstrating enrichment of androgen response, MYC targets, mTORC1 signaling, protein secretion, and fatty acid metabolism, while non-recurrent tumors showed stronger immune and inflammatory signaling. These findings indicate that postoperative recurrence is associated with coordinated pathway-level reprogramming rather than isolated gene-level alterations, supporting the relevance of systems-level transcriptomic analysis in understanding recurrence biology.

KEYWORDS: prostate cancer, biochemical recurrence, radical prostatectomy, transcriptomics, pathway enrichment

1. INTRODUCTION

Prostate cancer is one of the most common malignancies in men globally and continues to represent a major clinical and public health burden. The development of diagnostic and treatment methods has led to better survival rates, but since the disease is heterogeneous and not uniform in its clinical course, it becomes hard to manage effectively. Indolent tumors to aggressive ones with high probability of recurrence and metastasis are the ends of the disease spectrum, which highlights the importance of better risk stratification and biological knowledge (Raychaudhuri et al., 2025). According to epidemiological data, prostate cancer is a significant cause of cancer in men around the world, and there is substantial geographic and demographic variation, which is due to both environmental and genetic factors (Rawla, 2019). Screening has increased the diagnosis at localized stages, but issues remain in the ability to distinguish clinically significant disease and low-risk ones (Pinsky & Parnes, 2023).

Radical prostatectomy is a mainstay of localized prostate cancer treatment, especially in patients who have an intermediate- to high-risk disease. Although surgery may be curative, a significant percentage of patients develop biochemical recurrence, which is usually characterized by an increase in the levels of prostate-specific antigen after surgery. This recurrence reflects residual or recurrent disease and represents a major challenge in long-term patient management (Costello, 2020). Not only is biochemical recurrence common, but also clinically significant, which may lead to metastatic progression and influence the outcome of survival negatively. Modern clinical decision making is based heavily on risk stratification models that include parameters like PSA levels, Gleason score and tumor stage. Even though these factors do offer important prognostic data, they may not be enough to sufficiently address the underlying biological complexity of the disease (Shore et al., 2024). The comparative study of Gleason grading and PSA correlation has shown that predictability can vary, and there is a problem with the use of conventional clinicopathological parameters only (Rani et al., 2023). On the same note, correlations between the imaging measures, histopathological and PSA levels are not constant across patient groups, which highlights the importance of the molecular-level knowledge (Gündoğdu et al., 2020).

With the advent of high-throughput sequencing technologies, the full characterization of tumor biology on a transcriptomic scale has become possible. Transcriptomics offers a dynamic perspective of gene patterns of expression, which represent functional cellular states and regulatory processes of tumors. It has become an increasingly significant method in precision oncology, where molecular profiling is employed to inform the diagnosis, prognosis, and treatment choices (Srivastava, 2023). The developments in transcriptomic analysis have eased the process of identifying molecular signatures that relate to tumor progression, response to treatment, and clinical outcomes in different types of cancer. Transcriptomic research in prostate cancer has shown that there are changes in pathways linked to androgen signaling, cell cycle, and metabolic processes that provide insight into disease mechanisms and therapeutic targets (Supplitt et al., 2021).

Recent integrative studies have also emphasized the multifaceted nature of prostate cancer progression, showing that transcriptional alterations can be scattered across a number of genes and pathways, as opposed to being caused by a single dominant alteration. These studies highlight the significance of systems-level approaches in tumor biology, especially regarding disease progression and recurrence (Marzec et al., 2021). Moreover, transcriptomic profiling has resulted in the discovery of potential biomarkers that have potential clinical implications, but the challenge of reproducibility and validation in independent cohorts is still unresolved (Alkhateeb et al., 2019). Although these have been achieved, the body of research on transcriptomic predictors of early biochemical recurrence in the context of radical prostatectomy, especially with well-characterized clinical outcome information, is relatively sparse.

An acute deficit thus exists in correlating transcriptomic changes to postoperative outcomes in a clinically significant way. Although past research has presented useful information on the biology of prostate cancer, a number of them are deficient in specific clinical outcome measures of recurrence or lack homogeneity in study design and access to data. Additionally, gene-level studies might not be sufficiently sensitive to reflect the coordinated biological mechanisms working together to produce recurrence, particularly in small cohort studies where statistical power is limited. This underscores the importance of critical models that combine both the gene-level and pathway-level views in explaining the molecular events of recurrence.

The current research, in this respect, seeks to explore transcriptomic variations and correlations with biochemical recurrence of prostate cancer following radical prostatectomy. The study aims to determine the candidate genes and describe the underlying biological pathways associated with postoperative outcomes by comparing the gene expression patterns of patients who do and do not experience recurrence. A special focus is on the pathway-level analysis that can capture coordinated transcriptional programs that cannot be identified by the analysis of individual genes only. In this way, the research aims to add to a better comprehension of the molecular mechanisms of recurrence of prostate cancer and to guide future research towards more effective prognostic stratification and therapeutic targeting.

2. METHODOLOGY

2.1 Research Design

In this study, a retrospective, exploratory transcriptomic study was used to examine molecular differences that were related to postoperative biochemical recurrence in prostate cancer. Comparative design was taken where the gene expression profiles of patients who have recurrence and those who do not were compared to each other after radical prostatectomy. Since the size of the cohort was small, the analytical framework was both gene-level and pathway-level enrichment to identify coordinated biological changes. Instead of setting up predictive biomarkers, the study aimed to determine transcriptional regulation patterns, thus in line with a systems-level investigative strategy.

2.2 Data Source

The data used in the current research were gathered through a publicly available transcriptomic study of genome-scale RNA sequencing of prostate cancer patients subjected to radical prostatectomy. The data includes formalin-fixed paraffin-embedded tumor samples of patients who have and who do not have biochemical recurrence, and the related clinical and histopathological data. It contains high-depth RNA sequencing data produced on the Illumina NovaSeq 6000 platform and has introduced technical replicates to make sure that the data is reliable.

2.3 Data Preprocessing and Quality Control

Raw expression data were imported and organized into an expression matrix, whereby the genes are the rows and the samples are the columns. Patient identifiers, clinical grouping (biochemical recurrence versus non-recurrence), and replicate information were extracted as corresponding metadata were read. Technical replicates were found and pooled by averaging expression values so that a representative profile was available in each patient. The value of the gene expression was log2-transformed in order to stabilize the variance over samples. Filtering was done on low-expression genes by only retaining genes that were expressed above a low threshold level in at least 20% of samples, which decreases noise and enhances statistical strength in downstream applications. After preprocessing, samples that were biochemically persistent and those that were found to be outliers were eliminated to have a consistent comparison between recurrence and non-recurrence groups.

2.4 Differential Expression Analysis

To determine transcripts that were related to recurrence status, a differential gene expression analysis was conducted. Welch's t-test was used to compare the expression values in recurrence and non-recurrence groups to compare them, taking into consideration unequal variances across groups. The difference between the means of expression between groups was computed as the log2 fold change value. To manage the multiple testing of hypotheses of a large number of genes, the p-values were adjusted with the false discovery rate (FDR) of Benjamini-Hochberg. The genes were prioritized according to statistical significance and the effect size, and the prioritized ones were kept for further interpretation through exploratory analysis.

2.5 Gene Set Enrichment Analysis

Since the changes in gene expression are distributed at the level of gene sets, the analysis of the pathways was performed by gene set enrichment analysis (GSEA). A composite metric that included both fold change and statistical significance was used to rank genes. Enrichment was done with respect to the Hallmark gene set collection, which is a curated collection of biological processes with less redundancy. To determine the extent of pathway activation or suppression in recurrence and non-recurrence groups, normalized enrichment scores (NES) were computed. Permutation-based testing was used to determine statistical significance, and pathways with an FDR less than 0.25 were considered enriched, as is the common practice of GSEA when conducting an exploratory study.

3. RESULTS

3.1 Cohort characteristics after preprocessing and quality control

Following the preprocessing, sample harmonization and quality control, 15 tumor samples with complete transcriptomic and clinical data remained to be analyzed further. All samples were associated with different patients. The group included 7 patients who experienced biochemical recurrence (BCR) and 8 patients without recurrence (No BCR), which offered a balanced system of comparative analysis (Table 1).

Table 1. Clinical cohort summary after preprocessing and quality control

Metric	Value
Total samples	15
Total unique patients	15
Outcome groups	2
BCR (n, %)	7 (46.67%)
No BCR (n, %)	8 (53.33%)

3.2 Global transcriptomic variation across recurrence groups

It was analyzed using principal component analysis (PCA) to assess global transcriptomic differences between outcome groups. The initial two major items accounted for 19.6% and 18.1% of the overall variance, respectively. There was a partial separation of BCR and No BCR samples, but this separation was only to a significant degree, suggesting that transcriptional differences related to recurrence are present but not overwhelming at the global scale. The plot demonstrates partial clustering of recurrence and non-recurrence samples, with overlap indicating modest global transcriptomic separation (Figure 1).

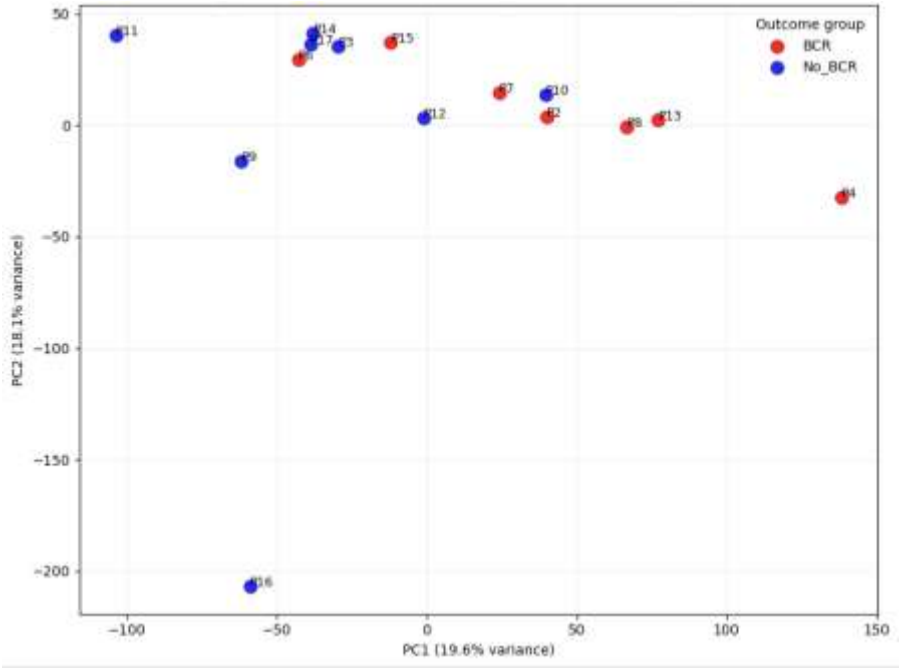

Figure 1. Principal component analysis of the final study cohort

3.3 Differential gene expression identifies candidate transcripts

The differential expressions also indicated that there were a number of genes that had moderate fold changes and low nominal p-values (Table 2). A group of genes had stable directional changes and were preserved as candidate transcripts to be interpreted through exploration.

Table 2. Top-ranked candidate genes differentially expressed between biochemical recurrence and non-recurrence groups

Gene ID	Gene symbol	log2FC	P value	Adjusted P value
ENSG00000181513	*ACBD4*	-1.1847	1.62e-05	0.3153
ENSG00000137166	*FOXP4*	-0.8122	6.10e-05	0.3815
ENSG00000174327	*SLC16A13*	-0.9597	7.00e-05	0.3815
ENSG00000105698	*USF2*	-0.5900	1.63e-04	0.3815
ENSG00000186174	*BCL9L*	-0.5589	2.27e-04	0.3815
ENSG00000139182	*CLSTN3*	-0.8089	2.41e-04	0.3815
ENSG00000067836	*ROGDI*	-1.0999	3.12e-04	0.3815
ENSG00000172830	*SSH3*	-0.5807	3.41e-04	0.3815
ENSG00000001561	*ENPP4*	1.1705	3.58e-04	0.3815
ENSG00000126562	*WNK4*	-1.3700	3.59e-04	0.3815

3.4 Differential expression patterns

The volcano plot was used to visualize the distribution of changes in genes at a level (Figure 2). The bulk of the genes that were clustered around zero-fold change had moderate statistical significance, as expected with weak transcriptional differences between groups. A subset of genes showed greater fold changes and lower nominal p-values; however, these did not remain significant after multiple testing correction.

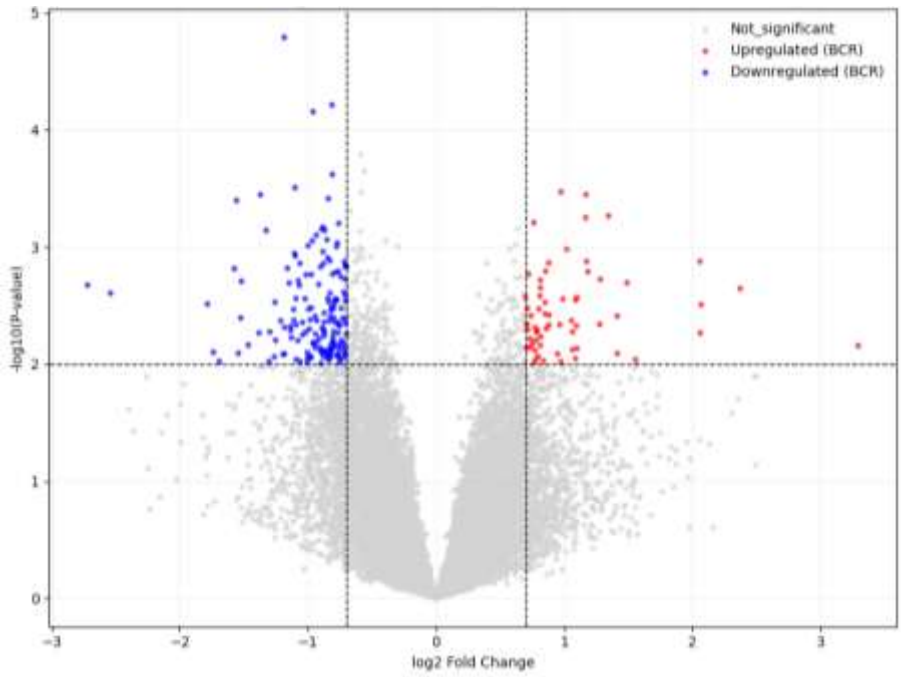

Figure 2. Differential expression volcano plot

3.5 Pathway-level enrichment reveals coordinated biological alterations

Since statistically significant individual genes were not found after correction, the pathway level analysis was carried out by gene set enrichment analysis (GSEA), which utilizes Hallmark gene sets. In total, 34 pathways were significant (FDR < 0.25) and pointed to a coordinated transcriptional difference related to recurrence status.

Pathways involving androgen signaling, cellular proliferation and metabolism, such as androgen response, MYC targets, mTORC1 signaling, and fatty acid metabolism, were enriched in tumors of patients with biochemical recurrence (Table 3). On the contrary, immune and inflammatory pathways, such as interferon gamma response, TNF-α signaling through NF kB, and interferon-α response, were enriched in tumors without recurrence.

Table 3. Significantly enriched Hallmark pathways associated with biochemical recurrence

Pathway	NES	Nominal P value	FDR q value
Androgen Response	1.8854	0.0	0.0
Protein Secretion	1.8267	0.0	0.0
TNF-α Signaling via NF kB	-1.5994	0.0	0.0
Interferon Gamma Response	-1.6976	0.0	0.0
Apical Junction	-1.6637	0.0	0.0
Fatty Acid Metabolism	1.6979	0.0	0.0038
Wnt β Catenin Signaling	-1.5527	0.0	0.0042
Interferon-α Response	-1.5684	0.0	0.0050
mTORC1 Signaling	1.5615	0.0	0.0051
MYC Targets V1	1.7581	0.0	0.0051

The most enriched pathways were visualized in order to make interpretation easy using normalized enrichment scores. Pathways that were enriched with positive scores in BCR and negative scores in No BCR, respectively, exemplified a distinct difference between proliferative and immune-related programs. Positive enrichment scores correspond to pathways associated with recurrence, whereas negative scores indicate enrichment in non-recurrent tumors (Figure 3).

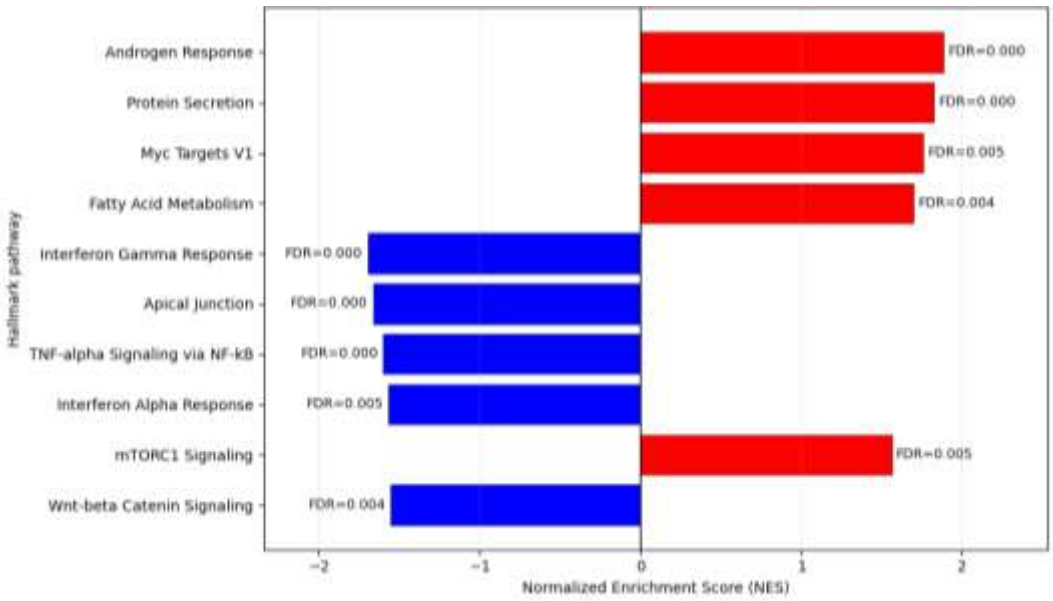

Figure 3. Top enriched Hallmark pathways associated with recurrence

Pathway-level analysis demonstrated strong and biologically consistent transcriptional programs related to recurrence, which showed that coordinated molecular events and not individual-gene changes are behind postoperative outcomes in this cohort.

4. DISCUSSION

The pathway level of molecular profile that is associated with postoperative biochemical recurrence was more clearly defined than the level of individual transcripts. The most notable pattern was an increase in androgen response, protein secretion, fatty acid metabolism, mTORC1 signaling and MYC target programs in recurrent tumors along with a relative down-regulation of interferon signaling, TNF-α signaling, apical junction and other immune or structural pathways. This combination indicates that recurrence following radical prostatectomy might be predetermined by a biologic state that is growth-permissive, metabolically-adaptive and less restricted by inflammatory surveillance. Practically, the recurrent group is observed to have a transcriptional architecture to maintain the fitness of tumor cells even after their local therapy has been finalized. The enrichment of androgen-associated signalling reflects the persistent role of androgen receptor activity in driving disease progression, indicating coordinated activation of an androgen-linked transcriptional network rather than isolated gene effects. Instead of a single dominant transcript, the findings suggest that there was a concerted activation of an androgen-linked network, which is more in line with the biology of recurrence than a specific gene effect. This can be analogously interpreted when the programs of MYC and mTORC1 are both activated at once. Collectively, these results suggest that recurrent tumors could perpetuate biosynthetic need, proliferative signaling, and metabolic rewiring in a way that prefers survival or re-emergence following surgery. Meanwhile, the comparative loss of interferon and TNF-α pathway activity and impaired enrichment of epithelial organization pathways, including apical junction, point to recurrence not being purely a matter of proliferative strength. It can also entail the weakening of tumour-immune interaction and tissue architecture deformity. This bilateral trend is significant as it suggests that postoperative failure can be expected to occur due to a combination of phenotype and not due to a purely proliferative one. This is further supported by the fact that the results after multiple-testing correction at the gene level are not statistically significant: the signal in this cohort does not seem to be localized in a limited number of strong transcript changes. That trend is perfectly consistent with a clinically heterogeneous disease like prostate cancer and is in line with the systemic-level exploratory nature of the current analysis.

The androgen response enrichment of recurrent tumors is not a new finding, as the role of androgen receptor signaling has been a key factor in prostate cancer progression, adaptation, and resistance to treatment, even in the metastatic or treatment-resistant state (Feng and He, 2019). The evidence underpinning this opinion is that decades of clinical development of therapeutic suppressions of androgen receptor activity, despite its effectiveness, is an axis of disease control, which emphasizes the constitutive role of incessant androgen dependence in progression biology (Estebanez-Perpina et al., 2021). The observed pattern of pathways is also in line with literature highlighting the heterogeneity of androgen receptor signaling overall, such that different cellular states and receptor states can cause disease progression and resistance rather than a homogenous transcriptional program (Jamroze et al., 2021). Recent evidence that downstream effectors of the androgen receptor, such as those of variant signaling can drive tumor progression, can be used to provide a biologically consistent view of how androgen-related enrichment can nonetheless be present in recurrent disease post-surgery (Teramoto et al., 2024). The simultaneous amplification of targets of the MYC and mTORC1 signalling is conducive towards a broader oncogenic interpretation where recurrence is an indication of a coordinated proliferative and metabolic activation. Early analyses of other tumor models have shown that Akt-mTOR signaling pathways greatly facilitate the occurrence of c-Myc-induced oncogenesis, showing that the

two pathways can co-occur and not act independently due to their biological plausibility (Xu et al., 2019). Recurrence-oriented studies have also been capable of identifying molecular predictors of aggressive post-treatment, especially in prostate cancer, which can be used to support the idea that transcriptomic features can be capable of identifying early indicators of biochemical relapse (Wei et al., 2022).

Of particular interest is the relative inhibition of the TNF-α and interferon-related mechanisms in recurrent tumors. The involvement of TNF-α in cancer is complicated, whereas its association with antitumor immunity and immune activation allows its relative depletion with an immune-permissive tumor microenvironment (Mercogliano et al., 2021). Similarly, there is larger evidence suggesting that the immune evasion programs caused by microenvironmental stress responses often promote tumor progression, such as pathways associated with hypoxia and inhibition of efficient immune surveillance (You et al., 2021). In line with developing attempts to rely on computational and molecular models to characterize androgen receptor expression as a prognostic character in prostate cancer, the presence of androgen-related programs is eminent in the recurrent cluster (Zhang et al., 2025). It is also consistent with clinical findings that post-radical prostatectomy progression, especially in high-risk disease, can be predetermined by biologic characteristics of more persistent or treatment-adaptive tumor behavior (Nishino et al., 2024).

These results have both biological and clinical implications. On the biological level, they indicate that recurrence of postoperative recurrence can be better conceptualised as a system-level condition characterized by the coordinated androgenic, metabolic and proliferative activation, and a decline in immune-related signalling. This clinically helps to argue that pathway-based molecular profiling could be more interpretive than, e.g., individual transcripts in small or heterogeneous surgical cohorts. The findings also indicate a conceptual framework where recurrence risk can be associated with residual tumor burden as well as the existence of certain signaling programs that prefer regrowth following local therapy. This view could prove valuable in risk stratification efforts of the future and prioritizing therapeutic avenues to explore in recurrent disease.

One must consider a couple of limitations. The size of the cohort was small, limiting statistical power to make inferences on a gene-level and preventing the possibility of more detailed subgroup analyses. It had to be limited to bulk transcriptomic data, which does not allow resolving cell-type-specific contributions by tumor, stromal, or immune compartments. No independent cohort was conducted to validate the external validation, the external validation of the pathway profile is yet to be decided. Moreover, despite the complementary molecular information underlying the resource, the current study was restricted to transcriptomic patterns and thus lacks multi-omic interactions, which can further hone recurrence biology.

These results need to be confirmed in future research in larger and independent prostatectomy cohorts that have standardized clinical follow-up. A combination of transcriptomic profiles with methylation, spatial, or single-cell data would contribute to the understanding of the androgen-metabolic and immune-suppressed phenotype observed here, occurring due to intrinsic tumor cell programming or microenvironmental remodeling, or both. Future research could also help elucidate the potential of these pathway signatures to enhance the postoperative risk assessment or help to predict those patients who might be subjected to therapeutic intervention beforehand.

5. CONCLUSION

The recurrence of biochemical abnormalities post radical prostatectomy seems to be linked to concerted transcriptomic reprogramming as opposed to single-gene alterations. The current results suggest that recurrent tumors are marked by androgen-responsive and proliferative pathways, as well as metabolic pathways, and relative inhibition of immune- and inflammation-related signalings. This trend is in agreement with the observation that the postoperative course is partly influenced by a concerted molecular phenotype that predisposes tumor survival, adaptive expansion, and down-regulation of the immune system. These findings also show that pathway-level interrogation can be useful in small, clinically annotated cohorts, in which gene-level effects can be small and diffuse. Translationally, these data indicate that systems-level molecular profiling could be a more informative system of analysis of recurrence biology than transcript-based markers in isolation. Even though the external validation is still required, the specified signaling programs provide a biologically consistent foundation to future prognostic models and therapeutic research. Collectively, the research contributes to the existing knowledge on the molecular determinants of surgical outcomes in prostate cancer and the identification of biologically significant pathways that can be associated with recurrence following definitive treatment, based on the local therapy.

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