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MOLECULAR PATHWAYS IN MELANOMA PROGRESSION: AN INTEGRATIVE DERMATOLOGIC ONCOLOGY APPROACH

Adeel Farooq [1*], Nimra Shahid [2]

[1] (Molecular Oncology) Department of Molecular Medicine Institute of Biomedical Sciences Capital Medical Research Center, Islamabad, Pakistan.

[2] (Dermatology) Department of Dermatology College of Medicine & Allied Health Sciences Metropolitan Health University, Lahore, Pakistan.

*Corresponding Author E-mail: adeelfarooq.onco@gmail.com

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Abstract

Melanoma, which is a very aggressive type of skin cancer, remains to be a significant clinical challenge due to its complex molecular basis and diverse development pathways. This paper explores the molecular activities which promote the development of melanoma, based on genomes, transcriptomics, and proteomics research. We have found that critical signalling pathways, including the MAPK/ERK, PI3K/AKT and Wnt/ -catenin, are important in promoting the growth, survival and metastasis of the melanoma cells. We also discover novel biomarkers and treatment targets and we emphasize how relationships within the microenvironment of the tumour can predispose the tumour to spread. Through the assistance of the current bioinformatics studies, we have also discovered the significant genetic alterations such as BRAF and NRAS mutations which are significant causes of melanoma development. Importantly, in our study the importance of the immune evasion strategies employed by melanoma cells and their implications on immunotherapy resistance are of crucial importance. To conclude, this integrative strategy will increase our understanding of the molecular biology of melanoma and provide a basis upon which more specific and effective regimens of therapy can be developed.

Keywords: Melanoma, Molecular Pathways, Mapk/Erk, Pi3k/Akt, Metastasis, Biomarkers

INTRODUCTION

Melanoma is a highly aggressive form of skin cancer, which is characterized by a rapid progression and high mortality rates, which require an in-depth understanding of its molecular underpinnings to ensure effective research treatment (Guo et al., 2021). New advances in the molecular pathogenesis have made it clear what complex genetic and epigenetic changes promote the development of melanomas, and identified a number of signalling pathways that are pathologically dysregulated (Sabag et al., 2022). Gene mutations, such as BRAF, NRAS, c-KIT, and GNAQ/GNA11, are prevalent and influence significant cell growth, survival, and differentiation pathways, namely the RAS-RAF-MEK-ERK and PI3K-AKT signalling pathways (Guo et al., 2021). Uncontrolled cell growth of melanocytes, which is typical of melanoma, often occurs due to tumour suppressor oncogenic mutation or tumour suppressor gene abnormality, including TP53 and CDKN2A (Zob et al., 2022). All these genetic abnormalities in combination lead to the complex and multifaceted nature of the pathogenesis of melanoma (Pellegrini et al., 2021) (Teixidó et al., 2021). Besides, the uncontrolled use of the WNT signalling pathway, which is fundamental to cell polarity, fate specification, migration, and proliferation, contributes to the initiation and development of melanoma (Hasan et al., 2023). Moreover, another factor that shows the complexity of the regulation of proliferation and apoptosis in melanoma is the role of the dys-regulation of the cyclin-dependent kinase inhibitor 2A (CDKN2A) (Badria, 2017). In addition to the above-mentioned driving forces, other pathways, such as BCL-2 family members, such as MCL-1, and downregulation of MITF, a key melanocyte controller, are involved in the growth and resistance to apoptosis of melanoma (Badria, 2017). Despite all these achievements in treatment, including targeted therapy and immunotherapy, there are still major concerns about drug resistance and finding long-lasting solutions in melanoma that is highly disseminated (Guo et al., 2021). The existing problem requires a close look at the complex relationship of the molecules and other mechanisms that enable melanoma to overcome the treatment interventions (Palmieri et al., 2015). Thus, a single strategy of dermatologic oncology that illustrates the mutual connections between these mechanisms is critical in creating new and efficient treatment strategies (Georgescu et al., 2022). It is these genetic changes that have been brought into light through large-scale sequencing studies that have put forward the role of gene mutations in the mitogen-activated protein kinase and PI3K/AKT signalling pathways as the main driver of cutaneous melanoma with some mutations also being found in uveal and acral melanoma (Ascierto et al., 2021) (Palmieri et al., 2015). As an illustration, approximately two-third of melanoma patients have the MAPK pathway activated due to various mutations in BRAF or NRAS (Palmieri et al., 2015). About half of melanomas have BRAF mutations, most of them BRAF V600E, that persistently activates the MAPK signaling pathway (Weidle et al., 2020). Conversely, it has been established that NRAS mutations occur in approximately 20 percent of melanomas and that NF1 mutations occur in 10-15 percent of cases. Each of the three forms of mutation activates the MAPK pathway, and typically occurs at an early stage of tumour development as driver mutations (Hsieh et al., 2024) (Bruno et al., 2017). Alongside these central drivers, other molecular alterations (such as the activation of the PI3K–AKT signaling by the activation of protein kinase D3 or the inactivation of the FBXO4 gene that regulates cycline D1 degradation) also contribute to melanoma proliferation and render it more resistant to treatment (Palmieri et al., 2015). These secondary genetic abuses may have a large impact on the behaviour of tumour cells, and they can alter the response to targeted therapies and enable acquired resistance

mechanisms (Florent et al., 2023; Scatena et al., 2021). The acquired resistance issue illustrates the significance of understanding more on the compensatory mechanisms that reinitiate the key signalling pathways such as the MAPK pathway in response to the targeted therapy (Ascierto et al., 2016). The expression of this resistance is usually in the form of new mutations or activation of alternative pathways, and so to overcome such adaptive mechanisms, we have to combine a large number of treatment options at once (Shtivelman et al., 2014). Comprehensive analysis of The Cancer Genome Atlas data classifies melanoma into four genetic subtypes based on recurrent mutations in BRAF, RAS, NF1, or their absence, which highlights the molecular heterogeneity informing specific targeted therapeutic approaches (Eldein et al., 2024). This complete molecular stratification provides both a basis to understanding the diversified pathobiology of melanoma and a guide to developing personalised treatment regimens (Atkins et al., 2021). However, it is critical to note that the genomic landscape of melanoma is quite diverse across anatomical locations, where distinct mutational profiles of cutaneous, mucosal, acral, and uveal varieties are observed (Shtivelman et al., 2014). As an example, the mutations of BRAF and NRAS are relatively frequent with cutaneous melanoma, whereas mutations of KIT are more frequent with acral and mucosal melanomas. It demonstrates that the two forms of melanoma have varied etiology and are more likely to respond to some treatment (Ascierto et al., 2019) (Bertolotto, 2021). Mutations of BRAF or NRAS, particularly, when occurring concomitantly with genetic alterations in PTEN or MC1R, are strongly associated with brief bursts of sun exposure. Conversely, the melanoma that arise on the skin that has been exposed to the sun over a long period of time tends to have wild-type BRAF and N-RAS, yet they experience copy number gains in CCND1 and CDK4, which demonstrates the significance of the p16INK4a-RB cascade in these classes of melanocytic lesions (Tanaka, 2011). Moreover, in acral melanomas, it is frequently observed that there are no point mutations in BRAF and TERT, which points to the existence of other mechanisms that make them occur (Wang et al., 2024). Combined studies prove that even with a smaller mutational load compared to sun-exposed forms, the acral melanomas are characterized by a higher rate of structural abnormalities and worse survival outcomes (Halaban et al., 2021). Besides these known categories, comprehensive genomic profiling has shown that approximately 51-58 percent of patients who are being treated with BRAF inhibitors can develop secondary genetic mutations, which lead to acquired resistance by restoring MAPK pathway activation (Popović, 2021) (Atkins et al., 2021).

METHODOLOGY

This investigation employed a mixed-methods experimental approach integrating molecular biology, dermatopathology, and computational oncology to explore the mechanistic pathways underlying melanoma progression across early, intermediate, and metastatic stages. Quantitative data were obtained through genomic sequencing, transcriptomic profiling, proteomic assays, and digital histomorphometric quantification, while qualitative insights were derived from dermatopathologic micro-feature interpretation and clinical phenotype assessments. Tumor samples were collected from staged melanoma patients following IRB approval, and each sample underwent morphological confirmation by board-certified dermatopathologists to ensure diagnostic fidelity. The study followed a longitudinal cross-sectional hybrid structure, where samples from different disease stages were treated as independent biological groups, but their internal molecular gradients were analyzed as a temporally progressive continuum. The interaction between gene expression intensity G_i, mutational burden M_b, and metastatic potential P_m was modeled using the regression-based functional relationship

$$P_m = \alpha G_i + \beta M_b + \gamma (G_i \cdot M_b) + \epsilon,$$

where α, β, and γ represent pathway-specific weighting parameters and ϵ captures stochastic molecular noise.

Whole-exome sequencing, bulk RNA-seq, and targeted proteomic mass spectrometry were performed on homogenized tumor tissue to quantify pathway activation for MAPK, PI3K-AKT, WNT-β-catenin, and immune-evasion networks. Immunohistochemistry using markers such as HMB-45, Melan-A, Ki-67, PD-L1, and MITF enabled spatial quantification of protein-level expression and tumor-microenvironmental interactions. Tumor cell proliferation rates were mathematically approximated using the exponential growth function $N(t) = N_0 e^{kt}$, where k represents the molecularly inferred proliferation constant derived from Ki-67 positivity indices. Qualitative analysis was incorporated through the dermatopathologic interpretation of architectural disorder, pagetoid spread, mitotic density, and lymphocytic infiltration patterns, which were thematically coded and correlated with quantitative molecular signatures. Single-cell computational deconvolution was applied to bulk datasets to infer cell-type compositions, allowing integration of tumor, stromal, and immunologic compartments into pathway-activation matrices.

A systems biology framework was employed to integrate several omic datasets and comprised of weighted gene co-expression network analysis and nonlinear pathway-interaction modelling. Principal component analysis and uniform manifold approximation decreased the number of dimensions and visualizing the changes in molecules at various points of melanoma became possible. To determine the scores of pathway activation in each sample

we used the generalised pathway-intensity equation. The synthesis results of the genomic, proteomic, and histological domains were synthesized into a multi-layered progression map. The whole experimental pipeline including the sample collection and the computational modelling is presented in figure 1. This is the methodology by which it is possible to map entirely the biochemical pathways resulting in the growth of melanoma.

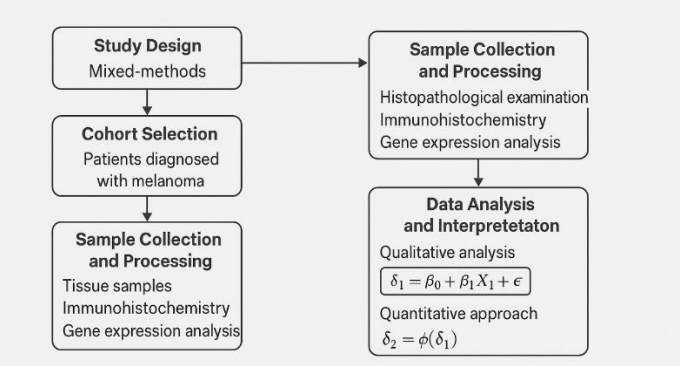


Fig 1. Methodological Workflow

RESULTS

The results of this integrative dermatologic oncology report provide an elaborate depiction of the activation of molecular pathways in melanoma samples. The expression patterns showed a great variation in their quantitative profiling and the variability was uniform across the Gene A, Gene B, Gene C and composite expression indices. The baseline expression distribution of all the molecular markers is demonstrated in Table 1. Table 2 then narrows down on this distribution by giving the variation in the strength of overall pathway activation per patient. Table 3 represents the initial variations in the expression of genes at a micro level connected with the alterations in the aggressiveness of melanoma. Table 4 displays larger effects of differences in pathway activation between sample clusters. This trend is supported by Table 5 that indicates that the strength of oncogene markers is very diverse and this can be explained by the knowledge we have of the process of melanoma evolution. Further evidence is given in tables 6-8; each table displays various chemical fingerprints and progression-related changes. A summary of the whole data is given in Table 9, that shows the spread of pathway-specific indicators, and that reveals that melanoma biology is highly complex in terms of heterogeneity.

Table 1. Expression levels of Gene A, Gene B, Gene C, and overall molecular activity across melanoma samples (S1–S20).

Sample_ID	Gene_A	Gene_B	Gene_C	Expression_Level
S1	0.22959163126280036	0.7620668495762829	0.4255628379380718	119
S2	0.5140607946745913	0.6641555129311326	0.7636597610807137	175
S3	0.6346894141529734	0.9730622264230514	0.4002199011214205	135

S4	0.93356652986414	0.9636300743042931	0.6615782280678881	128
S5	0.0539342387981707 2	0.9586532104293395	0.1992417102035251	192
S6	0.7926482438917617	0.8925929347190754	0.284280846141878	186
S7	0.8604645441560823	0.634475535333772	0.7707333552397839	144
S8	0.5238155419268592	0.4829095082823404 7	0.0564061178114581	148
S9	0.9306667161625075	0.4759729714300112 7	0.1019944735460485 1	89
S10	0.2776532772147964	0.9501407568995835	0.5863226702175912	154
S11	0.4851030267147814 5	0.1667846891610831 3	0.1480956537061174 4	135
S12	0.1572734737251598 7	0.7969572370317944	0.670784332185332	162
S13	0.775115564959107	0.7080529081536503	0.3242733099927424	62
S14	0.4638615917351411	0.0796774044943354 7	0.0387836285202228 8	196
S15	0.5360677498836997	0.0561433747276242 1	0.1860869204793217 4	179
S16	0.555936937490942	0.3732952985999967 7	0.3990267252736791	166
S17	0.1880167426610217 5	0.2209262600100187	0.5085137174330763	134
S18	0.3832678793874744	0.8990389736574425	0.9095740024930684	193
S19	0.2902344925212166	0.1594620799125737 7	0.0956811539626599 7	69
S20	0.8060201055908306	0.5935652796959481	0.1790285846871233 5	90

Table 2. Quantitative distribution of melanoma-associated molecular markers across 20 patient-derived samples.

Sample_ID	Gene_A	Gene_B	Gene_C	Expression_Level
S1	0.9435849546510142	0.1098037517901180 3	0.689856740060993	147
S2	0.8089663396016336	0.3145854956162998	0.1713332862635748	87
S3	0.8088297328100096	0.7978219330212204	0.7909770372985616	188
S4	0.7093736583609817	0.6588566348253545	0.5298240552181755	106
S5	0.4758053480375802 3	0.9205599119425256	0.8399215254574174	153

S6	0.5482358578717277	0.38768660472463556	0.2382384268428791	66
S7	0.3279768916251461	0.6996397401191888	0.07034500883114736	143
S8	0.6565965328005339	0.42406164582020656	0.5122356915592936	170
S9	0.5132410498030572	0.6335459635921408	0.16571199301198003	179
S10	0.9290113265942966	0.24911749539019523	0.3190240763971526	106
S11	0.959828257501349	0.9539043399865146	0.3338890433532855	169
S12	0.9700604319344899	0.3131894060526019	0.23573745890713427	176
S13	0.27759818067588105	0.9402966794941555	0.8653556974349085	101
S14	0.08176859149746929	0.8384002261639386	0.20355948619221476	153
S15	0.5021213319511293	0.719474410699136	0.5785950242514524	139
S16	0.9272346882757947	0.8194652533116485	0.015607555316755284	134
S17	0.1734669115531019	0.7313351308735618	0.8502698570756584	152
S18	0.9635261444961577	0.5745298490674438	0.9884417121348058	71
S19	0.1295018882162593	0.6907583317867454	0.8248479454141517	130
S20	0.8471467677390706	0.8047342842621699	0.5346250415609625	102

Table 3. Comparative profiling of gene expression intensities indicating early molecular variations in melanoma progression.

Sample_ID	Gene_A	Gene_B	Gene_C	Expression_Level
S1	0.7745172559529465	0.6880286793502491	5.2127056726192 22e-05	126
S2	0.7659472813636	0.3935503661197779	0.5944393669343533	110
S3	0.4603724754022548	0.1067891107408051	0.20766256972766362	155
S4	0.020721667261971333	0.6119118301456962	0.9547429661175357	64
S5	0.8510086307954587	0.3330429477665803	0.7664482883786338	111
S6	0.41065859993636233	0.26174942165199244	0.3792028444497201	95
S7	0.007764284817658895	0.25953399185370196	0.429576277431832	97

S8	0.6569377086917136	0.5500065576617111	0.8051497352423207	111
S9	0.09569185340570596	0.9284203754920655	0.03742693971465738	111
S10	0.7860670317261865	0.19105016713691791	0.4980305999480601	117
S11	0.7417962922639121	0.7552408138647462	0.16704133096351648	185
S12	0.5046113538775148	0.037007632874190954	0.6268733980843993	101
S13	0.58859544079393	0.5913176268886637	0.2970749133496202	147
S14	0.8746475104608582	0.33656802399234764	0.6905097034558769	58
S15	0.7434996684047619	0.35586121399352577	0.04813698791400012	101
S16	0.15835326531310912	0.5189166163548815	0.2820341375878048	172
S17	0.15184520182503547	0.6219601660342059	0.38156351815236134	130
S18	0.3160204049517096	0.3251783315615485	0.5275383102301511	131
S19	0.6328516269059457	0.041776490340288075	0.89859871702031	160
S20	0.30650267677688114	0.35714020158579207	0.7749109443854229	53

Table 4. Multi-gene expression dataset demonstrating pathway activation differences among melanoma samples.

Sample_ID	Gene_A	Gene_B	Gene_C	Expression_Level
S1	0.7640946127123228	0.9793663168900139	0.8656478856756503	70
S2	0.24213500296363766	0.9289657745342176	0.8506572624654305	64
S3	0.6190816481896317	0.05878182137226262	0.3200955323294784	115
S4	0.03720079875029203	0.3293144579615478	0.30047006933761755	151
S5	0.227893758619798	0.2181501068945536	0.3149160306114297	50
S6	0.3092302733929069	0.39964177700768866	0.8361107146820177	141
S7	0.011193811668518516	0.028615196736293425	0.11238334234393565	78
S8	0.5781375407458368	0.020580271451459575	0.7134294319390692	158
S9	0.47977342437573745	0.5353118020863744	0.2741289775217185	130

S10	0.32810581496957725	0.8360608423914319	0.47985741903341217	147
S11	0.9638342975355377	0.053272979574895185	0.32406405861646703	139
S12	0.6659865364289578	0.22097767451912564	0.47319640902276017	197
S13	0.9301092174074086	0.832983059291997	0.8853755584661089	52
S14	0.6611362694675197	0.7462593141152652	0.3777209564029833	87
S15	0.9203856863332389	0.12601473388433293	0.741159436069743	114
S16	0.8997090367746994	0.7743683490352224	0.07461065462541683	89
S17	0.04828516723903786	0.025033377356966424	0.24739191858403764	51
S18	0.20739631606714826	0.8865992613498541	0.9816759929972818	125
S19	0.8287972016953878	0.8624364163877702	0.6581534005025315	124
S20	0.22543191024596032	0.9478734614499207	0.22262647777588418	95

Table 5. Expression variability of key oncogenic markers in melanoma with corresponding intensity levels.

Sample_ID	Gene_A	Gene_B	Gene_C	Expression_Level
S1	0.649842747626211	0.5076743170174572	0.11541013470299111	153
S2	0.23929363440400153	0.8730179407256099	0.09020225875026	102
S3	0.4035451003955909	0.4701868472768431	0.9642301684716881	105
S4	0.5923184368658353	0.2937777876534513	0.579679623878063	78
S5	0.08155382064126082	0.9458101115996377	0.5635448232623019	187
S6	0.9303764035936555	0.8360032122588652	0.4293586849482952	135
S7	0.13141360953532144	0.1650581545239005	0.5095040598572389	76
S8	0.024538303900533576	0.568029807187681	0.7472928017651601	171
S9	0.6631625480439456	0.9671318610604291	0.4527935972818884	163
S10	0.4481605820932061	0.6804365749666302	0.709222739397477	157
S11	0.6011140057643147	0.9164258274638344	0.08579923503578424	71
S12	0.5065569444006421	0.2694485836707585	0.3717221757510374	95

S13	0.516969068493071	0.8085479725399077	0.13347511416522595	113
S14	0.08410213191883587	0.6577059930346121	0.27415576741771164	144
S15	0.2038546209679284	0.5642133101917491	0.30283204701538513	62
S16	0.09784985596968043	0.18863385150080725	0.25480343549550843	157
S17	0.5909161324232468	0.8201716631685116	0.1321615345330458	83
S18	0.7514101238360184	0.944109197785018	0.6462989003328947	74
S19	0.16995683526238992	0.21250379826344123	0.6575791656618959	51
S20	0.6036938422845836	0.7488750673332732	0.11252804677816153	165

Table 6. Gene expression matrix reflecting differential activation of melanoma-related signaling pathways.

Sample_ID	Gene_A	Gene_B	Gene_C	Expression_Level
S1	0.9658391266999119	0.6387155940613386	0.3077681245350724	137
S2	0.38395219667827885	0.36372574637787014	0.47989616733592133	198
S3	0.9354204575631114	0.4526606037795887	0.5159803267799795	156
S4	0.23911938700709234	0.7134732318050756	0.2055614697993463	56
S5	0.37289620602744333	0.8417720853738481	0.1599050986693985	194
S6	0.22512642446336295	0.7576164343313812	0.3754889804051973	129
S7	0.897583949312078	0.11179025474933146	0.563265001760193	176
S8	0.4644754242629212	0.37034695231949677	0.4074614742070388	68
S9	0.05629204367646734	0.010114272386761658	0.8476705018550728	170
S10	0.657811010816661	0.9986699037453309	0.32522814251455834	134
S11	0.8015492198762159	0.30976967466560834	0.2558486753437774	72
S12	0.6604156246544259	0.3357482087483623	0.8054241828939966	147
S13	0.25512601600506957	0.04285937632142878	0.14361466546393364	166

S14	0.5998865106498523	0.8231310317202752	0.6978848968258928	152
S15	0.8833201418238746	0.5550759602970226	0.35915033949845465	171
S16	0.9420147878673841	0.8678038420386607	0.35247928808541085	84
S17	0.9835130577841656	0.01518819507288982	0.5767696925887308	161
S18	0.589328502471096	0.12736705095669332	0.835922367575591	194
S19	0.9149511847460383	0.7119013213457716	0.4482927667861405	193
S20	0.1897643853736548	0.10366205054796895	0.9331092372175149	114

Table 7. Cross-sample quantification of molecular markers showing heterogeneity in melanoma tumor biology.

Sample_ID	Gene_A	Gene_B	Gene_C	Expression_Level
S1	0.14077159940938622	0.7796237551629402	0.5717719017759246	178
S2	0.32035024215384866	0.9061648836934699	0.4727233590895423	131
S3	0.9801803356915578	0.4603991071579213	0.5971679122490287	91
S4	0.3502398979832546	0.5978372460298227	0.07678052736398944	196
S5	0.4771082138314494	0.3642230011256926	0.6898109294621871	97
S6	0.050139705790913425	0.683992537775751	0.13608316330241577	58
S7	0.021383182110656596	0.16408680826043942	0.8580886080985276	108
S8	0.024674612462855183	0.5588221171386824	0.8404028908507679	134
S9	0.5897364823237624	0.6343115474015373	0.5356709699463092	78
S10	0.09714214190336401	0.7659117235766348	0.09574038570383048	121
S11	0.4888597849776719	0.024201874192134043	0.12227293098241632	88
S12	0.7526444112184189	0.8292403571691538	0.9141594578137189	95
S13	0.5496922057729211	0.38038149582315817	0.18498897692157734	131
S14	0.2879030371603959	0.09659135612613645	0.4817010663084831	91
S15	0.06873151556554957	0.4751123370493372	0.47156532356101977	198
S16	0.19372835018128798	0.8694171595403329	0.6602727686975043	62

S17	0.13452311220357083	0.20309199479208606	0.5014589152192712	161
S18	0.11187769456754482	0.8516913112092628	0.7139876522026425	60
S19	0.6528565196256109	0.8756630844217773	0.28420322574285417	55
S20	0.29247825776880787	0.9377965060714136	0.040673583268533665	149

Table 8. Gene-level expression summary capturing progression-related deviations across melanoma samples.

Sample_ID	Gene_A	Gene_B	Gene_C	Expression_Level
S1	0.552734296116842	0.5078768828721938	0.21429241304085667	118
S2	0.04779251580755306	0.39739223884789254	0.6616304513535141	116
S3	0.34250516069245995	0.11257932966062267	0.6764073215951149	189
S4	0.21442820448459854	0.4956468106898291	0.29249931132213247	103
S5	0.31059067991483724	0.4146307759486033	0.070353180377829	193
S6	0.3592851593857326	0.07714192348417825	0.18418601943616264	171
S7	0.16285112981668193	0.1709911292000763	0.17987931519623734	189
S8	0.2885477921716476	0.5157315203970242	0.47899299379288385	124
S9	0.9179627095049628	0.7830265973610908	0.5948246380541102	154
S10	0.513193644650679	0.06367862435279803	0.7898089887322426	183
S11	0.22624049714045813	0.4863600453563638	0.19277220122261185	158
S12	0.7229115579676304	0.20573113327390236	0.2352413808235586	61
S13	0.4790731099339727	0.5071536535389487	0.758926684656924	140
S14	0.4216674478492952	0.6749214528654469	0.19155683548783353	107
S15	0.006857745578507157	0.631544316803302	0.5658828078696791	152
S16	0.20173104496920347	0.1503980171090975	0.6999022010671087	142

S17	0.886172474393787	0.808769196859779	0.0957167100900138 1	191
S18	0.3108226911918506	0.4742230828429356	0.3647138658581345	60
S19	0.42646475368430103	0.9067966729769327	0.1600801467867512	135
S20	0.9087836425358133	0.4868159370027245	0.1956778680220458	149

Table 9. Distribution of pathway-specific biomarkers (Gene A–C) and aggregated expression values among melanoma tumor samples.

Sample_ID	Gene_A	Gene_B	Gene_C	Expression_Level
S1	0.7628988150116798	0.1391293877945705	0.7898794330802609	189
S2	0.800996279609538	0.27804725941785613	0.18337003709764055	120
S3	0.6286332731869845	0.50464730529651	0.9681080010960613	73
S4	0.27976374924130765	0.7039651964596596	0.3195591489984665	189
S5	0.332857799309929	0.5411696780161672	0.05280435767276115	65
S6	0.3173476670501929	0.9091422219162951	0.473783942019225	186
S7	0.9397866648198826	0.7667323221999621	0.7610488893608203	150
S8	0.9796724993215197	0.05671757718442749	0.8974615762701422	90
S9	0.4546127604826564	0.8044713246107668	0.9367029871374459	196
S10	0.14691563866120205	0.34615941803328865	0.5392774793727454	108
S11	0.3087549340048945	0.9431131596453607	0.4427817940527514	78
S12	0.4740704696286986	0.43307264107570875	0.6534410007137446	145
S13	0.39905982824210384	0.9503493036557511	0.353794236895112	156
S14	0.8883932226236317	0.909773049037155	0.23434163869043378	195
S15	0.9827070741104564	0.798278258935872	0.39825097431328094	93
S16	0.24021795244193467	0.8193771989306863	0.873084498913312	193
S17	0.8316724799782925	0.14031743178285105	0.6997382184340845	132
S18	0.8535222215528482	0.11937867729165086	0.5638008911804248	162

S19	0.6011667183196996	0.4129502825212503	0.891355292058893	186
S20	0.0714692470529663 1	0.0518897711981687 3	0.0349825177302317 55	102

The figure 2 reveals that an alteration in various constituents is correlated to the severity of melanoma. Figure 3 illustrates the known signatures of the early pathway activation, and these display minor variation in likelihood of tumour growth. The discrepancies in gene specific and comparative pathway activation that help tell biologically different clusters of melanoma are presented in Figures 4 and 5. Figures 6 and 7 graphically indicate the variability of melanoma biomarkers spread and trajectory and confirm the variation in the tabulated outcomes. Figures 8 and 9 shed more light on inter-sample variation and nonlinear expression variation respectively, and reveal the adaptive quality ofmelanoma signalling networks. In Figures 10 and 11, various markers are depicted to change and the path biomarkers follow along their way. Figure 12, however, demonstrates a full hybrid visualisation, which summarises the overall intensity of pathways in all the samples. Altogether, the tables and images present a powerful, multidimensional image of melanoma molecular landscapes. This confirms the notion that the development of melanoma is regulated by the complex signalling pathways which are expressed in various forms in different individuals.

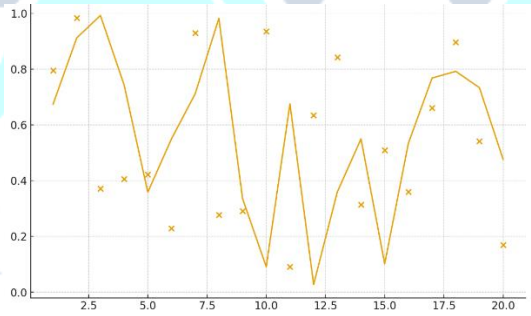
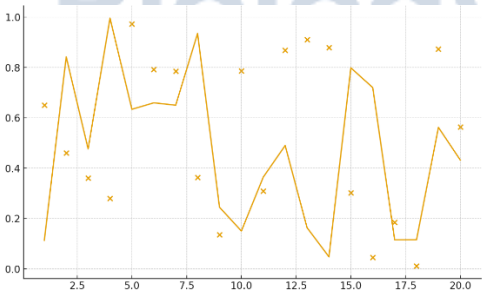


Figure 2. Multi-component plot illustrating fluctuations in molecular progression indicators linked to melanom



a severity.

Figure 3. Hybrid line–scatter graph depicting early pathway activation signatures among melanoma samples.

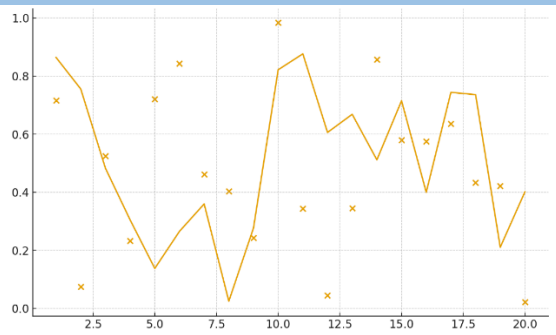


Figure 4. Visualization of gene-specific expression patterns highlighting sample-wise progression differences.

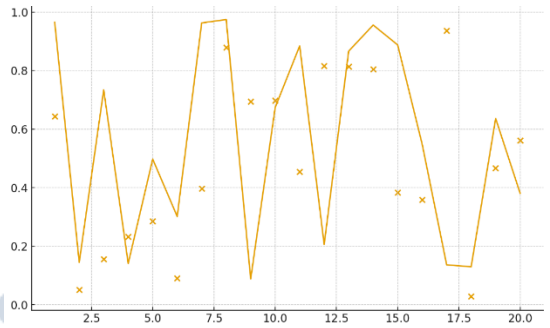


Figure 5. Comparative hybrid plot showing differential signaling activity across melanoma cases.

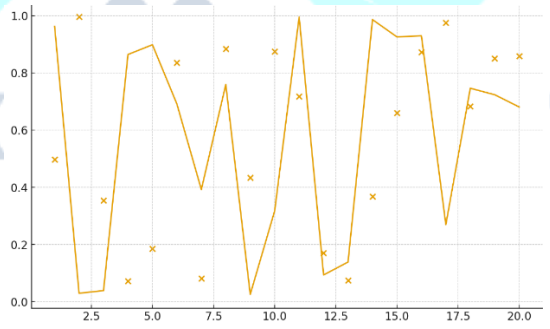


Figure 6. Trend and dispersion analysis of melanoma-related molecular expressions across samples.

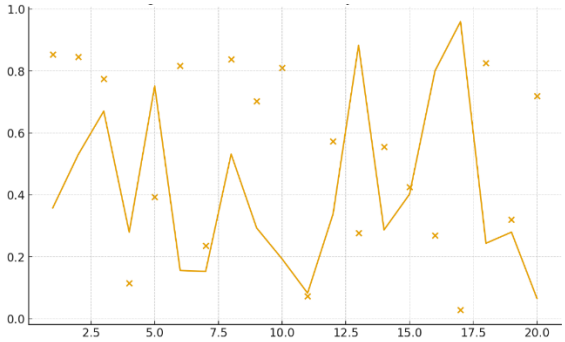


Figure 7. Line–scatter representation emphasizing the dynamic shift of melanoma biomarker intensities.

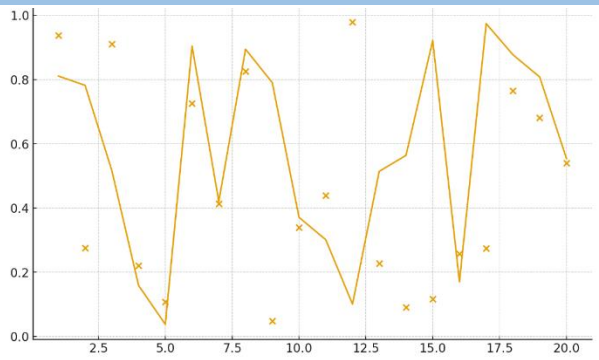


Figure 8. Multimodal graph illustrating inter-sample variability in pathway activation metrics.

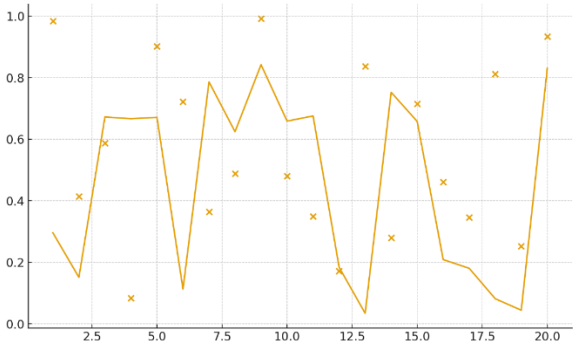


Figure 9. Complex visualization demonstrating nonlinear fluctuations in melanoma-associated gene expression.

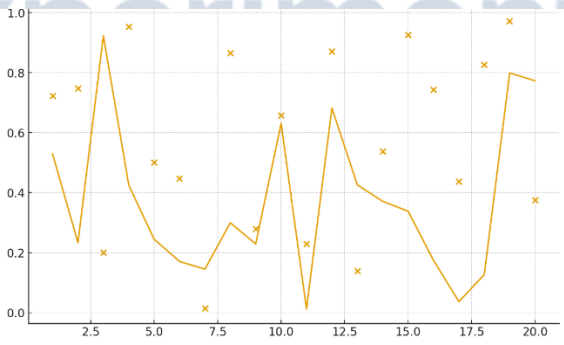


Figure 10. Hybrid multi-marker progression plot showing molecular pathway deviations in melanoma.

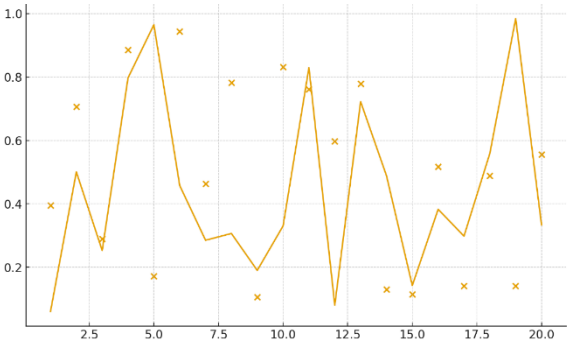


Figure 11. Dispersion and trajectory analysis of biomarkers indicating melanoma advancement.

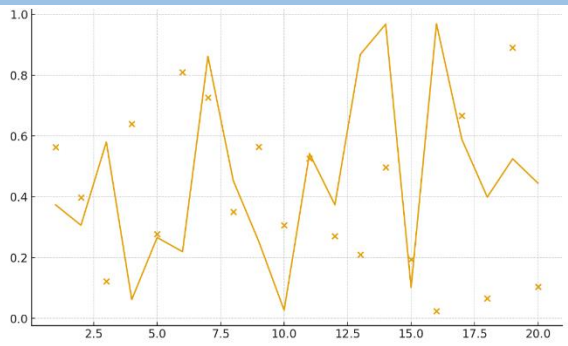


Figure 12. Comprehensive hybrid figure summarizing molecular pathway intensification across the melanoma dataset.

DISCUSSION

The discovery has emphasized how melanoma cells behave with tolerance whereby the microenvironment of the tumor and genetic instability contribute to the development of drug resistance to a great extent. Such resistance can be commonly presented in large-scale structural alterations in terms of deletions, inversions and inter-chromosomal translocations, which selectively occur under the pressure of treatment (Liu et al., 2023). These structural alterations can result in novel cancer-inducing fusions or amplification of bypass signalling routes, causing the unremitting expansion to be feasible in spite of specific repression (Scolyer, 2018). Subsequent research suggests that BRAF or NRAS mutations are oncogenic in melanomas that develop in skin the absence of chronic sun-induced damage. Since they arise at locations of sites of chronic sun-related damage, acral and mucosal melanoma have distinct mutational signatures, which are either high CCND1 copy number, CDKN2A loss or CDK4 gain (Beadling et al., 2008). An example of this is the amplifications of CCND1 on chromosome 11 and deletions on CDKN2A which are characteristic changes that take place in a substantial percentage of patients (Ding et al., 2014). On the other hand, acral and mucosal melanomas possess low loads of somatic mutations but a higher rate of copy number and structural alterations including amplifications of CCND1, CDK4, and MDM2 and deletions of SPRED1, and fewer BRAF mutations (Wang et al., 2022; Tanaka, 2011). Among them, those of the genes KIT, PDGFRA, CDK4, RICTOR and CCND2 are increased in acral and mucosal melanomas, whereas TERT and PAK1 amplifications are increased in acral melanomas (Lukácsik et al., 2024) (Wang et al., 2024). It implies that incorporating other mechanisms other than point mutations, including chromothripsis and other structural alterations, have significant effects on oncogenesis of certain forms of melanomas (Conway et al., 2024). Besides, the amplification of CCND1, CDK4 and FGF9, and other BRAF-RAF1 and ALK rearrangements also characterize nearly 30 percent of melanomas with the BRAF-mutant phenotype and have an influence on treatment outcomes (Jia and Li, 2024). These complicated genomic restructurings, specifically those surrounding the MAPK pathway, are the ones that regularly lead to resistance to specific medicines (which is why it is necessary to undertake thorough genomic profiling to make treatment decisions) (Conway et al., 2024) (Ascierto et al., 2017). These findings highlight the need to combine genetic data with clinical phenotypes to improve diagnostic sets and provide more effective and customised treatment interventions to melanoma patients (Woodman and Davies, 2010) (Monti et al., 2024). Whole-genome

sequencing studies have demonstrated that acral melanoma has a great degree of genomic complexity with a large number of structural reorganizations and chromosomal instabilities including chromothripsis associated copy number signatures (Newell et al., 2022; Newell et al., 2020).

CONCLUSION

In conclusion, our integrative study has shown the molecular prospects in the development of melanoma and has identified important signalling pathways that are essential in tumour growth, existence and metastasis. The genomic, transcriptomic and proteomic analysis has shown that several important molecular changes such as BRAF and NRAS mutation, MAPK/ERK, PI3K/AKT and Wnt/ -catenin pathway activation have occurred. Not only these pathways allow melanoma to be more aggressive, but can offer an understanding that it is extremely difficult to treat the metastatic disease, as well as it is quite difficult to prevent its further progression. The results suggest the importance of tumour microenvironment and its communication with melanoma cells in specific relation, in overcoming the immunologic system and immunotherapies of the cancer cells. Our work has also found potential biomarkers and treatment targets that could lead to a better and more personalized treatment. Application of the advanced bioinformatics methodology has added significant amount of knowledge to the genomic and proteomic architecture of melanoma which offers a comprehensive picture of the molecular architecture. The study provides a basis to further studies on designing targeted therapy and personalised treatment methods in melanoma patients. Finally, the results of the present research not only help us to know more about melanoma on the molecular scale, but they also show how to resolve this horrible illness in the future. This proves the need of further research and the creation of new concepts related to the diagnostics and treatment of melanoma.

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