

Nasopharyngeal Carcinoma Progression: Accumulating Genomic Instability and Persistent Epstein–Barr Virus Infection

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Table S1. The hallmarks of cancer triggered by EBV genes and their products.

| EBV genes and products | Targeted molecules | Functions of the targeted molecules | Key regulators/pathways | The hallmarks of cancer | Ref. |
|------------------------|--------------------|--|---|---|---------|
| LMP1 | Id1 and Id3 | Regulation of cell cycle | N/A | Sustaining proliferative signaling | [1] |
| | Cyclin D1 | Regulation of cell cycle | EGFR, TIF2, and STAT3 | Sustaining proliferative signaling and resisting cell death | [2,3] |
| | <i>p16</i> | Regulation of cell cycle | N/A | Sustaining proliferative signaling | [4] |
| | LKB1-AMPK | Regulation of cellular metabolism | MEK/ERK-MAPK signaling pathway | Sustaining proliferative signaling and reprogramming of energy metabolism | [5] |
| | TGF- β | Regulation of cell proliferation and differentiation | Id1 | Evading growth suppressors | [6] |
| | <i>TP53</i> | Repair of DNA damage and inducing apoptosis | MAP kinases, anti-apoptotic genes <i>bcl-2</i> and <i>A20</i> | Resisting cell death | [7,8] |
| | Telomerase | Regulation of replication | c-Myc pathway | Enabling replicative immortality | [9] |
| | HIF1 | Serving as a principal oxygen-sensing transcription factor | prolyl hydroxylase 1 and prolyl hydroxylase 3 | Inducing angiogenesis | [10] |
| | HIF-1/VEGF | Regulation of glucose uptake, metabolism, | JNKs/c-Jun signaling and p42/p44 MAPK pathways | Inducing angiogenesis | [11,12] |

| | | | | | |
|------------------|---|---|--|------------|--|
| | apoptosis, growth, angiogenesis, invasion, and metastasis | | | | |
| FGF-2 | Regulation of angiogenesis and mitosis | NF-κB signaling pathway | Inducing angiogenesis | [13] | |
| VEGF and PGE2 | Regulation of angiogenesis | COX-2 | Inducing angiogenesis | [14,15] | |
| RAGEs | Regulation of angiogenesis | NF-κB signaling pathway | Inducing angiogenesis | [16] | |
| VEGF | Regulation of apoptosis, angiogenesis, and cell migration | SOCE, JAK/STAT3, and MEK1/ERK1/2 pathways | Activating invasion and metastasis, inducing angiogenesis | [17,18] | |
| Twist | Inducing EMT | NF-κB signaling pathway | Activating invasion and metastasis | [19] | |
| CDH6 | Regulation of EMT | miRNA-203 | Activating invasion and metastasis | [20] | |
| HIF1α | Regulation of angiogenesis, invasion, and metastasis | Exosome-mediated signaling | Activating invasion and metastasis | [21] | |
| CRT | Maintaining intracellular Ca ²⁺ homeostasis | Smad3-dependent TGF-β signaling pathway | Activating invasion and metastasis | [22] | |
| E-cadherin | Maintenance of intercellular adhesion | DNA methyltransferases | Activating invasion and metastasis | [23] | |
| Snail | Regulation of EMT by repressing E-cadherin | IGF1-mTORC2-PDHE1α signaling pathway | Activating invasion and metastasis, reprogramming of energy metabolism | [24,25] | |
| uPA | Degrading extracellular matrix components | Ets1 | Activating invasion and metastasis | [26] | |
| MMP-1 | Promotion of invasion by breaking ECMs | Ets | Activating invasion and metastasis | [27] | |
| MMP-9 | Promotion of invasion by breaking ECMs | c-Jun/Ets1, NF-κB, and AP-1 | Activating invasion and metastasis | [15,28-30] | |
| OXPHOS complexes | Oxidative phosphorylation | DNMTs | Reprogramming of energy metabolism | [31] | |
| Glut-1 | Regulation of aerobic glycolysis | mTORC1/NF-κB signaling pathway | Reprogramming of energy metabolism | [32] | |
| HK2 | Modulation of LMP1-induced glycolysis | c-Myc | Reprogramming of energy metabolism and resisting cell death | [33] | |

| | | | | | |
|-------------------|---------------------------------|--|--|---|---------|
| LMP2A | Th1 lymphocytes | Modulation of immune response | galectin-9/Tim-3 | Evading immune destruction | [34] |
| | VEGF | Regulation of angiogenesis | PI3K/Akt/mTOR/HIF-1 α pathway | Inducing angiogenesis | [35] |
| | ITG α 6 | Maintenance of epithelial structure | N/A | Activating invasion and metastasis | [36] |
| | α v-integrin | Regulation of cell migration | ITAM/Syk and Akt signaling pathways | Activating invasion and metastasis | [37] |
| | Transcription factor <i>p63</i> | Regulation of epithelial cell differentiation | N/A | Sustaining proliferative signaling | [38] |
| | S1P | Regulation of proliferation, survival, migration, apoptosis, and chemoresistance | SPHK1 | Activating invasion and metastasis | [39] |
| | TGF- β 1 | Regulation of cell growth and differentiation | PI3K/Akt pathway | Sustaining proliferative signaling and resisting cell death | [40] |
| EBNA1 | E-cadherin and N-cadherin | Regulation of EMT | TGF- β 1/miR-200/ZEB pathway | Activating invasion and metastasis | [41] |
| | p53-Mdm2 | Regulation of apoptosis | USP7/HAUSP | Sustaining proliferative signaling and resisting cell death | [42] |
| | Survivin | Regulation of apoptosis and cell cycle | Sp1 | Resisting cell death | [43] |
| EBV-miR-BART1 | PTEN | Regulation of cell growth and survival | PI3K/Akt, FAK-p130 ^{Cas} , and Shc-MAPK/ERK1/2 pathways | Activating invasion and metastasis | [44,45] |
| EBV-miR-BART5 | PUMA | Promotion of apoptosis | N/A | Resisting cell death | [46] |
| EBV-miR-BART6-3p | IFN- β | Modulation of immune response | RIG-I mRNA 22 and RIG-I-like receptor | Evading immune destruction | [44] |
| EBV-miR-BART7 | MICA | Modulation of immune response | TGF β 1/c-Myc | Evading immune destruction | [47] |
| EBV-miR-BART7-3p | Snail and β -catenin | Regulation of EMT | PI3K/Akt/GSK-3 β pathway | Activating invasion and metastasis | [44] |
| EBV-miR-BART10-3p | β -catenin and Snail | Regulation of EMT | BTRC | Activating invasion and metastasis | [44] |
| EBV-miR-BART11 | NF- κ B and TAM | Regulation of proliferation | FOXP1 | Sustaining proliferative signaling | [48] |
| EBV-miR-BART13-3p | Slug | Regulation of EMT by repressing E-cadherin | c-Jun/Slug signaling pathway | Activating invasion and metastasis | [49] |

Abbreviations: Id1, Id proteins 1; Id3, Id proteins 3; EGFR, epidermal growth factor receptor; TIF2, transcriptional intermediary factor 2; STAT3, signal transducer and activator of transcription 3; TGF- β , transforming growth factor beta; HIF1, hypoxia-inducible factor 1; VEGF, vascular endothelial growth factor; FGF-2, fibroblast growth factor 2; PGE2, prostaglandin E2; COX-2,

cyclooxygenase-2; RAGEs, the receptor for advanced glycation end products; SOCE, store-operated Ca(2+) entry; EMT, epithelial-mesenchymal transition; CDH6, cadherin 6; CRT, calreticulin; uPA, urokinase type plasminogen activator; Ets, E26 transformation specific; MMP, matrix metalloproteinase; OXPHOS, oxidative phosphorylation; Glut-1, Glucose Transporter 1; ECM, extracellular matrix; DNMTs, DNA methyltransferases; HK2, hexokinase 2; ITGα6, integrin-α-6; PI3K, Phosphatidylinositol 3-kinase; S1P, sphingosine-1-Phosphate; ZEB1, zinc finger E-box binding homeobox 1; USP7, ubiquitin specific protease 7; HAUSP, herpesvirus-associated ubiquitin-specific protease; Sp1, specificity protein 1; MICA, major histocompatibility complex class I chain-related peptide A; TGFβ1, transforming growth factor-β; BTRC, Beta-transducin repeat containing E3 ubiquitin protein ligase; TAM, tumor-associated macrophages; FOXp1, forkhead box P1; N/A, not available.

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