#	HPV type	Experimental format in HaCaT	Key outcome with References (PMID #)
1	16, 18, 6b, 11	Co-transfection of origin-containing plasmids plus E1/E2 helpers	Sustained low-copy episomal replication detectable for >3 weeks; copy number tightly linked to E1/E2 expression. 21248030 https://pubmed.ncbi.nlm.nih.gov/21248030/ [1]
2	18	Re-circularized full-length genome ± reporter tags; 2-D/3-D gel analysis	Initial amplification proceeds via bidirectional θ intermediates, then shifts to recombination-dependent unidirectional forks. 26522968 https://pubmed.ncbi.nlm.nih.gov/26522968/ [2]
3	16	Pseudovirion infection of HaCaT monolayers	Efficient cell entry but limited early gene expression compared with primary keratinocytes, highlighting restriction at post-entry steps. 24281871 https://pubmed.ncbi.nlm.nih.gov/24281871/ [3]
4	11	Introduced full circular HPV11 genome into HaCaT cells in basal -like medium-confirmed episomal replication over many passages. Established HPV11.HaCaT line used in drug screening.	Showed the HPV11.HaCaT cells have stable E6/E7 expression and that introducing HPV11 increased host cell proliferation and S/G2–M cell cycle. 24874507, https://pubmed.ncbi.nlm.nih.gov/24874507/ 29100527 https://pubmed.ncbi.nlm.nih.gov/29100527/ [4, 5]
5	11, 16, 45	Transient "early infection" model in HaCaT for multiple HPV types.	Performed global gene expression profiling, revealing both shared and distinct host responses to different HPV types (e.g., HPV16/45 upregulating oncogenesis-related genes, HPV11 affecting immune/cytoskeletal genes). It was concluded that HPV genomes can be initially established episomally in HaCaT and induce type-specific transcriptomic changes. 22808421 https://pubmed.ncbi.nlm.nih.gov/22808421/ [6]
6	16	Transfected HaCaT with a luciferase reporter plasmid containing HPV16 LCR (origin of replication) and used co-transfected neo for selection.	Studied the impact of histone deacetylase inhibitors (HDACi).There was an unexpected integration of the transfected episomal DNA into host genome. This study warns that certain treatments or stresses can trigger integration of HPV episomes in HaCaT, highlighting the need for careful monitoring of viral DNA state. 27705914 https://pubmed.ncbi.nlm.nih.gov/27705914/ [7]
7	16	Stable HaCaT line with integrated high-risk oncogenes. Generated HaCaT cells stably	This model lacked episomal replication and was used to show how continuous E6/E7 expression alters cellular pathways relevant to HPV-mediated carcinogenesis: 36188003 https://pubmed.ncbi.nlm.nih.gov/36188003/ [8]

#	HPV type	Experimental format in HaCaT	Key outcome with References (PMID #)
		expressing HPV16 E6 and E7 (via a lentiviral vector).	
8	18 (E5/E6/E7)	Immortalized HaCaT with all HPV18 oncogenes – model of early transformation. Stable cell lines established.	Although the full HPV18 genome is not present, this stable line helped dissect how HPV oncoproteins cooperate to create a replication- and cancer-permissive cellular milieu. 37853061 https://pubmed.ncbi.nlm.nih.gov/37853061/ [9]

Table S3. Use of HaCaT cells in previous HPV Replication Studies. HaCaT is competent for HPV entry and transient E1/E2-driven DNA replication from origin of replication (ORI), and it can host stable HPV11 genome–positive states. For robust long-term maintenance of episomes across many HPV types. PMID #= PubMed ID Number and Pubmed links provided. The references are added to the main article.

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