

## A Commentary on WNT7A Implication in Cervical Cancer Development

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Cervical Cancer (CC) is the fourth leading cause of cancer deaths in women worldwide and is associated directly with Human papillomavirus (HPV) infection [1]. Many authors have reported that HPV can immortalize human cells without leading to cell transformation by itself [2,3]. Thus, cervical carcinogenesis is a multistep process involving HPV infection and additional alterations. In 2005, canonical Wnt signaling pathway activation was proposed as a second hit during epithelial malignant transformation but this hypothesis remains controversial [3,4]. However, it is undeniable that Wnt signaling pathway is altered during CC progression.

The Wnt signaling pathway participates in cell differentiation, proliferation, migration, cell polarity, and cell fate determination, playing an important role during embryogenesis, tissue regeneration, stem cell maintenance, homeostasis, and under pathologic conditions including cancer [5]. At least three different pathways have been described: the canonical Wnt/ $\beta$ -catenin cascade, and two non-canonical pathways: the Planar cell polarity (PCP) pathway and the Wnt/ $\text{Ca}^{2+}$  pathway [6]. Neither the 19 Wnt ligands nor the 10 Frizzled receptors described to date can be classified as activators of one or another signaling pathway. Indeed, although it appears that some ligands preferentially activate a specific pathway, factors such as cell context, receptors, and inhibitors require consideration [7].

Concerning Wnt signaling pathway participation in cervical carcinogenesis, for many years attention in this regard has been focused on the canonical  $\beta$ -catenin-dependent cascade. However, instead of evaluating canonical Wnt ligand participation, the majority of the works have studied the  $\beta$ -catenin protein, demonstrating its increased expression during cervical cancer (CC) progression thus, canonical Wnt signaling pathway is associated with tumorigenesis [3,8-11].

In the recently published article entitled "Expression of WNT genes in cervical cancer-derived cells: Implication of Wnt7a in cell proliferation and migration", Ramos-Solano et al. report the first evidence of the non-canonical Wnt7a ligand implication in CC [12].

Wnt7a is a 39kDa glycoprotein that plays controversial roles in different types of cancer, such as many of the Wnt ligand family members. Wnt7a can act both as a canonical or a non-canonical ligand, and its expression has been associated both with the maintenance of a normal cell phenotype and with tumor development [13-19].

Ramos-Solano et al. [12] analyzed the differential expression profiles between two CC-derived cell lines —HeLa and SiHa— and a human non-tumorigenic immortalized keratinocyte cell line —HaCaT— finding that 38 Wnt signaling pathway genes were up- or down modulated. Specifically, Wnt7a expression was strongly down regulated in these cell lines, as shown by qPCR and Western blot assays. This decreased expression was confirmed in 10 CC biopsies on comparing these with nine cytology samples from women without cervical lesions. But why did Wnt7a capture their attention? Previous studies in Non-small cell (NSC) lung cancer and leukemic cell lines revealed an inhibitory role of Wnt7a in cell proliferation and the same scenario could be happening in CC [13,17]. Ramos-Solano et al. [12] demonstrated that restoration of Wnt7a expression in HeLa cells strongly decreased cell proliferation, cell viability, and migration rates.

Conversely, silencing Wnt7a in HaCaT cells induced an increase in cell proliferation and migration rates. These results suggest that the loss of Wnt7a expression probably contributes to increased cell proliferation and migration during cervical tumor development.

As responses always lead to new questions, the next step was to elucidate the way in which Wnt7a ligand expression was being repressed. Wnt7a is known to possess tumor suppressor properties in several cancers and is frequently inactivated due to CpG-island methylation in pancreatic cancer, NSC lung carcinoma, clear cell renal cell carcinoma, and oral squamous cell carcinoma [15,20-22]. In CC, the authors associated loss of Wnt7a expression in HeLa and SiHa cell lines to CpG island methylation. Indeed, the three CpG islands assessed within the Wnt7a promoter were found methylated in HeLa cells, and the first in SiHa cells, while no methylation was observed in non-tumorigenic HaCaT cells.

As  $\beta$ -catenin-dependent and independent WNT signaling are well known to antagonize each other the widely reported activation of the canonical pathway during cervical carcinogenesis and the current discoveries on Wnt7a down regulation lead us to suggest that activation of the canonical pathway could be due to the inactivation of the non-canonical Wnt7a ligand [23,24]. However, the role of the non-canonical Wnt pathway in normal and malignant epithelia remains controversial. Last year, upregulated expression of another non-canonical ligand (Wnt5a) was associated with metastasis and progression of CC [25].

Although the behavior of the Wnt7a protein in human cancer appears to be tissue-specific, Ramos-Solano et al. [12] demonstrated, for the first time, its tumor suppressor properties in CC-derived cell lines. Down regulation of Wnt7a could comprise an important step during cervical carcinogenesis. However, future experiments with samples from patients with or without cervical lesions must be performed in order to fully understand the participation of Wnt7a in CC progression. Moreover, it remains to be elucidated which actors are involved in Wnt7a promoter methylation. Do HPV oncoproteins play a role in the process? An *in vitro* study showed that E6 and E7 oncoproteins are involved in transcriptionally active  $\beta$ -catenin nuclear accumulation and subsequent activation of Wnt signaling in HPV16-positive oropharyngeal squamous cancer cell lines [26]. Additionally, HPV16 E6 enhances canonical Wnt signaling in skin epidermis from transgenic mice [27]. However, to date there is no evidence of HPV

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oncoprotein participation in the modulation of Wnt non-canonical signaling pathways. Upcoming discoveries in this area are promising. Undoubtedly, future work will aid us in better understanding the complex world of Wnt signaling and cervical cancer development.

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