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Role of *p14^{ARF}* alterations in endometrial tumorigenesis: a mini-review

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1. ABSTRACT

In the current mini-review, we present a short overview of genetic as well as immunohistochemical p14^{ARF} alterations either in primary human endometrial carcinomas (ECs) or in metastatic lesions originated from malignant endometrium. The prognostic utility of p14^{ARF} in uterine malignancies has also been briefly discussed.

2. INTRODUCTION

The INK4B-INK4A locus, located on human chromosome 9p21, encoded two cyclin-dependent kinase inhibitors, p15^{INK4b} and p16^{INK4A}, and an un-related protein encoded ARF (known as p14^{ARF} in human and p19^{ARF} in mouse; Figure 1) (1, 2, 3). Interestingly, mouse and human proteins differs in amino-acid sequences and are composed of 169 and 132 amino acids, respectively (1, 4). They are

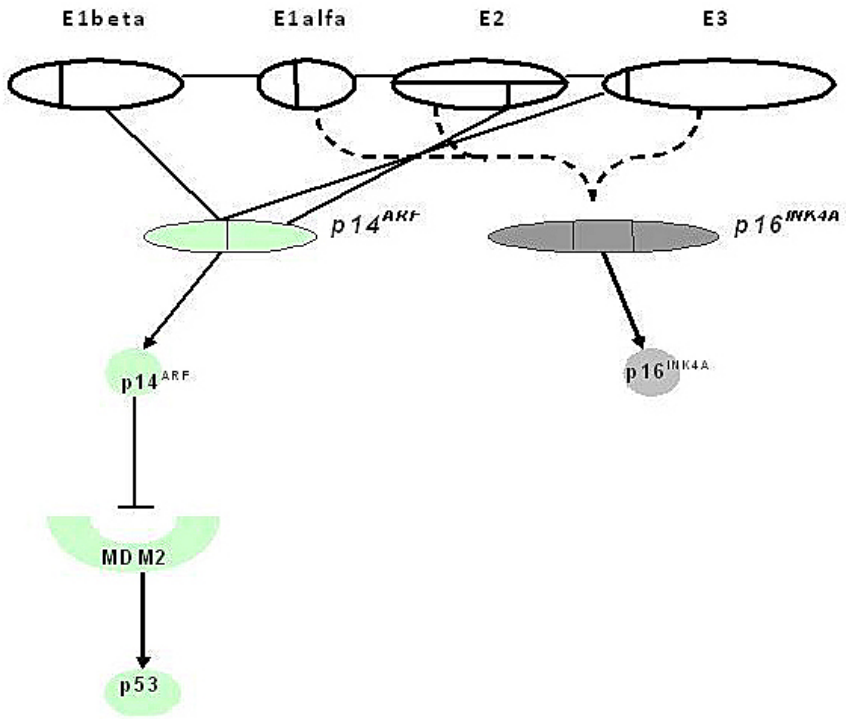

Figure 1. The *CDKN2A* locus, encoding two different genes – $p14^{ARF}$ and $p16^{INK4A}$. $p14^{ARF}$ protein acts through the p53-pathway, interacting with the MDM2 protein. MDM2 stabilized p53, resulting in arrest of the cell cycle at the G1/G2 phases.

both composed of more than 20% arginine residues conferring them highly basic and hydrophobic properties (4). Nuclear $p14^{ARF}$ consists of 132 amino acids and mediates cell-cycle arrest at G1 and G2/M phases by interfering with p53/MDM2 (4, 5). It is well-known that alterations at *CDKN2A* locus represent a convergence of two major cell-cycle regulatory pathways involved in human tumorigenesis: the TP53-pathway and the pRb-pathway (5, 6). Indeed, deletion at the ARF-INK4a simultaneously impairs not only INK4A-cyclin D/CKD4/6-Rb but also ARF-MDM2-p53 pathways (7). $p14^{ARF}$ induced an increase in MDM2 (a member of the pRb-pathway) and $p21^{WAF1/CYP1}$, resulting to cell-cycle arrest not only at G1 but also at G2/M phases (1, 9). Moreover, $p14^{ARF}$ in negatively regulated by p53, and it is known to bind directly to MDM2 (1, 5, 9).

In the current mini-review, we discuss the role of $p14^{ARF}$ alterations during endometrial carcinogenesis as well as the immunohistochemical protein expression in primary and metastatic human ECs (Endometrial Carcinomas). Finally, the prognostic utility of $p14^{ARF}$ in uterine malignancies has also been briefly discussed.

3. $p14^{ARF}$ ALTERATIONS IN ENDOMETRIAL CARCINOGENESIS

Alterations of p53-pathway members, including $p14^{ARF}$, has been reported to be one of the most important mechanism in the development of various human malignancies (4, 10, 11, 12, 13, 14, 15, 16, 17), including tumors developing from the female genital tract organs (18, 19, 20, 21, 22). Interestingly, mutations at $p14^{ARF}$, specifically splice-site variants, are causal in a subset of melanoma patients independently of $p16^{INK4A}$ (23). On the other hand, no relationship between bladder cancer recurrence and $p14^{ARF}$ methylation was previously reported (24).

In human uterine malignancies, Tsuda and co-investigators (19) described a homozygous deletion at the *CDKN2* with subsequent loss of $p16^{INK4a}$ and $p14^{ARF}$. At this locus, point mutations and allelic imbalance were rarely identified (25). Ozenne and co-workers (4) stated that "…germline mutations affecting specifically exon 1β have not yet been identified, and mutations that specifically target exon 1β are rare in human tumors". Moreover, there were no mutations detected in the three exons of the *CDKN2* by Koul and co-workers (26). Recently, no point mutations at the $p14^{ARF}$ were described (20). These authors suggested that PCR-SSCP analysis, applied in their research, may not detect every genetic distortions in ECs. As reported in the literature, the sensitivity of this technique to detect gene alterations (point mutations and/or homozygous deletions) has been shown to be extremely high (up to 90%!) (27, 28, 29). Other mechanisms apart from point mutation, homozygous deletions or CpG promoter methylation, for example RNA spicing errors, may also be implicated in gene distortions (20).

Esteller and co-investigators (30) previously found $p14^{ARF}$ promoter methylation in 15% of endometrial tumors evaluated. Promoter methylation was no detected in any normal tissue, including human endometrial tissue

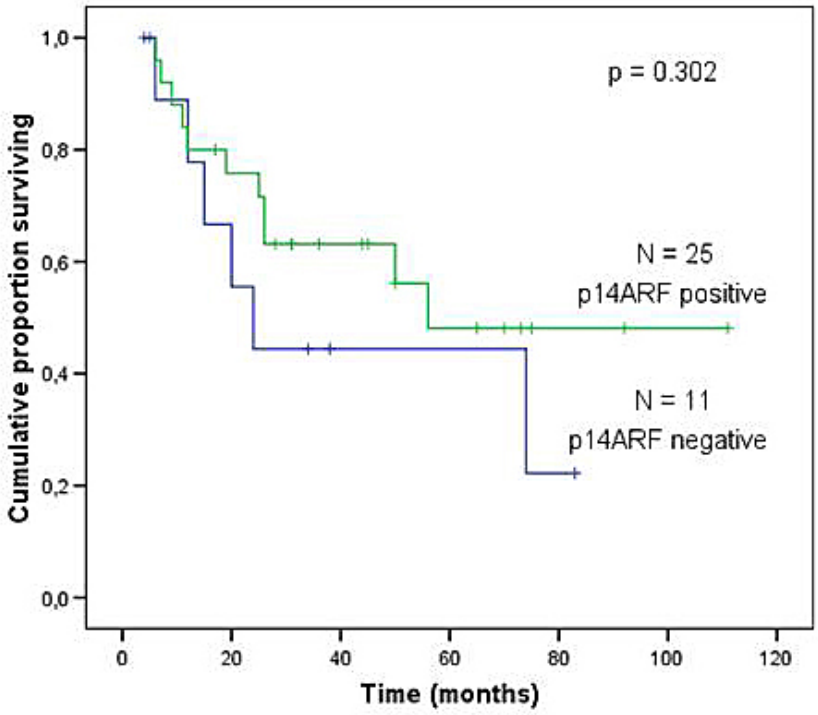

Figure 2. Kaplan-Meier survival curves according to $p14^{ARF}$ expression in primary human ECs (p=0.302; log-rank test).

(30). Finally, they suggested that "…..after a screening of more than 500 primary human tumors of different cell types, *p14*^{ARF} promoter hypermethylation was found as a relatively common event in several neoplasms, including colorectal, gastric, and uterine tumors" (30). In another study, three out of 50 (6%) carcinomas showed methylation in the 5'CpG island in the promoter region of the gene (20). None of the five *p14*^{INK4A}-negative carcinomas revealed promoter methylation. As suggested by Watanabe and co-investigators (31), *p14*^{ARF} promoter methylation might be a late event during endometrial carcinogenesis due to the fact that lack of $p14^{ARF}$ immunoreactivity was reported at high rate in poorly-differentiated endometrioid-type ECs.

4. $p14^{ARF}$ IMMUNOSTAINING IN NORMAL, PRECANCEROUS AND CANCEROUS HUMAN ENDOMETRIAL TISSUES

There is a limited number of studies analyzing $p14^{ARF}$ immunoreactivity in normal, precancerous and cancerous human endometrial tissues up to now (20, 31, 32, 33, 34). Nuclear $p14^{ARF}$ immunostaining was detected in the ten normal endometrial slides whereas only in 5 out of 64 (7,8%) endometrioid-type ECs revealed abnormal protein immunoreactivity (20). No significant differences between $p14^{ARF}$ expression pattern and clinical stage or histological grade was reported (20). In the largest cohort published up to now, Watanabe and co-investigators (31) showed positive $p14^{ARF}$ immunoreactivity in 55%, 60%, and 62,1% of normal, hyperplasic and neoplastic human endometrial slides, respectively. The frequency of $p14^{ARF}$ immunoreactivity was inversely correlated with the histological grade (G1 versus G3, p=0.0159). Moreover, the staining score was significantly higher in endometrioid-type ECs than in endometrial hyperplasias (p<0.05); whereas $p14^{ARF}$ in uterine tumors was correlated inversely with the labeling index of Ki-67, but not with cell-cycle regulators studies (cyclins A, D1 and E, cdk2, p27 or p53). Finally, the authors concluded that "high expression of $p14^{ARF}$ is induced in endometrial adenocarcinomas, especially in G1 tumors, in which E2F-1 might be overexpressed" (31). Interestingly, none of 8 primary squamous cell carcinomas of the endometrium revealed $p14^{ARF}$ expression immunohistochemically (32). Expression of p53 with low MDM2 and $p14^{ARF}$ immunostaining may be a characteristic features of poorly-differentiated uterine malignancies (33). Data published recently from our laboratory (34) showed $p14^{ARF}$ protein expression in 68% of advanced-stage ECs and in 60% of metastatic lesions. Interestingly, a trend existed between the $p14^{ARF}$ expression pattern in primary ECs and the presence of the neoplasms in the fallopian tube, but none of other clinico-pathological features of cancer was related to protein immunoreactivity in advanced-stage human uterine neoplasms (34).

It has been previously proposed that endometrial carcinoma cells, uterine-papillary serous carcinoma (UPSC) in particular, may exfoliate, transverse the tube lumen, and finally implant into the peritoneum (35, 36, 37). Snyder and co-investigators (37) suggested that "… aberrant cell-cell adhesion secondary to a mutation in an adhesion molecule gene that results in the overexpression of a defective protein or lack of expression of that protein

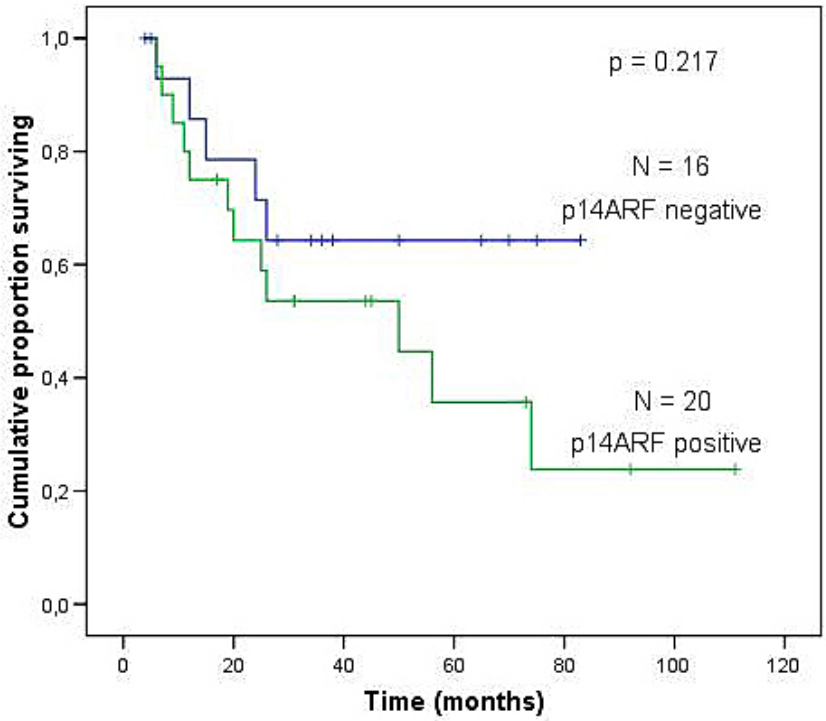

Figure 3. Kaplan-Meier analysis for $p14^{ARF}$ expression in corresponding metastatic lesions (p=0.217; log-rank test).

altogether causes less cell to cell adhesion." Various molecules, including E-cadherin, p120 and/or CD44, may influence of endometrial cancer cells to behave clinically aggressive (38, 39, 40, 41). This mechanism may be occasionally related to early-stage uterine tumors, only superficially infiltrated the myometrial wall (37). Retrograde transtubal implantation, an under-recognized mechanism of uterine cancer metastasis, as well as lymphatic/vascular space invasion (LV), are two major postulated routs of neoplasmatic dissemination. Alterations at *p14*^{ARF} as well as aberrant protein immunoreactivity may also be involved in this process (34) but further studies are required to determine the exact role of $p14^{ARF}$ in ability of ECs to transtubal route of spread.

5. $p14^{ARF}$ AND PATIENTS OUTCOME

In the literature, Kawamoto and co-workers (42) showed a significantly poorer outcome of patients affected by human bladder cancer with $p14^{ARF}$ promoter methylation that those without. They assumed that *p14*^{ARF} may be a useful biomarker for the pathological stage and outcome of patients affected by bladder carcinomas (42). Simultaneous hypermethylation of both $p16^{INK4a}$ and $p14^{ARF}$ was greater prognostic value in patients affected by sporadic human colorectal cancer (43). $p14^{ARF}$ immunoreactivity index constituted independent predictive factor for recurrence of urothelial neoplasms of the human bladder (24), and in myxoid/round cell liposarcomas (44).

Various genetic and immunohistochemical markers were evaluated as perspectives molecular tools in early- and advanced-stage uterine malignancies (45, 46, 47, 48, 49, 50, 51, 52, 53, 54). Members of the p53-pathway, p53 and MDM2, were reported to be implicated as poor prognosticators of patients affected by ECs (55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65). However, up to now only one study evaluated the impact of $p14^{ARF}$ expression as a prognostic tool in advanced-stage ECs (34). $p14^{ARF}$ expression/overexpression pattern was not related to un-favorable outcome of women, either in primary ECs (p=0.302; Figure 2) or in corresponding metastatic lesions (p=0.217; Figure 3). As a conclusion, this marker should not be used as a prognosticator in women suffered from advanced-stage uterine malignancies (34). Further study is required to assess the prognostic utility of $p14^{ARF}$ expression pattern/genetic alterations in early-staged ECs or even precancerous lesions of human endometrium.

6. FUTURE PERSPECTIVES

p14ARF alterations, especially promoter (hyper)methylation, may influence on the development and progression of various endometrial malignancies. In the future perspectives, the relation between p14ARF, MDM2 and p53 should be carefully overlapped, particularly in early-staged ECs. Indeed, influence of aberrant p14ARF promoter methylation on outcome of women affected by early/advanced-ECs should also be evaluated in multi-center, cohort research.

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