THE DYNAMICS OF KERATIN EXPRESSION IN MALIGNANT TRANSFORMATION OF CERVICAL EPITHELIUM: A REVIEW

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Conclusions: It is possible to distinguish the various epithelial types in the normal cervix based on their keratin expression patterns. Reserve cells display a bidirectional keratin pattern, comprising keratins typical of both squamous and simple types of differentiation, reflecting the bipotential nature of these cells. Cervical intraepithelial neoplasia can be divided into two subpopulations, one characterized by the reserve cell keratin phenotype and the other by a keratin phenotype typical of nonkeratinizing squamous epithelia. The first population also contains the simple keratins, the relative percentage of which increases with increasing degree of dysplasia. We therefore suggest that these lesions are progressive in nature. Carcinomas show a differentiation-related keratin expression pattern in addition to the basic reserve cell keratin phenotype. Adenocarcinomas also have been shown to express most of the reserve cell keratins. The latter observation indicates a common progenitor for both carcinoma types. (Obstet Gynecol 1993;82:465–74)

Intermediate filament proteins are important constituents of the cytoskeleton in eukaryotic cells. They seem to be involved in providing internal stability within the cell, transport functions, and gene regulation. Six different groups of intermediate filament proteins have been discovered, which are to a certain extent expressed in a tissue-specific fashion. Keratins represent the class I and class II families of intermediate filament proteins and are by far the most complex group. The 20 members of the keratin family are distinguishable on the basis of their molecular weight, isoelectric pH, amino acid sequence, and immunologic properties. They have a number of interesting characteristics, justifying the extensive studies into their nature and tissue distribution, which follow certain rules.

These human keratins, which have been catalogued and numbered 1–20 in this review, are expressed in pairs combining a class I (acidic) and a class II (basic or neutral) protein. Many of the various types of epithelial differentiation in the body express specific keratin combinations. For example, in epithelia with skin-type differentiation (keratinization), the most characteristic keratins are 1, 2, and 10. If squamous epithelium does not display keratinization, keratins 4 and 13 are found, along with keratins found in both keratinizing and nonkeratinizing squamous epithelia, eg, keratins 5 and 14. In the so-called simple epithelia, keratins 8 and 18, often in combination with keratins 7, 19, and 20, are the most important intermediate filament proteins. A complex epithelial lining, eg, glands or the urinary tract, is found to express both simple epithelial keratins as well as keratins found in squamous epithelia. Keratins 6 and 16 have been associated with hyperproliferation of squamous epithelial cells.

Another important characteristic of intermediate fil-
ament proteins, making them extremely interesting for further research, is that their patterns of expression are to a great extent preserved during malignant transformation. Thus, an epithelial neoplasm will frequently express those keratins that are found in the epithelial tissue from which it originated.\(^5\) The rapid development of monoclonal antibodies specific for most of the individual keratins\(^6\) has allowed accurate mapping of many epidermis. The aims of this review were as follows: 1) to summarize the literature on keratin expression in the normal cervix and in cervical neoplastic lesions, 2) to discuss the patterns of keratin expression in both endocervical and ectocervical epithelia,\(^7\) \(^23\) and 3) to analyze the complex keratin expression of reserve cells in the context of their role as progenitor cells for benign metaplastic processes, immature and mature squamous metaplasia, and in the deralement of normal differentiation in cervical intraepithelial neoplasia (CIN) lesions, which may eventually progress into cervical carcinoma.

It has previously been suggested that the keratin phenotype of these lesions may supply valuable information on whether a CIN lesion is progressive or regressive in nature.\(^14\) \(^35\) The keratin phenotypes of carcinomas are compared to those of reserve cells. We also consider the possible implications of keratin expression patterns on the classification of the various types of cervical cancer.\(^16\) The keratin patterns in CIN lesions and cervical cancers may have diagnostic implications. A number of possibilities to distinguish cervical carcinomas from carcinomas arising in other organs based on their keratin phenotypes will be discussed briefly. Finally, suggestions are offered for possible future studies in which results from keratin studies may be combined with observations from molecular biologic research in cervical pathology.

**Keratin Expression Characteristics**

**Epithelia Lining the Normal Cervix**

Based on gel electrophoretic analyses, endocervical nonkeratinizing epithelium was shown to contain type II keratins 1, 4, 5, and 6 and type I keratins 13, 14, 15, and 19, with also some variable expression of keratins 2, 8, 10, 11, 16, and 17 (Figure 1A).\(^7\) \(^12\) \(^14\) \(^15\) \(^17\) Based on immunocytochemical evaluations\(^14\) \(^15\) \(^17\) using mostly monoclonal antibodies to the individual cytokeratins, endocervical epithelium (Figure 1A) was shown to have a specific keratin distribution pattern with very little variation (Figure 1, B–F). Keratins 4 and 13 (Figure 1F), characteristic for nonkeratinizing epithelia, are expressed in the suprabasal cell compartments. Basal cell keratins 5, 14, and 15 were detected in the ectocervical basal cell layer, but also sometimes in the parabasal cell compartment with keratin 14 (Figure 1D) and keratin 15 well into the intermediate cell layer. Keratins characteristic of keratinization (keratins 1 and 10), and found abundantly in the epidermis, were occasionally found in ectocervical nonkeratinizing epithelium, with only incidental cells in the intermediate and superficial cell layers staining. Keratins 6 and 16, which are considered to be associated with hyperproliferative epithelia, demonstrated a rather surprising expression pattern. Keratin 6 was frequently detected in the parabasal, intermediate, and superficial cell layers, thus indicating a differentiation-related but not a hyperproliferation-related expression. Keratin 16 showed a more or less expected pattern; it was detectable in the proliferating basal cell compartment and was also often found in the overlying epithelial layers (Figure 1G), which are at an end stage of differentiation.\(^17\) The keratins characteristic of simple epithelia (eg, Figure 1B) were found only sporadically in ectocervical epithelium, with the exception of keratin 19 (Figure 1C), which was always present in the basal cell layer.

As observed in gel electrophoretic studies, columnar cells (Figure 1H) lining the endocervical canal were immunohistochemically shown to express the simple keratins 7, 8 (Figure 1I), 18, and 19 (Figure 1J). It is surprising that considerable expression of keratins 4, 16 (Figure 1N), and 15 was found in morphologically normal columnar cells. Keratin 4, a marker for nonkeratinizing squamous epithelium, has already been described in other (noncervical) columnar cell types.\(^24\) These unexpected features of columnar cell keratin expression will be discussed below in light of the reserve cell keratin phenotype. Columnar cells have been shown sporadically to contain keratin 20, which is mainly restricted to glandular epithelia lining the gastrointestinal tract.\(^3\) Therefore, keratin 20 coexpression may indicate intestinal metaplasia of endocervical columnar cells before it becomes morphologically evident. Keratins 5, 6, 14, 15, and 17 are also sporadically found in columnar cells when they lie above reserve cells, in which these keratins are abundant (Figure 1, H–N).

**Reserve Cells and Metaplastic Epithelia**

As opposed to normal endo- and ectocervical epithelia, which can be considered to be in an end stage of differentiation from which metaplastic changes into other types of epithelium do not occur,\(^25\) reserve cells and immature squamous metaplastic epithelia retain the capacity to proliferate and to differentiate. The span of differentiation phenotypes of reserve cells
Figure 1. Schematic overview of the keratins expressed in ectocervical nonkeratinizing squamous epithelium (A), endocervical columnar cells and reserve cells (F), and immature squamous metaplastic epithelium (O). Immunoperoxidase staining patterns are shown for ectocervical epithelium (B-G), endocervical epithelium (I-N), and immature squamous metaplastic epithelium (P-U) after incubation with antibodies reactive to K8 (B, I, P), K19 (C, J, Q), K14 (D, K, R), K17 (E, L, S), K13 (F, M, T), and K16 (G, N, U). Numbers indicate numbers in catalogue of Moll et al. Numbers without parentheses indicate distinct expression; numbers in parentheses indicate weak expression.
under physiologic conditions extends from pure reserve cell hyperplasia through the various phases of immature squamous metaplasia to mature squamous metaplastic epithelium. Furthermore, there is evidence that reserve cells are not only progenitors of mature squamous metaplastic epithelium, but may also differentiate into endocervical columnar cells. The complex keratin expression pattern of the progenitor reserve cells (Figure 1, H–N) provides support for the multidirectional differentiation capacity of these cells into columnar cells as well as into squamous metaplastic epithelia. Reserve cells have been shown to contain the simple keratins 7, 8 (Figure 1I), 18, and 19 (Figure 1J), which are all found in (mature) endocervical columnar cells.

Furthermore, keratins 14 (Figure 1K), 15, and 16 (Figure 1N) are usually found in reserve cells, and keratins 5 and 6 are sometimes found. These keratins, often found in nonkeratinizing squamous epithelia, are expressed along with keratin 17 (Figure 1L), which is more related to metaplastic squamous epithelium. With differentiation into immature squamous metaplasia (Figure 1, O–U), reserve cells lose keratins characteristic of simple epithelium (eg, keratin 8) (Figure 1O), with the exception of keratin 19 (Figure 1Q), and show an increased expression of keratins 5, 6, 14 (Figure 1R), 15, and 16 (Figure 1U), which are normally found in squamous epithelia. Oddly enough, keratin 17 expression (Figure 1S) decreases as immature metaplastic epithelium matures, but it usually does not disappear entirely. Keratins 4 and 13 (Figure 1T) have as yet not been demonstrated in reserve cells. Expression of these keratins emerges during immature squamous metaplasia, eventually becomes compartmentalized, and ultimately appears in suprabasal cells of nonkeratinizing squamous epithelia. Keratin 4 is also found in 50% of columnar cells. Transformations in the keratin phenotype of immature squamous epithelium are accompanied by distinct morphologic changes, characterized by stratification and compartmentalization.

A comparison of the keratin expression patterns between reserve cells and endocervical columnar cells shows that many of the keratins found in reserve cells are also found in columnar cells, albeit to a lesser degree. As endocervical columnar cells are in an end stage of differentiation and probably display very little metaplastic activity, we propose that these cells are derived from reserve cells, most of which lose expression of keratins 5, 6, 14, and 15 during differentiation into columnar cells and for unexplained reasons initiate expression of keratin 4. When reserve cells proliferate and transform into squamous metaplastic epithelium, the keratins found in simple epithelia cease to be expressed, and synthesis of keratins characteristic of nonkeratinizing epithelia, such as keratins 4 and 13, is initiated. Based on these observations, we consider reserve cells to be a common progenitor of both immature squamous metaplasia and endocervical columnar cells.

In mature squamous metaplastic epithelium, keratin expression is identical to that found in ectocervical epithelium with the exception of keratin 17, which is sporadically expressed in the basal cell layer of ectocervical epithelium. Furthermore, keratin expression is not compartmentalized as strictly as in the ectocervical noncornifying epithelium. This probably indicates that mature squamous metaplastic epithelium, though it seems mature based on morphologic criteria, is not yet fully matured based on its keratin phenotype.

Cervical Intraepithelial Neoplasia

More than 90% of dysplastic cervical lesions are thought to arise from the transformation zone between the ecto- and endocervical epithelium, also referred to as the squamocolumnar junction. Preferentially at this site, reserve cells situated below the columnar cells can proliferate into mature squamous metaplastic epithelium as described above. However, if the stimulus inducing proliferation also blocks differentiation of the reserve cells into a mature lesion, they may proliferate into an atypical immature squamous metaplastic epithelium, also described as one of the three grades of CIN. In this respect, it is important to note that many CIN lesions are not really progressive in nature, but represent a nonspecific tissue response to chronic irritation or inflammation. Therefore, the objective of research in this field should be directed toward a search for prognosticators capable of indicating whether an individual CIN lesion is progressive or regressive in nature. Because the progressive or indolent nature of a lesion cannot be predicted from light microscopic examination only, a search for discriminating markers is a prerequisite in solving this diagnostic dilemma.

Early studies of keratin expression in CIN lesions showed that keratin 8, as detected with CAM 5.2, was found in a high percentage of CIN III lesions and to a lesser extent in CIN II lesions. All squamous cell carcinomas of the cervix stained with this antibody. On this basis, it was concluded that those CIN lesions expressing K8 were progressive in nature, whereas those not expressing this simple-type keratin were considered to be regressive. Later studies elaborated on this work by using more extended panels of antibodies and all grades of CIN lesions. Because reserve cells are the progenitor cells for CIN lesions, the detection of keratin 8 is not surprising, but this
observation elicits some questions. 1) Which other “reserve cell keratins” are also found in CIN lesions? and 2) Why do a number of CIN lesions not express “reserve cell keratins,” when keratin expression is thought to be conservative?

Studies on fresh CIN lesions gave an answer to the first question; the keratin phenotype of most CIN lesions was comparable to that of ectocervical and mature squamous metaplastic epithelium (Figure 2, A–N). Approximately 10% of CIN I and CIN II lesions expressed the combination of keratins found in reserve cells, with discrete expression of the combination of keratins 8 (Figure 2B) and 18 and also keratin 17 (Figure 2E). In general, the level of expression of individual keratins was highly variable. Keratins 6 and 16 (Figure 2, G and N), related to hyperproliferation, displayed an increased level of expression with increasing atypia of the lesion.

Comparison of the keratin phenotypes between CIN III lesions (Figure 2, H–N) and CIN I and II lesions showed profound differences. The expression of reserve cell keratin phenotypes was increased up to about 50% of cases, and the intensity of expression of simple epithelial keratins had increased considerably. In our series, the combination of keratins 8 (Figure 2I) and keratin 18 expression, found in up to 80% of CIN III lesions, was considerably higher than the percentages found by Bobrow et al and Angus et al, possibly because of the effect of formalin fixation and paraffin embedding. In lesions demonstrating the complete reserve cell keratin profile, keratins typical for nonkeratinizing squamous epithelia were expressed to a lesser extent. The hyperproliferation-related keratins 6 and 16 (Figure 2N) showed a more intense expression than observed in lower grades of dysplasia.

Based on these observations, we advance the following theory regarding the origin and character of CIN lesions. Lesions expressing the keratin phenotype of reserve cells, in particular keratins 8, 17, and 18, are progressive in nature. Lesions morphologically classified as CIN I, II, or III but containing the keratin combination found in nonkeratinizing ectocervical epithelium, without expression of the reserve cell keratins 8, 17, and 18, are regressive in nature or will persist without progression. Observations in cervical carcinoma support this hypothesis.

Cervical Cancer

Studies on the changes in keratin expression of CIN III lesions progressing into carcinoma allow an alternative classification of carcinomas. These studies also have provided some evidence for the hypothesis that cervical squamous cell carcinomas and adenocarcinomas have common progenitor cells.

The keratin phenotype of keratinizing squamous cell carcinoma of the cervix was very complex (Figure 3A), with expression of simple epithelial keratins 8 (Figure 3B), 18, and 19 (Figure 3C) in all cases, and less frequently keratin 7. Most of these carcinomas combined expression of the simple epithelial keratins and keratin 10 (Figure 3G), an ultimate marker for keratinization. In addition, keratins characteristic of nonkeratinizing epithelia, ie, keratins 4, 5, 6, 13 (Figure 3F), 14 (Figure 3D), 15, and, to a certain extent, keratin 17 (Figure 3E), were always found in these keratinizing carcinomas.

Nonkeratinizing cervical squamous cell carcinomas (Figure 3H) expressed most of the keratins found in the keratinizing variety, although keratin 10 (Figure 3N), indicating keratinization, and keratin 13 (Figure 3M) were expressed to a lesser extent. Again these squamous cell carcinomas also usually expressed keratin 8 (Figure 3I), keratin 17 (Figure 3L), keratin 18, and keratin 19 (Figure 3I).

All adenocarcinomas contained the simple keratins 7, 8 (Figure 3P), 17 (Figure 3S), 18, and 19 (Figure 3Q). It is surprising that keratin 14 (Figure 3R) was also frequently present, and keratins related to squamous differentiation, eg, keratins 4, 5, 10 (Figure 3U), and 13 (Figure 3T), were sometimes found.

To explain these observations, we hypothesize that reserve cells containing the basic keratin expression pattern proliferate through grades of squamous metaplastic CIN and, during this progression, their keratin phenotype changes as outlined in the above paragraph. A number of CIN III lesions will progress into a carcinoma of the keratinizing variety, which expresses all the keratins found in reserve cells, combining markers of simple epithelium and markers of squamous differentiation. As the carcinoma shows signs of keratinization, synthesis of keratin 10 begins. If the CIN III lesion progresses to a nonkeratinizing carcinoma, its keratin expression pattern also reflects this type of differentiation.

Variable expression of keratin 10 indicates that the carcinoma is of the keratinizing variety. We noticed the existence of a subgroup of morphologically nonkeratinizing carcinomas that, based on their pattern of keratin 10 and high keratin 13 expression, would be better classified as being of the keratinizing variety.

The keratin expression pattern of adenocarcinomas was considerably more complex than expected from the results obtained with adenocarcinomas arising in other tissues. Expression of keratin 17 was always found and keratin 14 frequently observed. Furthermore, sporadic expression of keratins 4, 5, 10, and 13
Figure 2. Schematic overview of the keratins expressed in CIN I and CIN II lesions (A) and in CIN III (H). Immunoperoxidase staining patterns are shown for CIN I and CIN II (B-G) and for CIN III (I-N) after staining with antibodies reactive to K8 (B, I), K19 (C, J), K14 (D, K), K17 (E, L), K15 (F, M), and K16 (G, N). Abbreviations as in Figure 1.
Figure 3. Schematic overview of the keratins expressed in keratinizing squamous cell carcinoma of the cervix (A), nonkeratinizing squamous cell carcinoma of the cervix (H), and adenocarcinoma (O) after incubation with antibodies reactive to K8 (B, I, P), K19 (C, J, Q), K14 (D, K, R), K17 (E, L, S), K13 (F, M, T), and K10 (G, N, U). Abbreviations as in Figure 1.
was seen. None of these above keratins are present in the normal columnar cells lining the endocervical canal, although these are considered to be progenitor cells for this type of carcinoma. To explain this apparent discrepancy, we propose that cervical adenocarcinoma does not usually arise from columnar cells but from reserve cells. A CIN III lesion may thus evolve into an adenocarcinoma with persistence of all the reserve cell keratins except keratins 5, 6, and 16, which are only occasionally found. These latter keratins are usually not expressed in normal reserve cells. The foregoing would then suggest a continuum of different types of cervical carcinoma with, at one end, the keratinizing squamous cell variety and, at the other end, the adenocarcinoma. We therefore recommend that when classifying a cervical carcinoma, one consider not only the results of hematoxylin and eosin and mucin staining, but also the keratin phenotype.

Can Keratin Antibodies Elucidate the Origin of Endocervical Reserve Cells and Columnar Cells?

Ever since the first microscopic investigation of the endocervical canal, the presence of reserve cells was noted. The precise origin of these cells remains controversial. Some authors have suggested that they represent undifferentiated stem cells, which develop from the primitive cervical lining. Meyer proposed the columnar cells to be fully differentiated cells, present in each cervix. Flumann believed that reserve cells originate from the overlying columnar cells, based on the fact that these cells are found in endocervical tissue repair. Fairly strong evidence for a stromal origin was given by Song and Lawrence and Shingleton, who studied both embryonal and normal cervixes. They described "stromal" cells passing through the basement membrane, and supported their supposition with electron microscopic studies.

Based on immunokeratin phenotyping of the cervix, we believe that the discussion is again open after so many years. The reserve cells of reserve cells has been shown to be highly complex. Stromal cells have as yet not been shown to contain keratins. Vimentin, which has been found in all stromal cells, has not been observed in reserve cells. In general, transitions from one type of epithelium to another have been shown to be correlated with gradual keratin changes. It therefore seems highly unlikely that stromal cells migrating through a basal membrane will initiate the expression of up to ten different keratins, while in the transitional phase, when they are in the endocervical stroma, they contain no cytoskeletal proteins of the keratin type at all. In general, when nonepithelial cells obtain keratins, they normally represent only a limited subset of keratins 8 and 18.

We have shown that the keratin phenotype of reserve cells is more complex than that of endocervical columnar cells. Thus, columnar cells would have to initiate synthesis of a considerable number of differentiation-related keratins when transforming into reserve cells. This is an extremely unlikely pathway for the genesis of the reserve cell. In contrast, the argument is still valid that multipotent stem cells (reserve cells) are present in the endocervical canal, having originated there during embryonal development.

Diagnostic Implications of Keratin Expression

The results of the studies described above not only allow a more profound insight into the pathogenesis of cervical carcinoma but, equally important, they have diagnostic and therapeutic implications. Some of the results are already applicable; for others, there is strong evidence that further research in this field is justified and will provide a new impulse in the approach to the patient suffering from a cervical carcinoma or a CIN lesion.

In histopathologic diagnosis, it can be difficult to distinguish between a metastatic cervical adenocarcinoma and a metastatic carcinoma arising from the bowel, a decision with therapeutic implications. By determining the keratin phenotypes of these carcinomas using monoclonal antibodies, this dilemma may be solved. Adenocarcinomas of the colon have a simple keratin expression pattern consisting of keratins 8, 18, 19, and 20, whereas cervical carcinoma contains keratins 7 and 17, frequently keratin 14, and usually lacks keratin 20. Absence of keratin 5 (metastatic) in cervical adenocarcinoma can help distinguish this lesion from mesothelioma. In discriminating between (metastatic) cervical adenocarcinoma and ovarian serous or mucinous carcinoma, absence of keratins 14 and 17 in the ovarian malignancies may be a differential diagnostic tool. In lymph node metastases, knowledge of the keratin profiles of various (adenocarcinomas will often help to distinguish between such malignancies arising from various locations.

With respect to the differential diagnosis of keratinizing and nonkeratinizing carcinomas of the cervix, keratin antibodies may have some use. The keratinizing variety of carcinoma is suggested to have a poorer prognosis than the nonkeratinizing type. Taking the expression of keratins 10, 13, and 16 as being sufficient proof of keratinization would increase the group of keratinizing carcinomas considerably. In this way, it might be possible to select a subgroup of carcinomas.
that have a poor prognosis, versus a group with another keratin expression pattern that may have a better prognosis.

Another differential diagnostic consideration with therapeutic and prognostic implications is the distinction between poorly differentiated adenocarcinomas and poorly differentiated squamous cell carcinomas. This may be decided using antibodies to keratins 5 and 6, which are mainly absent in cervical adenocarcinomas.

The question of whether it is possible to distinguish between a progressive and a regressive CIN lesion based on keratin expression is still open. Our present studies have given some new insights in this regard. Keratin 17 is present in approximately 10% of CIN I and CIN II lesions. About 50% of CIN III lesions contain this keratin, and all cervical carcinomas are positive for this keratin subtype regardless of the type of differentiation. We therefore suggest that keratin 17 in a CIN lesion could be a marker of progression into a cervical carcinoma. The fact that its expression is maintained in cervical carcinoma is in keeping with the general rule that keratin expression is conserved throughout the entire evolution from reserve cell to cervical carcinoma. However, we can only speculate on the role of this keratin and also keratins 8 and 18, as there are exceptions to this rule regarding keratin expression.

**Future Studies**

Keratin expression studies in the normal, preneoplastic, and neoplastic cervix have been quite comprehensive because antibodies to most of the keratin subtypes have been tested in these epithelia. However, at present only one antibody is available to some of the keratins. Past studies have demonstrated that certain epitopes are not detected by certain keratin antibodies. For this reason, more than one antibody to the same keratin subtype is often used in staining assays. In practice, this means that the keratin phenotype of the cervix may be modified in the future based on newly developed keratin antibodies.

Necessary studies include determining the keratin phenotypes of primary and metastatic cervical cancer in an effort to see whether certain keratin phenotypes correlate with the metastatic capacity of these malignancies. Another important area of research involves the keratin expression patterns during embryonal development, as this may elucidate the origin of endocervical reserve cells and columnar cells.

The use of keratin expression as a prognostic indicator for the progressive or regressive nature of a CIN lesion needs a firmer basis before it can be applied in routine diagnosis. To this end, studies must examine the correlation between keratin expression and clinical outcome. These should be retrospective studies using archival material; however, such research is greatly hampered by the fact that most subtype-specific keratin antibodies are not reactive in formalin-fixed, paraffin-embedded tissue. We are now addressing this problem by testing conditions under which such immunoreagents become reactive in routinely processed tissue.

Finally, research should address the correlation between the expression of simple keratins and the presence of human papillomavirus (HPV), which is also a prognostic factor. Previous results have shown a collapse of the keratin network in human keratinocyes in the presence of HPV 16 late proteins. In summary, we can state that keratin expression patterns in the carcinogenesis of the cervical epithelia allow certain conclusions as to etiology and can be applied as diagnostic and prognostic markers.

**References**


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