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Detección, discriminación y cuantificación de pequeñas secuencias de nucleótidos por Espectroscopía Infrarroja por Transformada de Fourier (FTIR) en la identificación molecular del Virus Del Papiloma Humano

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RESUMEN

Antecedentes: La infección persistente por los subtipos oncogénicos del virus del papiloma humano (VPH) es la causa principal del desarrollo del cáncer cérvico-uterino. El aumento de casos presentados a nivel mundial ha propiciado la búsqueda de estrategias en la detección del VPH. La técnica de espectroscopía vibracional por transformada de Fourier (FTIR) es considerada una herramienta poderosa para la caracterización químico-estructural, de múltiples compuestos y biomoléculas como el ADN, lo que respalda su implementación para la investigación y diagnóstico viral.

Objetivos: Evaluar el uso de la técnica de espectroscopía infrarroja con transformada Fourier por reflexión total atenuada (ATR-FTIR) en la detección, discriminación y cuantificación de pequeñas secuencias de nucleótidos aplicado en la identificación molecular de genotipos de virus de papiloma humano (VPH).

Materiales y Métodos: Este es un estudio experimental. En una primera parte se generó un modelo de regresión para la cuantificación del porcentaje de nucleótido (%N, para cada nucleótido %A, %C, %T y %G) por el método multivariado de mínimos cuadrados parciales (PLS) y se analizaron las señales espectrales por ATR-FTIR de 35 secuencias de nucleótidos previamente diseñadas por la compañía Macrogen, Inc (Corea del sur). La segunda parte consistió en la implementación de ATR-FTIR para la identificación de genotipos de virus de papiloma humano. Se determinó la presencia de VPH 16, 18, 31, 35, 51 y 66 a través del análisis de la curva melting por ensayo SYBr Green mediante real-time PCR, en muestras de ADN obtenidas de una población de 19 mujeres con edades entre 17 y 26 años y vida sexual activa de la población estudiantil (USB).

Se generaron modelos multivariados por el método de análisis discriminante PLS (PLS-DA) para la predicción de los genotipos de VPH a partir de espectros de los productos de amplificados de ADN, controles positivos y negativos.

La adquisición de los espectros por espectroscopía FTIR de las diferentes secuencias nucleotídicas fue realizada en el intervalo espectral entre 4000–400 cm-1 utilizando un espectrómetro ALPHA FTIR spectrometer ATR, equipado con un cristal de diamante (Bruker Optics, Billerica, MA, USA), a una resolución espectral de 4 cm-1. A su vez, el procesamiento de datos y el análisis de espectros se desarrolló mediante el software Quant2™ de OPUS™ versión 4.2 (Bruker Optics).

Resultados: Se demostró la viabilidad de la técnica ATR-FTIR en la diferenciación de pequeñas secuencias de ADN de una sola cadena. Los resultados obtenidos del coeficiente de determinación (R^2) para el conjunto de predicciones y el sistema de validación cruzada (CV, cross validation) oscilaron entre 99,57 y 99,82, indicando el ajuste de los modelos. El error de los modelos (RMSEE) para la cuantificación del porcentaje de nucleótido (%N, para cada nucleótido %A, %C, %T y %G) por el método multivariado de PLS para la cuantificación del %N estuvo entre 0.9-1.2%, valores determinantes en el análisis de la capacidad de predicción. De las 19 muestras de ADN provenientes de raspados citológicos de mujeres, se obtuvo un total de 16 resultados positivos mediante real-time PCR para infección por VPH, donde los genotipos detectados fueron 51 y 66 en 14 y 2 muestras respectivamente. Tres muestras mostraron resultado negativo para los 6 tipos de VPH analizados.

El uso de diferentes regiones a lo largo del espectro identificadas según los diferentes parámetros como los rangos con mayor contribución en las variables para la discriminación entre estas, sugiere que es necesario abarcar todo el rango para un análisis y diferenciación más acertado entre las muestras.

Conforme a los resultados obtenidos con base al algoritmo PLS-DA, las matrices de confusión reportaron valores entre 0,88 y 1 correspondientes a los parámetros de sensibilidad, precisión, exactitud y F1-score, revelando la proporción de muestras que pertenecen al genotipo de VPH indicado que son correctamente identificadas por el modelo matemático. Lo anterior, afirma el excelente rendimiento del modelo creado para la clasificación y discriminación de las muestras de controles positivos amplificados para los genotipos de VPH, muestras amplificadas de ADN proveniente de los raspados cervicouterino positivas para VPH 51 y controles negativos que consistían en los espectros de las mezclas de todos los reactivos para PCR exceptuando ADN, así como los generados por la solución de la Master Mix.

Conclusiones: La técnica ATR-FTIR ofrece grandes ventajas por su alto rendimiento, poca cantidad de muestra empleada y la obtención de información química y estructural de diferentes muestras biológicas. En conjunto con el análisis multivariado PLS la técnica FTIR demostró su viabilidad en la diferenciación de

pequeñas secuencias de ADN monocatenario. Toda la región espectral se consideró informativa, considerando mayormente el rango de 1800-600 cm-1 por la aparición de bandas relacionadas a los constituyentes del ADN. El análisis de las Tm obtenidas mediante la técnica real-time PCR mostró la alta prevalencia de infección por VPH (16 de 19 casos) en este estudio, con 14 muestras para el genotipo VPH 51, considerado como un subtipo viral de alto riesgo oncogénico. La discriminación mediante análisis PLS-DA reafirmó la precisión de los modelos en la detección de genotipos de VPH 16, 18, 31, 35, 51 y 66, coincidiendo con los resultados por real-time PCR.

Palabras clave: ATR-FTIR, VPH, ADN, nucleótidos, cáncer cervicouterino, PLS, PLS-DA, real-time PCR.

ABSTRACT

Background: Persistent infection by oncogenic subtypes of human papillomavirus (HPV) is the main cause of the development of cervico-uterine cancer. The increase in cases presented worldwide has influenced the search for strategies in the HPV detection. The Fourier-transform Infrared (FTIR) is considered a powerful tool for the chemical-structural characterization of multiple compounds and biomolecules such as DNA, which supports its implementation for viral research and diagnosis.

Objective: To evaluate the use of the Attenuated Total Reflection-Fourier Transform Infrared (ATR-FTIR) spectroscopy technique in the detection, discrimination and quantification of small nucleotide sequences applied in the molecular identification of human papillomavirus (HPV) genotypes.

Materials and Methods: This is an experimental study. In the first part, a regression model was generated for the quantification of the nucleotide percentage (% N, for each nucleotide% A,% C,% T and% G) by the multivariate method of Partial Least Squares (PLS). We analyzed the spectral signals by ATR-FTIR of 35 nucleotide sequences previously designed by the Macrogen, Inc (South Korea) company. The second part consisted of the implementation of ATR-FTIR for the identification of human papillomavirus genotypes. The analysis of the melting curve by SYBr Green assay using real-time PCR, in DNA samples obtained from a population of 19 women with ages between 17 and 26 years and active sexual life of the student population (USB) determined the presence of HPV 16, 18, 31, 35, 51 and 66.

We generate multivariate models using the PLS discriminant analysis method (PLS-DA) for the prediction of HPV genotypes from the spectra of the DNA amplified products, positive and negative controls.

The acquisition of the spectra by FTIR spectroscopy of the different nucleotide sequences was carried out in the spectral interval between 4000-400 cm-1 using an ALPHA FTIR spectrometer ATR, equipped with a diamond crystal (Bruker Optics, Billerica, MA, USA), at a 4 cm^{-1} spectral resolution of. Data processing and spectrum analysis was performed using OPUS ™ version 4.2 Quant2 ™ software (Bruker Optics).

Results: The ATR-FTIR technique allows the differentiation of small single-stranded DNA sequences. The results obtained from the determination coefficient (R2) for the predictions set and the cross validation system (CV) ranged between 99.57 and 99.82, indicating the fit of the models. The models error (RMSEE) for the nucleotide percentage quantification (% N, for each nucleotide% A,% C,% T and% G) by the multivariate method of PLS for the quantification of% N was between 0.9-1.2%. These values are decisive in the analysis of the predictive capacity.

Of the 19 DNA samples from cytological scrapings from women, a total of 16 positive results were obtained by real-time PCR for HPV infection. The genotypes detected were 51 and 66 in 14 and 2 samples, respectively. Three samples were negative for the 6 types of HPV analyzed.

The use of different spectrum regions identified according to the different parameters as the ranges with the highest contribution in the variables for discrimination between them, suggests that it is necessary to cover the entire range for a more accurate analysis and differentiation between the samples.

The confusion matrices reported values between 0.88 and 1 corresponding to the parameters of sensitivity, precision, accuracy and F1-score. The results obtained based on the PLS-DA algorithm, affirm the excellent performance of the model created for the classification and discrimination of samples of amplified positive controls for HPV genotypes, amplified DNA samples from cervical scrapings positive for HPV 51 and negative controls that consisted of the spectra of the mixtures of all PCR reagents except DNA, as well as those generated by the Master Mix solution.

Conclusions: The ATR-FTIR technique offers great advantages due to its high performance, small amount of sample used and the obtaining of chemical and structural information from different biological samples. In conjunction with the multivariate PLS analysis, the FTIR technique demonstrated its viability in the differentiation of small single-stranded DNA sequences. The entire spectral region was considered informative, considering mainly the range of 1800-600 cm-1 due to the appearance of bands related to the constituents of DNA. The analysis of the Tm obtained using the real-time PCR technique showed the high prevalence of HPV infection (16 out of 19 cases) in this study, with 14 samples for the HPV 51 genotype, considered a viral subtype of high oncogenic risk. Discrimination using PLS-DA analysis reaffirmed the precision of the models in detecting HPV genotypes 16, 18, 31, 35, 51 and 66, coinciding with the results by real-time PCR.

KeyWords: ATR-FTIR, HPV, DNA, nucleotides, cervical cancer, PLS, PLS-DA, real-time PCR.

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