7.-INDICES

7.1.-Indice de Abreviaturas

AGCC	Acido graso de cadena corta
Al	Alanina
ARNt	Acido ribonucleico de transferencia
ADN	Acido desoxirribonucleico
ARN	Acido ribonucleico
mARN	ARN mensajero
APC	Gen Adenomatosis Polyposis Coli
ASO	***Allele specific oligonucleotide*** Oligonucleótido diseñado para detectar un alelo específico
BER	Reparación por excision de bases (base excision repair)
bp	Par de bases en una doble hélice de ADN
BPDE	Benzo (a)pireno diol epóxido
C	Citosina
cADN	ADN complementario, ADN sintetizado a partir de ARN mensajero
CBS	Gen Cistationina B sintasa
CCDN1	Gen Ciclina D1
CCR	Cáncer colorrectal
CYP1A1	Gen citocromo P450,familia 1,subfamilia A,polipéptido 1
DDCT	Gen D-Dopacromo Tautomerasa
dTMP	Desoxi Timidín monofosfato
dUMP	Desoxi Uridín monofosfato
DPD	Gen de la Dihidropririmidina deshidrogenasa, DPYD ,DHP
FAP	Poliposis adenomatosa familiar
GSTM1	Gen glutation transferasa M1
GSTT1	Gen glutation transferasa T1
GSTP1	Gen glutation transferasa Pi
HAPs	Hidrocarburos policíclicos aromáticos
Hinf I	Enzima de restricción clonada de Haemophilus influenzae ATCC 49824
Ile	Isoleucina
IMC	Indice de masa corporal en inglés BMI
K-ras	Gen ras (rat sarcoma) de Kirsten

5-FU	5-Fluorouracilo
HIV	Virus de la inmunodeficiencia humana
HPV	Virus del papiloma humano
HNPCC	Hereditary non polyposis colorectal cancer
IARC	International Agency For Research on Cancer
Kb	Kilobase, múltiplo de la unidad de medida del ADN ,equivale a 1.000 bases.
MSI	Microsatelite instability
ul	Microlitro
MTHFR	Gen Metilen tetrahidrofolato reductasa
MTR	Gen Metionina sintasa
MTRR	Gen Metionina sintasa reductasa
Msp I	Enzima de restricción clonada de Moraxella ATCC49670
dNTP	Mezcla de los desoxirribonucleótidos trifosfato: dATP, dTTP, dCTP, dGTP.
NCI	National Cancer Institute
NER	Reparación por escisión de nucleótidos (nucleotide excision repair)
OMIN	***On Line Mendelian Inheritance in Man*** .Base de datos de fenotipos clínicos y genotipos disponible por Internet.
PAI-1	Gen Inhibidor activador plasminogeno
PLA2G2A	Gen Fosfolipasa secretora 2A
TP53	Gen Tumor protein p53
RFLP	***Restriction fragment length polymorphism***. Polimorfismos de longitud de los fragmentos de restricción
SAM	S-Adenosil Metionina
SOD 2	Gen Superóxido dismutasa 2
SSCP	***Single strand conformation polymorphism.*** Técnica detección de mutaciones, basada en la movilidad del ADN según su conformación
T	Timina
TBE	Tris Borato EDTA
TFR	Gen Receptor Transferrina
TS	Gen Timidilato sintasa
Taq	Polimerasa de *Thermus Aquaticus*
uPAR	Gen Receptor Urocinasa
UV	Ultravioleta
Val	Valina
TCDD	2,3,7,8-tetraclorodibenzo p dioxina

7.2.-Indice de figuras

7.3.-Indice de tablas

8.-BIBLIOGRAFIA

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9.-RESUMEN

El cáncer colorrectal es una de las patologías mas frecuentes en nuestro País y en la Comunidad Valenciana con una incidencia creciente. Está asociado a factores genéticos, exposición a agentes etiológicos y a estilos de vida. La susceptibilidad individual al CCR puede ser parcialmente debida a variaciones en la capacidad de activar y detoxificar compuestos endógenos y exógenos y de reparar el daño que estos provocan en el ADN y otras macromoléculas.

Determinados polimorfismos en genes que codifican enzimas que intervienen en estos procesos, pueden dar lugar a variaciones en las actividades detoxificadoras y reparadoras y pueden influir en los niveles de moléculas tóxicas o carcinogénicas y de esta manera aumentar el riesgo individual de padecer una neoplasia colorrectal. Hemos estudiado las frecuencias del polimorfismo nulo en los genes de detoxificación ***GSTM1*** y ***GSTT1***, las frecuencias del polimorfismo de corte Msp I (T6235C) y Ile462Val (C4889G) en el gen ***CYP1A1*** de activación metabólica de hidrocarburos policíclicos aromáticos y por último las frecuencias del polimorfismo Ala677Val (C677T) en el gen ***MTHFR*** del metabolismo de los folatos que participa en los mecanismos de síntesis, reparación y metilación del ADN.

MATERIAL Y METODO. Se ha realizado un estudio observacional de casos y controles incidentes, en una población homogénea étnicamente (caucásicos) residentes en la misma área geográfica (Vega Baja Alicante). Constituye la muestra de casos, 93 pacientes con diagnóstico confirmado de adenocarcinoma colorrectal (anatomía

patológica) y los controles, 117 pacientes hospitalarios con patología no neoplásica (herniorrafias y colecistectomías).

Se extrajeron los ácidos nucleicos a partir de sangre total obtenida por venopunción. Se empleó kit de Qiagen para extraer y purificar el ADN y se resuspendió en 200 ul de TE conservándose a –20ºC hasta su utilización. Los polimorfismos nulos en GSTM1 y GSTT1 se analizaron mediante una multiplex con control interno de amplificación con fragmento del gen de la albúmina, siguiendo método descrito por Arand. Los polimorfismos en CYP1A1 se determinaron con el método descrito por Drakoulis (1994), por amplificación y corte con Msp I CYP1A1*2, y por ASO CYP1A1*3 para el polimorfismo A4889G con amplificación inicial de fragmento del gen de 1,5 Kb y heminested con pareja de oligonucleótidos específica para cada uno de los dos alelos posibles G y A. Por último el polimorfismo C677T en el gen MTHFR por el método de Frosst por PCR y posterior digestión del amplificado con la enzima de restricción Hinf. I.

Se recogieron datos de las siguientes variables de los pacientes: edad, género, peso, talla, índice de masa corporal, hábito de ingesta alcohólica, hábito tabáquico, localización tumoral, estadiaje de Dukes y tipo histológico del tumor. En el análisis de los resultados , se ha utilizado un modelo estadístico de regresión lineal, cálculo de odds

ratio y valor de P. Se ha realizado un análisis individualizado de cada variable frente a riesgo de patología y análisis de algunas asociaciones entre los genotipos y las variables clínicas e epidemiológicas recogidas.

RESULTADOS. En nuestra serie se asocian significativamente a riesgo de cáncer colorrectal los pacientes portadores de los polimorfismos**:** **GSTM1*1 OR=1,90** (IC 95% 1.52-2.28) P<0.05, **GSTT1*0 OR=3.09** (IC 95% 2.34-3.85) P<0.05 y **MTHFR*2 OR=3.08** (IC 95% 1.81-4.36) P< 0.05**.** El genotipo nulo en **GSTM1*0 OR=0.7 (IC95% 0.48-0.92) P<0.05** está asociado significativamente a protección.

En el resto de polimorfismos estudiados no se obtuvieron valores significativos de asociación o de P : GSTT1*1 OR=0.90 (IC 95% 0.73-1.07) P<0.05.CYP1A1*1 OR=1.47(IC 95% 1.16-1.77) P>0.05; CYP1A1*2 OR=2.32 P>0.05; CYP1A1*1/*2 OR= 1.7 (IC95% 1.06-2.33) P>0.05; CYP1A1*3 OR=2.79 (IC 95% -0.31-5.85) P>0.05; CYP1A1*1/*3 OR=1.07 (IC95% 0.65-1.49) P>0.05 ; MTHFR*1 OR=1.36 (IC 95% 0.99-1.74) P>0.05 y MTHFR*1/*2 OR=1.35 (IC95% 0.98-1.71) P<0.05. Tan sólo este último genotipo con valor significativo de P y OR en el límite de valores de asociación a riesgo.

Se obtuvieron valores no significativos en el análisis de las asociaciones entre GSTM1*0, GSTT1*0 y MTHFR*2 y el hábito de fumador para los distintos grupos. Ni de GSTM1*0, GSTT1*0 y MTHFR*2 para el hábito de ingesta alcohólica en los distintos grupos. Ni de MTHFR*2 para los distintos grupos clasificados en función del índice de masa corporal.

En el análisis de la asociación entre los polimorfismos GSTM1*0, GSTT1*0 y MTHFR*2 y la localización tumoral proximal o distal los valores fueron P>0.05 en todos ellos.

Se obtuvo un valor significativo de P<0.05 en la localización distal en relación al genero, siendo más frecuente en hombres 64% frente a mujeres 36%.

En el análisis de los genotipos de riesgo en función a los grupos de edad de los pacientes :15-44 años, 45-64 años y >65 años se obtuvieron valores significativos de asociación a riesgo y de P en los polimorfismos siguientes: **GSTM1*1 OR=1.57** (IC95% 1.45-1.69) P<0.001,**GSTT1*0 OR=3.98** (IC 95% 3.88-4.1) P<0.001 y **MTHFR*2 OR=5.49** (IC95% 5.35-5.63) P<0.001 **en el grupo de edad de > 65 años.** Y del resto de grupos de edad y polimorfismos tan sólo están próximos a alcanzar valores significativos el MTHFR*2 en el grupo de edad 45-64 años con un OR=1.17 (IC 95% 0.93-1.41) P<0.001 y GSTT1*0 OR=0.85 (IC95% 0.69-1.02) P<0.001.

Las personas con un mayor riesgo son las portadoras de las siguientes combinaciones de polimorfismos, en el grupo de edad de > 65 años .

GSTM1*1 + GSTT1*0 OR= 3.99 (IC95% 3.9-4.1) P<0.001

GSTM1*1 + MTHFR*2 OR=5.49 (IC95% 5.3-5.6) P<0.001

GSTT1*0+MTHFR*2 OR=7.17 (IC 95% 7.02-7.3) P<0.001

GSTM1*1+GSTT1*0+MTHFR*2 OR= 13.9 (IC95%13.8-14.0) P<0.001.

También fueron significativos en el grupo de edad 45-64 años las asociaciones **GSTT1*0 + MTHFR*2 OR= 1.53** (IC 95% 1.2-1.8) P<0.001 y **GSTM1*1+GSTT1*0+MTHFR*2 OR=2.98** (IC 95% 2.8-3.2) P <0.001.

CONCLUSIONES. Se han identificado factores genéticos asociados significativamente a riesgo frente a adenocarcinomas colorrectales esporádicos en la población de la Vega Baja. Su análisis puede contribuir a la identificación de grupos de riesgo y la elucidación de factores implicados en la carcinogénesis colónica. Nuestros resultados en el polimorfismo nulo en GSTT1 están en concordancia con los obtenidos en otros trabajos y asociado a la menor eficacia en los procesos de detoxificación de carcinógenos inherente a la falta de la transferasa codificada por el citado gen.

Los resultados con relación al polimorfismo nulo en GSTM1 son contrarios a la hipótesis de partida de asociación a riesgo, aunque los resultados en la bibliografía no son concluyentes. En nuestra serie el genotipo nulo se asocia significativamente a protección y es el genotipo salvaje el que se asocia a riesgo significativo. La explicación de ciertos autores es que la transferasa codificada por GSTM1 provoca la eliminación de isotiocianatos dietarios de conocido efecto anticarcinogénico.

Los polimorfismos en CYP1A1 , CYP1A1*2 y *3 se asocian a riesgo pero con valores no significativos, dado que la población de portadores con estos genotipos en nuestra población es muy pequeña.

Se confirma la hipótesis de que la metilen tetrahidrofolato reductasa de menor actividad, es decir la codificada por la variante MTHFR*2 confiere un mayor riesgo frente al CCR, en la población estudiada. Esta situación se produce cuando los niveles tisulares de folatos condicionan la síntesis, reparación y estabilidad de los a.nucléicos.

Posiblemente se de en la población estudiada una ingesta insuficiente; de folatos aunque no se pueden excluir otras razones como una menor biodisponibilidad, factores fisiológicos o genéticos que condicionen una menor absorción de la vitamina B9 de la dieta.

La asociación de dos o más genotipos de riesgo, de una forma especial GSTM1*1-GSTT1*0 y MTHFR*2 en un mismo sujeto confiere un riesgo elevado en especial en el grupo de edad de mas de 65 años, lo que plantea la conveniencia de investigar el potencial preventivo de suplementos dietarios con alimentos ricos en folatos o prescripción farmacológica con ácido fólico, como ya se hace en algún país.

10.-EPILOGO

En estas últimas semanas de elaboración de la tesis doctoral una idea emerge con fuerza, factores de riesgo que la población tiene asumidos asociados al cáncer en general , como por ejemplo el tábaco, con relación al cáncer colorrectal tienen poca influencia. Sin embargo, el hombre del siglo XXI, a pesar de los trabajos de Arsuaga sobre nuestros antepasados, ***no tiene conciencia de cuán determinante es la evolución en nuestras características genéticas personales y como estas son decisivas en nuestra salud y enfermedad****. Como el chasis y el motor que nos ha deparado la historia evolutiva no es el óptimo para afrontar con éxito la brutal transformación dietética, ambiental, social y laboral a la que estamos sometidos. Sólo la generosidad y el compromiso como cualidades humanas y la inteligencia como cualidad biológica del homo sapiens puede a través del ejercicio de las profesiones sanitarias adaptar nuestro vehículo para que se desplace sin riesgo en las autopistas actuales y futuras y reparar las averías que el tiempo depara.*

La ruta metabólica de los folatos se estudia en Bioquímica como ejemplo del mecanismo de acción de fármacos antineoplásicos como el el 5-FU y el metotrexato, inhibidor de la Timidilato sintasa el primero y antagonista del a.fólico el segundo. Pero quizá, la enseñanza de esta materia, no centra convenientemente la atención sobre el hecho de que en esta ruta metabólica, descansa el mecanismo por el que ciertos alimentos aportan los nutrientes necesarios para la síntesis y la necesaria reparación de la molécula de la vida, el ADN.

*La contemplación y el estudio del ciclo de los **FOLATOS**, sorprende al ver claros principios evolutivos ¿ porqué sino, dejar la fabricación de una molécula tan importante a expensas de la ingesta de unos alimentos como las hojas ?.*

La evolución no comprometió la especie y garantizó su desarrollo al dejar la síntesis y reparación de los ácidos nucleicos a expensas del aporte de un nutriente universalmente presente, cuya obtención no requería esfuerzo, a diferencia de proteínas y lípidos de animales de caza.

Sin embargo, el poco sabor de los alimentos vegetales, el escaso conocimiento entre la población del peso que la evolución tiene en el diseño del hombre y la escasa valorización que los profesionales sanitarios hacen de ellos, dan lugar al bajo consumo que contribuye a la génesis de varias patologías que comprometen la vida del hombre moderno.

Confío en que esta tesis contribuya de una manera eficaz a cambiar esta percepción.