RESUMEN

En este trabajo de tesis se ha investigado la relación de las enzimas esfingosina quinasa 1 (SphK1) y hemoxigenasa 1 (HO-1) con el cáncer. En el caso de la primera de estas enzimas se ha podido demostrar que se encuentra sobre expresada en carcinomas escamosos de cabeza y cuello y que su presencia se correlaciona con una menor sobrevida de los pacientes. Se ha aportado evidencia indicando que dicha correlación puede ser la manifestación de una relación de causa y efecto en la que esta quinasa estimula la proliferación celular disminuyendo los niveles de $p21^{Cip1}$, e inhibe la apoptosis al disminuir los niveles de caspasa 3 clivada e incrementar los de p-Bad.

En cuanto a HO-1 se ha explorado su relación con el cáncer en el carcinoma escamoso de cabeza y cuello y en cáncer de pulmón y de mama, tanto en tumores humanos como en modelos animales.

En carcinomas escamosos de cabeza y cuello se ha demostrado que HO-1 se encuentra sobre expresada y que se correlaciona con el grado tumoral. Se ha comprobado que la enzima presenta localización nuclear además de su típica localización citoplasmática, que dicha localización es mayor en las células tumorales que en los tejidos epiteliales adyacentes y que se correlaciona con tumores más agresivos y de peor pronóstico y con la progresión tumoral.

En cáncer de pulmón HO-1 se detectó en las células epiteliales del tumor mostrando una localización principalmente citoplasmática en comparación con tejidos pulmonares de aspecto normal donde los niveles de expresión fueron menores y con localización nuclear más frecuente. También se observó que se correlacionaba con estadios más avanzados de la enfermedad, con el tamaño tumoral y con la presencia de metástasis ganglionares.

En cáncer de mama se han realizado por primera vez estudios de expresión de HO-1 en tumores humanos comprobándose que se correlaciona con una mayor sobrevida de los pacientes. Se ha identificado un modelo animal adecuado para estudiar la relación de la enzima con este tipo de cáncer. Utilizando este modelo se ha comprobado que la activación de la misma conduce a un menor desarrollo tumoral. Se ha aportado evidencia indicando que los mecanismos que conducen a esta disminución del volumen tumoral, y tal vez también a la mayor sobrevida global de los pacientes, son la disminución en la

supervivencia celular, debida a un efecto pro apoptótico, y la inhibición de la migración celular producidas por esta enzima. También se ha comprobado en este carcinoma la localización nuclear de la enzima y se ha aportado evidencia indicando que una forma truncada en el extremo carboxilo terminal se localiza en el núcleo. Esta localización nuclear no se correlaciona con la sobrevida global de los pacientes.

Finalmente, los resultados obtenidos en esta tesis sugieren que ambas enzimas pueden ser de potencial interés como factores pronósticos y/o blancos terapéuticos y señalan la necesidad de continuar investigando los mecanismos celulares y moleculares que la desregulación de estas enzimas podría estar afectando contribuyendo así al desarrollo del cáncer.

ABSTRACT

In this thesis the relation between the enzymes sphingosine kinase 1 and heme oxygenase 1 with cancer has been investigated. In the case of the former one it has been demonstrated that it is over expressed in head neck squamous cell carcinoma and that its presence correlates with a shorter patient survival. Evidence has been provided showing that such correlation could be due to a cause-effect relationship in which this kinase stimulates cellular proliferation by down regulation of $p21^{Cip1}$ levels and inhibits apoptosis through a decrease in the levels of cleaved caspase 3 and an increase in p-Bad.

Regarding heme oxigenase 1, its relation with cancer has been investigated in head neck squamous cell carcinoma, lung and breast cancer both in human tumors and animal models.

In head and neck squamous cell carcinoma the enzyme was shown to be over expressed and to correlate with tumor grade. Furthermore, nuclear localization of the enzyme has also been demonstrated. It has also been detected that such nuclear localization is more frequent in tumor cells that in adjacent non malignant tissues. Furthermore this nuclear localization correlates with lower differentiation grades and with tumor progression.

In lung cancer the heme oxygenase 1 has been detected mainly in the cytoplasm of epithelial cells whereas it was more frequently localized in the nucleus in normal lung tissues. Additionally, enzyme levels have been demonstrated to be higher in tumor tissues than in non malignant adjacent ones and to correlate with advanced stages of the disease, with tumor size and with lymph node metastasis.

This is the first study showing heme oxygenase 1 protein expression in human breast tumor tissues and its correlation with longer patient survival. This research has also identified an adequate animal model to study the relation between the enzyme and this type of cancer. In this animal model the enzyme activation leads to a decrease in tumor burden. Evidence has also been provided showing that the mechanisms responsible for this decrease in the tumor volume are the reduction in cellular survival due to a pro apoptotic effect and the inhibition of cellular migration. A nuclear localization of the enzyme in this tumor type has also been demonstrated. Evidence has also been provided

that this nuclear heme oxygenase 1 is a C-terminal truncated protein. This nuclear localization does not correlate with patient survival.

Finally, the results obtained in this thesis suggest that both enzymes could be potentially interesting as prognostic factors and/or therapeutic targets and they encourage future investigations regarding the cellular and molecular mechanisms modulated by these enzymes and whose deregulation could contribute to cancer development.

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