PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

GW5638: a new antiestrogen

ArticleInfo		
ArticleID	:	3781
ArticleDOI	:	10.1186/bcr-2001-68484
ArticleCitationID	:	68484
ArticleSequenceNumber	:	53
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	3
ArticleHistory	:	RegistrationDate : 2001–6–21 Received : 2001–9–13 Accepted : 2001–9–13 OnlineDate : 2001–9–13
ArticleCopyright	:	Biomed Central Ltd2001
ArticleGrants	:	

ArticleContext	:	1305833

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Keywords

Antiestrogen, breast cancer, GW5638, tamoxifen resistance

Context

Approximately two-thirds of breast tumors are ER-positive (ER+), and therefore suitable for some type of endocrine therapy. Tamoxifen has been the standard hormonal therapy for the last 30 years. Nevertheless, less than two-thirds of ER+ tumors respond to tamoxifen, and eventually the majority of advanced tumors develop resistance to the drug. Even when the new hormonal agents are used, sublines of resistant cells may develop. Clearly, no single endocrine therapy will be enough to treat all ER+ breast cancer patients and new agents are needed. The authors tested GW5638 for potential activity against breast cancer.

Significant findings

When MCF-7 xenografts were treated with either tamoxifen or GW5638, different conformational changes were induced in the ER thereby exposing different surface peptides. These drugs therefore work by distinct mechanisms. Most importantly, tumoristatic doses of GW5638 inhibited growth of tamoxifen-resistant xenografts, both in the presence and in the absence of tamoxifen, as well as in ovary-intact animals (estradiol presence). These results suggest that GW5638 may be clinically useful for the treatment of both tamoxifen-naive and tamoxifen-resistant ER+ tumors.

Comments

This study adds some new data to our, still incomplete, knowledge of the complexity of ER and tamoxifen pharmacology. Furthermore, it presents the first results of a potentially clinically useful

antiestrogen, suitable for treatment of both tamoxifen-naive and tamoxifen-resistant ER+ breast tumors. The only available antiestrogen that has activity on these types of tumors, FaslodexR, has a different mechanism of action: receptor degradation induction. Equally important will be to compare GW5638 to aromatase inhibitors, and to study its potential use in combination with or after failure of these agents, as their target and mechanism of action are completely different. GW5638 will soon be introduced in the clinic under the name of DPC-974. The authors hypothesize that ER is a versatile transcriptional factor that exhibits different biological actions in different target cells. They also suggest that ER pharmacology is likely to depend on specific conformational changes that each individual ligand induces in its structure. These changes would expose certain peptides in the ER-ligand complex that would allow the interaction with specific coactivators, which are differently expressed in all target cells. This could also explain tamoxifen's partial agonist activity. The conformational changes induced in the ER upon exposure to either GW5638 or tamoxifen support their hypothesis.

Methods

Phage affinity selection; phase ELISA; cell culture and transient transfection; animal models; MCF-7 and MCF-7DU/TAM (tamoxifen-resistant) xenografts; statistical analysis performed with ANOVA, Kruskal-Wallis and multiple comparison tests

Additional information

References

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