

Cell membrane estrogen receptors resurface

To the editor—In their recent and informative *News and Views* “Estrogen hits the surface,” Collins and Webb¹ suggested that “newly discovered estrogen receptor-dependent signaling pathways demonstrate that estrogen functions in the cytosol as well as in the nucleus.” Although we agree wholeheartedly with the data cited, we regret that the authors failed to acknowledge that cell surface forms of estrogen receptors coupled to intracellular signaling pathways were first reported more than 20 years ago²⁻⁴. Thus, this work is not so much newly discovered as rather newly recognized due to profound deficiencies in the capacity of the nuclear transcription factor concept to integrate all aspects of estrogen action.

As noted by Collins and Webb¹, reports of rapid estrogen effects occurring in vasculature, breast, bone, uterus and neuronal tissues cannot be explained by prevailing theories. Yet it is still widely believed that the biological activity of estrogen in responsive cells is mediated only through a specific high-affinity es-

trogen receptor located exclusively in their nuclei. On binding estrogen, the nuclear receptor promotes association with target genes and permits regulation of selective gene transcription⁵. However, in addition to the latter pathway, it has been established that estrogen can also induce extremely rapid increases in the levels of intracellular second messengers, including calcium and cAMP, as well as activation of mitogen-activated protein kinase and phospholipase¹⁻⁴. The time course of these acute events parallels that elicited by peptides, lending support to the hypothesis that they do not involve the ‘classical’ genomic action of estrogen. Many of the rapid effects of estrogen are now attributed to the action of the hormone at the cell membrane, and these biologic actions seem to be mediated by membrane receptors that bind estrogen. The newer literature discussed by Collins and Webb should be evaluated in the fuller context of the substantial background in this field.

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Collins and Webb reply—In no way did we intend to give the impression that estrogen receptors on the surface of plasma membranes or intracellular coupling was a new concept.

Our *News & Views* discussed a recent paper⁶ that clearly stated that the existence of a putative membrane estrogen receptor is supported by studies spanning 20 years and that the origin and functions of this receptor are not well defined. Indeed this was the main thrust of our article. We wanted to convey that the surface estrogen receptor couples to a common intracellular signaling pathway in four different cells, as illustrated in our figure. These data reinforce the rapid, non-genomic estrogen-receptor dependent mechanisms of estrogen.

It is noteworthy that the research community is expanding the function of steroid hormone receptors beyond the confines of sexual differentiation and reproductive endocrine function. Gaining a better understanding of the rapid actions of estrogen may lead to new therapeutic strategies for the treatment of cell proliferative, neurodegenerative and cardiovascular defects.

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Viral phenotype and CCR5 genotype

To the editor—We thank D’Aquila *et al.*¹ for their comments on our recent *News and Views* article². We fully agree that both CXCR4 and CCR5 inhibitors should be evaluated in clinical trials, if suitable compounds are developed. However, we wish to clarify some aspects of the literature raised by D’Aquila *et al.* on the emergence of CXCR4-using syncytium-inducing (SI) HIV-1 strains *in vivo*. First, the study we cited³ for the lack of association of the SI viral phenotype with heterozygosity for CCR5 $\Delta 32$ was not, in fact, a study of “newly infected patients.” The subcohort of 406 HIV-1-infected subjects examined in that study was seroprevalent with an average time to AIDS of 5.8 years, compared with 9–10 years as seen in seroincident cohorts³. Moreover, although D’Aquila *et al.* did indeed find an association of the SI viral phenotype with CCR5 $\Delta 32$ heterozygosity in their study of 95 individuals⁴, larger studies have either not confirmed this observation⁵ or have found a non-statistically significant trend⁶. On these last points, we look forward to the results of meta-analysis (ref. 7 and T. O’Brien, personal communication) to provide more definitive evidence as to whether there is

any association of viral phenotype and chemokine receptor genotype.

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