New insights in oestrogen receptor (ER) research — the ERβ

J.-A. Gustafsson *

Department of Medical Nutrition, Karolinska Institute NOVUM, Huddinge University Hospital, S-14186 Huddinge, Sweden

During recent years we have seen a paradigm shift in our understanding of oestrogen action. This is mainly due to the discovery of a second oestrogen receptor, (ER)β, which is encoded by a separate gene from that of ERα [1]. ERβ is expressed in partially different tissues from ERα, notably prostate, ovary, lung, kidney, gastrointestinal tract especially colon, as well as in tissues where ERα is also found, e.g. breast, central nervous system (CNS) and testis. ERα predominates in uterus and liver. It seems quite clear at this stage that the two ERs have different biological properties and sometimes act in opposite manners to one another, like a yin-yang principle. One example is cell proliferation where we currently work with the hypothesis that ERα is mainly involved in promoting this process whereas ERβ seems to be inhibitory towards cell proliferation. For instance, in the vessel wall and in the prostate, ERβ seems to protect against smooth muscle cell proliferation [2] and prostate hyperplasia, respectively.

In collaboration with R. Hubbard's group in York, UK, as well as with KaroBio AB, Novum, Sweden, we have solved the three-dimensional structure of both ERα [3] and ERβ [4] ligand-binding domains (LBDs). Several interesting differences are noted, e.g. with reference to the position of helix 12 when the receptor is bound with various ligands. Furthermore, crystallisation attempts have shown the same preference of ERβ for binding genistein as previous *in vitro* binding assays, where this phyto-oestrogen has approximately two orders of magnitude better affinity to ERβ than to ERα. It is, thus, not inconceivable that ERβ could use dietary phyto-oestrogens as physiological ligands. This is of obvious interest in view of the many claims about the alleged health-promoting properties of phyto-oestrogens.

Much of our current research attempts to understand the physiological significance of ERβ focus on use of ERβ knock-out (K-O) mice, developed in collaboration with O. Smithies in Research Triangle Park, NC, USA [5]. Female ERβ (-/-) mice have serious reproduction disturbances and are only 20% fertile. Other interesting phenotypes include prostate hyperplasia and growth disturbances in bone [6]. Many other interesting phenotypes are under investigation. The discovery of ERβ has led to a significantly enhanced interest in the development of new drugs for hormone replacement therapy. The different tissue distribution of the two ER isoforms, as well as differences in their ligand-binding properties have stimulated the hope that it should be possible to develop drugs with more specific actions and with fewer side-effects, e.g. endometrial and breast cancer risks.

References

1. Kuiper GGJM, Enmark E, Pelto-Huikko M, Nilsson S, Gustafsson J-A. Cloning of a novel estrogen receptor expressed in rat prostate and ovary. *Proc Natl Acad Sci* 1996, **93**, 5925–5930.
2. Makela S, Savolainen H, Aavik E, *et al*. Differentiation between vasculoprotective and uterotrophic effects of ligands with different binding affinities to estrogen receptors α and β. *Proc Natl Acad Sci USA* 1999, **96**, 7077–7082.
3. Brzozowski AM, Pike ACW, Dauter Z, *et al*. Insights into the molecular basis of agonism and antagonism in the oestrogen receptor as revealed by complexes with 17β-oestradiol and raloxifene. *Nature* 1997, **389**, 753–758.
4. Pike ACW, Brzozowski AM, Hubbard RE, *et al*. Structure of the ligand-binding domain of oestrogen receptor beta in the presence of a partial agonist and a full antagonist. *EMBO J* 1999, **18**, 4608–4618.
5. Krege JH, Hodgin JB, Couse JF, *et al*. Generation and reproductive phenotypes of mice lacking estrogen receptor β. *Proc Natl Acad Sci USA* 1998, **95**, 15677–15682.
6. Windahl SH, Vidal O, Andersson G, Gustafsson J-A, Ohlsson C. Increased cortical bone mineral content but unchanged trabecular bone mineral density in female ERβ -/- mice. *J Clin Invest* 1999, **104**, 895–901.

* Tel.: +46-8774-9207; fax: +46-8779-8795.
E-mail address: jan-ake.gustafsson@cbt.ki.se (J.-A. Gustafsson).

0959-8049/00/$ - see front matter
PII: S0959-8049(00)00206-9