Progesterone Receptor Isoforms :
Functional Selectivity and Pharmacological Targeting

Progesterone receptor (PR) is an essential pharmacological target for contraception, female reproductive disorders as well as for hormone-dependent breast and uterine cancers. Human PR is expressed as two major isoforms PRA and PRB which behave as distinct transcriptional factors. PRA *vs* PRB expression is often altered under pathological conditions notably breast cancer through unknown mechanisms. In this thesis we demonstrate that down-regulations of PRB and PRA proteins are negatively controlled by key phosphorylation events involving distinct MAP kinase signaling. PRA is selectively stabilized by p38 MAPK whereas p42/44 MAPK specifically controls PRB stability leading to unbalanced PRA/PRB ratios in a ligand sensitive manner. In cancer cells, elevated extracellular stimuli such as epidermal growth factors or pro-inflammatory cytokines that preferentially activate p42/44 or p38 MAPK respectively may result in opposite variations in PRA/PRB expression ratio. These results may explain altered PRA/PRB ratios often associated with breast tumors. To get a mechanistic understanding of how varied PRA/PRB ratio contributes in cell signaling, we generated an original bi-inducible PR-isoform cell model allowing selective, reversible and dose-dependent expression of PRA and/or PRB, enabling fine-tune adjustment of PRA/PRB ratio in the same cells. Using this cell-based system, we undertook genome-wide transcriptomic studies to investigate transcriptional regulation driven by unliganded and liganded PR isoforms. We report that several aspects of PR signaling such as target gene selection/transcriptional regulation, cross-talk with growth factors and antiproliferative efficacy of antiprogestin are highly dependent upon variation in PRA/PRB ratio. A new potential therapeutic strategy in PR-dependent pathological conditions may rely on the use of PR antagonists. Most of the currently available antiprogestins such as mifepristone present partial agonist activity and are not selective to PR leading to undesirable side effects. Therefore, in a collaborative project we have synthesized and characterized several new PR antagonist compounds named as APRn. Structure-activity relationship studies allowed identification of the key substitutions in steroidal skeleton responsible for agonist/antagonist character of these molecules. Several selected APRn lack partial agonist effect, are PR specific and inhibit PR transcriptional properties through a new passive mechanism of action i.e. impaired recruitment of transcriptional coregulators. Such PR selective antagonists devoid of partial agonist character might provide important therapeutic perspectives for various reproductive tract abnormalities and hormone-dependent uterine and breast cancers. Altogehter, our results provide mechanistic insights into the functional selectivity of PR isoforms and their pharmacological targeting by the use of PR antagonists.

Key words: Progesterone, Progesterone receptor isoforms, PRA/PRB ratio, antiprogestins, transcription

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