

Androgen Receptor and covid19

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Function—

This gene encodes a protein that belongs to the serine protease family. The encoded protein contains a type II transmembrane domain, a receptor class A domain, a scavenger receptor cysteine-rich domain and a protease domain. Serine proteases are known to be involved in many physiological and pathological processes. This gene was demonstrated to be up-regulated by androgenic hormones in prostate cancer cells and down-regulated in androgen-independent prostate cancer tissue. The protease domain of this protein is thought to be cleaved and secreted into cell media after autocleavage.

Androgen receptor(AR) —

- The androgen receptor (AR), also known as NR3C4(nuclear receptor subfamily 3, group C, member 4), is a type of nuclear receptor that is activated by binding of androgen hormones in the cytoplasm and then translocating into the nucleus.
- The main function of the androgen receptor is as a DNA-binding transcription factor that regulates gene expression; however, the androgen receptor has other functions as well.
- Androgen administration altered significantly murine lung gene expression profiles; for example, by up-regulating transcripts involved in oxygen transport and down-regulating those in DNA repair and DNA recombination. Androgen exposure also affected the gene expression profile in a human lung adenocarcinoma-derived cell line, A549, by up- or down-regulating significantly some 200 transcripts, including down-regulation of genes involved in cell respiration.

Abiraterone acetate—

- Abiraterone inhibit biosynthesis of androgen through inhibition of CYP17

Enzalutamide—*Mechanism*

1. Inhibit binding of androgen to the ligand-binding domain of androgen receptor.
2. Inhibit nuclear translocation of androgen receptor.
3. Inhibit binding of androgen receptor to DNA.

Apalutamide—*Mechanism*

1. Inhibit AR nuclear translocation.
2. Inhibit AR binding to DNA.
3. Inhibit AR mediated transcription.

Darolutamide—

1. Inhibit AR nuclear translocation.
2. Inhibit AR mediated Transcription.
3. Inhibit AR binding to DNA.

Mechanism of AR on COVIT19 (TMPRSS2 GENE)—

- Androgen receptor(AR) which is found in chromosome X that is mainly expressed in pneumocytell, when androgen(ligand) bind to AR receptor,
- AR receptor (Protein) become stable & active in pneumocytell so AR (Transcriptional factor) will begin the expression of TMPRSS2 gene (transcription & translation) which is found on pneumocyte II.
- Expression process of TMPRSS2 gene which is found in chromosome 21 (DNA) of human body start by binding of AR protein to RNA polymerase II in the promotor of TMPRSS2 gene to produce mRNA.
- Then mRNA will encode the information by binding mRNA code(nucleotides) with amino acids to produce functional group called TMPRSS2 enzyme(protein).
- TMPRSS2 enzyme used to cleave COVID19 virus protein to enter to the host lung cell membrane and cause acute respiratory diseases(ARDS).

Mechanism of Enzalutamide, Apalutamide, Darolutamide on COVID19 virus protein (TMPRSS2) —

- Block androgen binding to AR receptor (protein) which is transcriptional factor on pneumocyte II thus prevent the expression of TMPRSS2 gene which is needed for production of TMPRSS2 enzyme that cause cleavage of TMPRSS2 S protein of COVID19 Virus and allow fusion of TMPRSS2 protein into host lung cell membrane to begin acute respiratory diseases (ARDS) and thus prevent replication of covid19 virus.

Mechanism of abiraterone acetate on COVID19 TMPRSS2 protein (enzyme) —

- Abiraterone inhibit binding of androgen thus inhibit AR stabilization and prevent expression of TMPRSS2 gene to produce TMPRSS2 protein (enzyme) which is necessary for cleavage of COVID19 TMPRSS2 protein and allow fusion of protein into lung cell membrane

Discussion —

- Because of AR receptor mutation (ARF876L) occur with enzalutamide and apalutamide treatment causing switch of antagonist activity into agonist and produce resistance to enzalutamide & apalutamide.
- But darolutamide has full ARF876L antagonist mutation thus not cause switch of antagonist to agonist activity and prevent resistance to darolutamide.
- Also enzalutamide and apalutamide could cross blood brain barrier (BBB)
- And thus increase risk of seizures but darolutamide exhibit the lower rate of penetration to BBB thus lower risk of seizures.
- The most proper drug as AR blocker is darolutamide.

Results —

Combination Therapy

- The use of abiraterone acetate to inhibit the synthesis of androgen with darolutamide as AR antagonist is a good combination therapy as they both prevent the expression of TMPRSS2 gene to produce TMPRSS2 protein which is used as enzyme to cleave COVID19 protein to allow TMPRSS2 spike protein fusion into lung cell membrane.
- And also abiraterone prevent the possibility of causing cancer by inhibit synthesis of androgen and darolutamide has full AR antagonist and lower risk of seizures.

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