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Unit – III

TOPIC: INHIBITING SIGNALING PATHWAYS THROUGH RATIONAL DRUG DESIGN

Dr. A. S. VIJAYAKUMAR
Guest lecturer
Department of Biomedical Science

Inhibiting Signaling Pathways through Rational Drug Design

RATIONAL DRUG DESIGN :

- The role of rational drug design is to use a methodological approach to come up with a new drug .

Example :

Angiotensin- converting enzyme (ACE), whose specific inhibition by several drugs has resulted in marked improvements in the clinical outcomes of patients suffering from congestive heart failure.

Once a target is selected, the most widely utilized approach toward the development of an inhibitor is the screening of large chemical libraries.

This involves the creation of an assay for the function of the targetand the application of thousands of test compounds to this assay to assess the ability of these to inhibit the function of the target.

TRADITIONAL DRUG DESIGN :

- Traditional drug discovery involves the origin of drug discovery, that evolved in natural sources , accidental events. It was not target based and not much systemised. The types of traditional drug design are:

    1. Random screening
    2. Trial and Error method
    3. Ethnopharmacology approach
    4. Serendipity method
    5. Classical Pharmacology
    6. Chemical structure based drug discovery.

1. RANDOM SCREENING :

- It includes random screening of synthetic compounds or chemicals or on natural products by bioassay procedures , it involves two types of approaches :

1. Screening for selected class of compounds like alkanoids, flavonoids, etc.

2. Screening of randomly selected plants for selected bioassays.

2. TRIAL AND ERROR METHOD :

- Trial and error method includes berries, leaves and barks could be used for medicinal purposes to alleviate symptoms of illness.

EXAMPLE : Willlow bark : contains salicilin – fever reducing.

3. ETHNOPHARMACOLOGY APPROACH :

- Depends on empirical experience related the use of botanical drugs for the discovery of biologically active new chemical entry.
- This process involves observation, description and experimental investigation of indigenous.

4. SERENDIPITY METHOD :

- Serendipity refers to an accidental discovery

5. CLASSICAL PHARMACOLOGY :

- It is also known as function based approach. Anciently, drug discovery programmes were often based- successfully on measuring a complex response in vivo, such as prevention of experimentally induced seizures, lowering of blood sugar or suppression of an inflammatory response.

❑ Rational drug design involves three general steps to create a new drug :

STEP 1: Identify a receptor or enzyme that is relevant to a disease they are going to design a drug for.

STEP 2: Elucidate the structure and function of this receptor or enzyme.

STEP 3: Use the information from step two in order to design a drug molecule that interacts with receptor.

TRANSFORMING GROWTH FACTOR b SIGNALLING AS A MODEL FOR DRUG DEVELOPMENT :

- Transforming Growth Factor b (TGF-b) is a prototypical member of a large family of growth factors in humans that include TGF-bs, Bone Morphogenic Proteins(BMPs) and activins.

- The action of these growth factors have been implicated in a wide variety of pathophysiological processes such as fibro proliferative diseases of the lung, kidney, arterial vascular disease and certain malignancies.

EXAMPLE :

- TGF-b is thought to play a central role in the pathogenesis of diabetic nephropathy. This disorder is thought to arise in part from the induction of TGF-b production by **glomerular mesangial cells** of the kidney in response to excessive hyperglycaemia.
- This growth factor then acts as a potent stimulus for the production of excessive extracellular matrix by cells within the glomerulus, which ultimately leads to glomerular sclerosis or fibrosis and a progressive decline in renal function.
- Inhibitions of the actions of TGF-b in experimental models of diabetic renal disease has resulted in significant improvements in renal function.
- Thus inhibition of TGF-b may be an attractive strategy for the therapy of diabetic renal disease and other disorders.

INTRACELLULAR SIGNALLING MECHANISMS:

- There are three types of cell surface receptors (I, II, III)
- The active forms of TGF-b binds to the type – III receptor at the cell surface and this complex subsequently interacts with transphosphorylates the cytoplasmic domain of type –I receptor.
- The phosphorylation event activates the type-I receptor kinase domain , which then propagates downstream signals within the cell.
- Once activated , the type- I receptor can specifically interact with a class of intracellular proteins known as smad proteins.
- These proteins act as substrates for the kinase domain present within the type- I receptor, and phosphorylation of the smads result in their activation and translocation to the nucleus, where they act as transcriptional effectors on a variety of target genes.

TYPES OF DRUG DESIGN :

- Rational drug design can be categorised into two categories they are:

1. STRUCTURE BASED DRUG DESIGN :

Relies on finding new medication based on the knowledge of the target. Also known as **direct drug design**.

2. LIGAND BASED DRUG DESIGN :

Relies on knowledge of other molecules that bind to the biological target of interest. Also known as **indirect drug design**.

STRUCTURE BASED DRUG DESIGN :

- Structure based drug design relies on knowledge of the three dimensional structure of biological target obtained through methods such as X-Crystallography or NMR Spectroscopy.
- Using the structure of the biological target , candidate drugs that are predicted to bind with affinity and selectivity to the target may be designed using interactive graphics and the intuition of medicinal chemist.
- Structure based drug design is one of the first techniques to be used in the drug design .
- In parallel , information about the structural dynamics and electronic properties about ligands are obtained from calculations.

LIGAND BASED DRUG DESIGN :

- Ligand- based drug design relies on knowledge of other molecules that bind to the biological target of interest.
- The other molecules may be used to derive a pharmacophore model which defines the minimum necessary structural characteristic a molecule must possess in order to bind to the target.
- A model of the biological target may be built based on the knowledge of what binds to it and this model in turn may be used to design new molecular entities that interact with the target.

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Thank you