Computational Advances in Chronic Diseases Diagnostics and Therapy - II

In continuation with computational advances in chronic diseases diagnostics and therapy – I [1], this part II consists of articles which contribute to develop new ideas, algorithm design and rational drug discovery techniques to antiviral drug targets of single-stranded ribonucleic acid (RNA) viruses, homeostasis in the cardiovascular system, ion channels as therapeutic targets for type 1 diabetes mellitus and amyloid beta (Aβ) in Alzheimer's disease (AD).

Dinesh et al. [2] demonstrated that antiviral drug targets of single-stranded ribonucleic acid (RNA) viruses cause chronic human diseases. RNA containing viruses associated with chronic diseases in humans are major threats to public health causing high mortality globally. Extremely high mutation rates of RNA viruses make them deadliest and thus difficult to design an effective drug. Chronic infections caused by human immunodeficiency virus (HIV-1) and hepatitis virus (HBV and HCV) lead to acquired immunodeficiency syndrome (AIDS) and hepatocellular carcinoma, respectively, they are the primary cause of human deaths. Effective preventive measures to limit chronic and re-emerging viral infections are absolutely necessary; and remains a challenging issue. Antivirals usually inhibit different stages of the virus life-cycle, instead of killing them as in the case of the bacterial antibiotics. Most often antiviral drugs are targeted against specific viral and host protein, whereas a few broad-spectrum drugs are available for targeting multiple viruses. In the recent past, an exponential increase in the number of available three-dimensional protein structures and advancements in the in silico approaches, have paved the way to design and develop several novel, highly specific small molecule inhibitors against protein drug targets. The present review briefly discussed about selected single-stranded (ss) RNA genome containing human pathogenic viruses, causing chronic infections and are of special importance for e.g. HIV-1, HCV, Flaviviruses, Ebola etc., their selected viral target proteins and an update about the available small-molecule inhibitors or antivirals acting against them have also been discussed.

Singh and Karnik [3] clearly summarized homeostasis in the cardiovascular system maintained by physiological functions of the renin angiotensin aldosterone system (RAAS). In pathophysiological conditions, over activation of RAAS leads to an increase in the concentration of angiotensin II (AngII) and over activation of angiotensin type 1 receptor (AT1R) resulting in vasoconstriction, sodium retention and change in myocyte growth. In the heart, it causes cardiac remodeling which results in left ventricular hypertrophy, dilation and dysfunction which eventually leads to heart failure (HF). Inhibition of RAAS using angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) has shown to significantly reduce morbidity and mortality due to HF. ACEi have been shown to have higher drug withdrawal rates due to discomfort when compared to ARBs; therefore, ARBs are the preferred choice of physicians for the treatment of HF in combination with other antihypertensive agents. Out of eight FDA approved ARBs, irbesartan and telmisartan are shown to have PPAR agonistic properties resulting in improved insulin intolerance. Olmesartan treatment also improves insulin sensitivity and produces anti-atherogenic and anti-inflammatory effects in patients with diabetic nephropathy. All the ARBs demonstrate beneficial effects similar to ACEi in the treatment of HF except the lower doses of losartan which leads to increase mortality in HF patients.Valsartan in combination with sacubitril therapy has shown to be a promising therapy for HF. Eprosartan has an effect on the sympathetic nervous system when compared to other ARBs and it is also able to reduce catecholamine release in animal models. Therefore, eprosartan therapy may have an additional beneficial effect in the treatment of heart failure. However, eprosartan has the shortest bioavailability (< 6 hours) when compared to other ARBs. Large numbers of studies that show beneficial effects on animals have been reported but there are limited studies on humans. Hence, more human studies are warranted. Recently, crystal structures of AT1R in inactive and active state structure have been solved. Using these crystal structures and cheminformatics tools, exploring structures similar to eprosartan with an increase in bioavailability and affinity may enhance the treatment of HF.

The review of Selvaraj et al. [4] demonstrated ion channels as therapeutic targets for type 1 diabetes mellitus. Ion channels are integral proteins expressed in almost all living cells involved in muscle contraction and nutrient transport. It plays a critical role in the normal function of the excitable tissues of the nervous system and regulates the action potential and contraction events. Dysfunction of genes, which encodes ion channel proteins that disrupt the channel function, leads to a number of diseases, which include type 1 diabetes mellitus (T1DM). Therefore, to understand the complex mechanism of ion channel receptors it is necessary to facilitate the diagnosis and management of treatment. In this review, we summarizes the mechanism of important ion channels involved in T1DM and the role in the regulation of insulin secretion along with the limitations for ion channels as therapeutic targets. Furthermore, we discussed the recent investigations of mechanism regulating the ion channels in beta cells, which suggest that ions channels are active participants in the regulation of insulin secretion.

Vijayan and C [5] discussed and summarized recent therapeutic strategies of amyloid beta (Aβ) in Alzheimer's disease (AD). AD is one of the most common forms of dementia and has been a global concern for several years. Due to the multifactorial nature of the disease, AD has become irreversible, fatal and imposes a tremendous socio-economic burden. Even though experimental medicines suggested moderate benefits, AD still lacks an effective treatment strategy for the management of symptoms or cure. Among various hypotheses which describe the development and progression of AD, the amyloid hypothesis has been a long-term adherent to the AD due to the involvement of various forms of Aβ peptides in the impairment of neuronal and cognitive functions. Hence, the majority of the drug discovery approaches in the past have focused on preventing the ac-
cumulation of Aβ peptides. Currently, there are several agents in the phase III clinical trials that target Aβ or the various macromolecules triggering Aβ deposition. Here, the author discussed some of the state-of-the-art knowledge on the functional aspects of the key players involved in the amyloid hypothesis. Furthermore, authors conferred about anti-amyloid agents present in phase III clinical trials.

We hope multidisciplinary topics discussed with the theme issue will promote further discussions between the researchers of computational advances in chronic diseases diagnostics and therapy.

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