Perspective

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Perspective on Antiplatelet Agent Ticlopidine for Acute ER Stress

Anna Tesei*

Biosciences Laboratory, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", 47014 Meldola, Italy

*Author for correspondence: noemi.marino@irst.emr.it

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Abstract

Different pathological conditions, including viral infections and cancer, can have a massive impact on the endoplasmic reticulum (ER), causing severe damage to the cell and exacerbating the disease. In particular, coronavirus infections, including SARS coronavirus-2 (SARS-CoV-2), responsible for COVID-19, cause ER stress as a consequence of the enormous amounts of viral glycoproteins synthesized, the perturbation of ER homeostasis and the modification of ER membranes. Therefore, ER has a central role in the viral life cycle, thus representing one of the Achilles' heels on which to focus therapeutic intervention. On the other hand, prolonged ER stress has been demonstrated to promote many pro-tumoral attributes in cancer cells, having a key role in tumor growth, metastasis and response to therapies. In this report, adopting a repurposing approach of approved drugs, we identified the antiplatelet agent ticlopidine as an interferent of the unfolded protein response (UPR) via sigma receptors (SRs) modulation.

Keywords: sigma 1 receptor (S1R) • endoplasmic reticulum (ER) • ER stress •cancer

Introduction

Endomembrane compartments, together with ER Coronavirus infection features a huge impact on the ER because Acyl four-hundredth of SARS-CoV-2 interacting proteins were recently related to of the big amounts of microorganism glycoproteins synthesized, resulting in the perturbation of ER physiological condition[1]. Moreover, viral infection modifies and exploits ER membranes: double-membrane vesicles (DMVs), the coronavirus ribonucleic acid synthesis web site and virus envelopes square measure derived from the ER membrane, and at the top of the replication and assembly cycle, virions bud from the ER-Golgi intermediate compartment. These observations highlight the central role of the ER within the microorganism life cycle and recommend that the ER might represent one in all the Achilles' heels on that therapeutic intervention will be targeted replication and assembly cycle, virions bud from the ER-Golgi.

Description

Ticlopidine exerts bigger toxicity within the LNCaP cell line in relation to the U87 cell line, representative of brain tumour multiforme, a sort of aggressive neoplasm mostly immune to current treatments. Ticlopidine seems to bypass inherent programmed cell death resistance of U87 cells by causation terminal UPR, notwithstanding to a lesser extent with relation to LNCaP cells[2,3]. This result's in line with the high sensitivity of LNCaP cells to endoplasmic reticulum (ER) stressors, that is reported within the literature. The promising results obtained recommend ticlopidine's potential within the treatment of COVID-19 patients, with a selected specialize in oncologic patients, that belong to the said vulnerable population. we tend to cannot forget that SRs modulators square measure below investigation for cancer treatment, notwithstanding the mechanisms underlying their growth nproperties square measure tortuous and not however absolutely

understood. To deal with the acute part of the ER stress condition, either evoked by cancer or microorganism infections, the cells exploit UPR pathways, and SRs appear to play a polar role in UPR modulation. the first and prolonged duration of UPR and consequent onset of "terminal" UPR sustained by SRs modulators could terribly quickly result in the death of the cells before they need the time to adopt a additional malignant composition or enable the microorganism life cycle completion. Thienopyridine derivatives with antiplatelet activity, together with ticlopidine, square measure wide prescribed for patients with vessel diseases [4]. additionally to their antiplatelet activity being closely associated with the inhibition of P2Y12 receptor, the literature knowledge highlighted their potential malignant neoplasm antimetastatic properties. haemostasis and inflammation square measure intimately coupled, causation and amplifying one another, and this interconnection contributes to several patho- logical things, together with infection, acute respiratory organ injury, reaction diseases, tumorigenesis and metastasis. The recent works by Gordon et al. [5] recommend the viability of targeting the host–virus interaction network to develop new and effective therapies against coronavirus infections. notably, within the case of SARS-CoV-2, the authors known sixty six druggable human supermolecule or host factors targeted by presently approved medication. The repurposing of approved medication totarget the host–virus interface will represent a viable and time-effective strategy to develop additional therapeutic choices, probably helpful once vaccines and virus-targeted medication can not be used and/or result ineffective. Notably, within the work by Gordon and collaborators, the drug screening by multiple microorganism assays at first showed anti-COVID-19 effectiveness only for the informational RNA translation inhibitors and for sigma-1 and sigma-2 receptors modulators (S1R and S2R, SRs). Gordon et al., in an exceedingly later article, known shared biology and potential drug targets among the 3 extremely unhealthful human coronavirus strains, i.e., SARS-CoV-2, SARS-CoV-1 and MERS-CoV, distinguishing seventy three host factors that, once depleted, caused important changes in SARS-CoV-2 cumulating proof shows that cells infected with coronaviruses exhibit enlarged expression of many proteins correlative with endoplasmic reticulum (ER) stress. especially, approximate replication. From this list of potential drug targets, they valid the biological and clinical relevancy of SR1, creating it a possible candidate for broad-spectrum treatment of coronavirus infections.

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Conflict of Interest

No conflict of interest

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