THEME SERIES - UPR in Cancer

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Over the past decade endoplasmic reticulum (ER) stress signaling pathways have collectively emerged as an essential mechanism at the crossroads of the cellular functions involved in key steps of cancer development. ER stress signaling has pleiotropic roles in cancer, and is involved at the level of cell transformation, tumor growth and metastasis as well as resistance to chemo- and radio- therapy. Indeed beyond the instrumental roles of the ER in the biogenesis of secretory and transmembrane proteins, or in the control of lipid balance and calcium homeostasis, this sub-cellular compartment is now viewed as a signal integration platform that not only orchestrates ER homeostasis maintenance, but also controls the metabolic status of the cell, the cell interactions with its (micro)-environment, in addition to the global management of stress signals at the organ levels in whole organisms on a cell non-autonomous manner.

Stress signals produce dramatic changes at the level of the ER membrane thereby eliciting the activation of select signaling pathways collectively known as the Unfolded Protein Response (UPR), which in turn reprogram the cell to either promote adaptation or eliminate irreversibly damaged cells by apoptosis. These functions associated with the biology of the ER have of course a significant impact on the understanding and treatment of complex disorders such as cancer. The field had suffered transforming changes in the last three years in the area of drug discovery, catalyzed by the identification of selective small molecules that can inhibit specific UPR signaling modules. Remarkably, an explosion of new studies in preclinical models of cancer have demonstrated that the pharmacological inhibition of two of the main UPR stress sensors (i.e. PERK and IRE1) have outstanding anticancer effects, which may even synergize with current chemotherapies available. Based on the emerging impact of the UPR to cancer, here we have coordinated an effort to overview the state-of-the-art in the field and thus invited several leading experts to provide discussion articles for a

theme series on the UPR and Cancer. The aim is to integrate different visions and provide readers with current insights and to identify major unresolved questions. In this series, 10 reviews articles focus on (i) the different cancer-associated stresses that elicit ER stress signaling pathways, highlighting the role of the microenvironment in solid tumors and its impact in cancer cell selection and transformation (Constantinos Koumenis [1]); (ii) the tools set in place by cancer cells to cope with stress and control proteostasis (Ted Hupp [2]; Serge Manié [3]; Ling Qi [4]); (iii) novel functions of the UPR in other aspects of cancer biology such as cell migration and genomic stability/DNA repair (Claudio Hetz [5]); (iv) the pharmacological molecules that were/are developed to block the IRE1 signaling pathway (Albert Koong [6]; Afshin Samali [7]); and finally (v) the biological impact of UPR signals on cancer cell immunogenicity (Guido Kroemer [8]; Patrizia Agostinis [9]), on tumor cell aggressiveness and invasion properties (Eric Chevet [10]) and, finally on the control of life and death decisions (Afshin Samali [7]).

We believe that readers will find the review articles in this Theme of interest and timely relevant. In addition, we hope that the concepts and evidence discussed in the articles will stimulate new avenues of research that hopefully will contribute to address unanswered, important questions regarding cellular mechanisms linking ER stress signaling and cancer biology. The new advances in the UPR field have demonstrated that strategies to target ER stress signaling with therapeutic agents such as small molecules is feasible in the context of cancer. In the short term, we hope some of these discoveries in preclinical models of cancer will translate into the development of novel clinical trials to fight this devastating disease.

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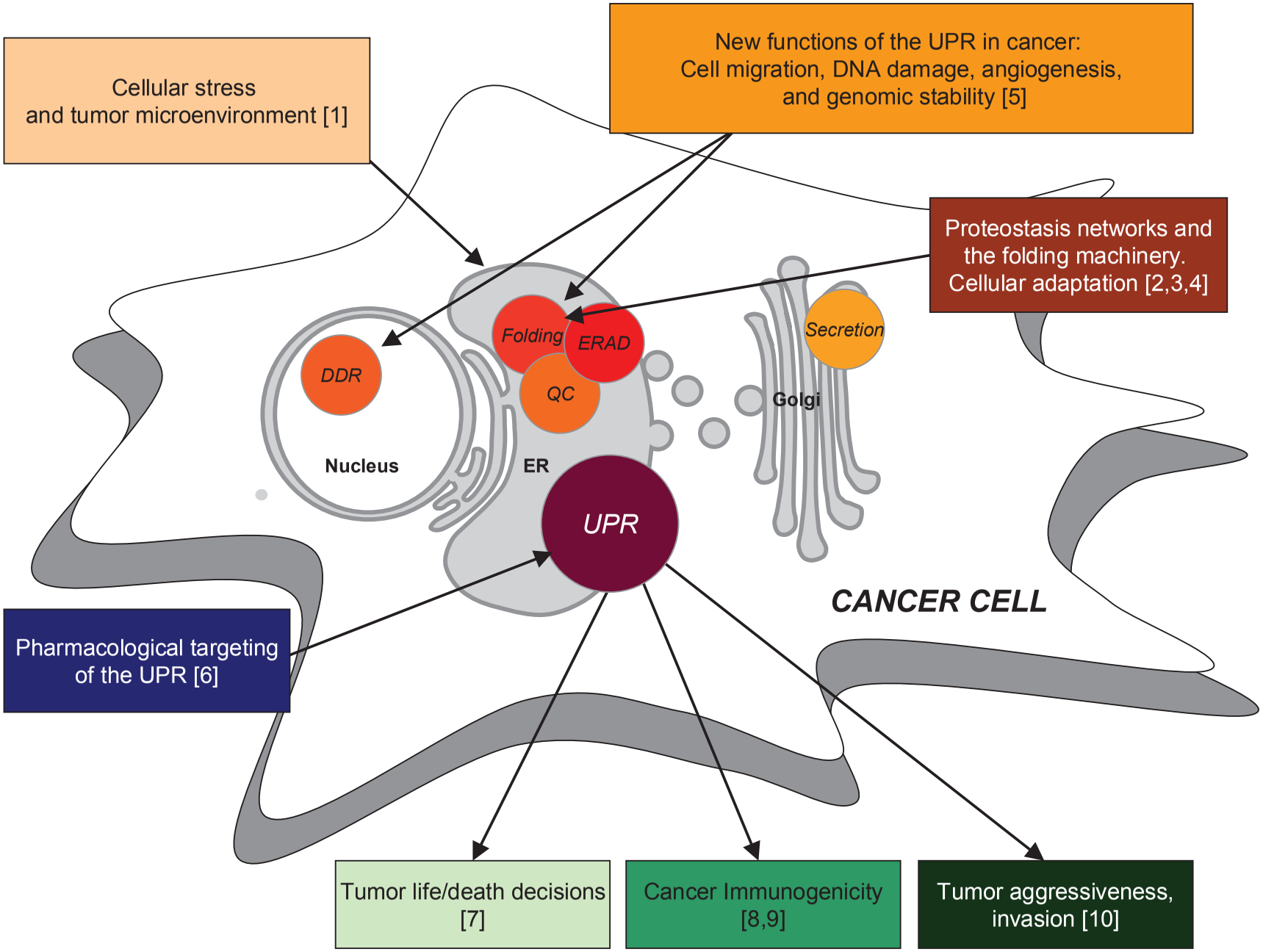
Figure 1. The biological impact of the UPR on cancer biology. Summary of topics discussed in this review series highlighting the interconnection between ER stress signaling and distinct aspects of cancer.


Cellular stress
and tumor microenvironment [1]
New functions of the UPR in cancer:
Cell migration, DNA damage, angiogenesis,
and genomic stability [5]
Proteostasis networks and
the folding machinery.
Cellular adaptation [2,3,4]
Folding
ERAD
QC
DDR
Nucleus
ER
Golgi
Secretion
UPR
CANCER CELL
Pharmacological targeting
of the UPR [6]
Tumor life/death decisions
[7]
Cancer Immunogenicity
[8,9]
Tumor aggressiveness,
invasion [10]