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Medicine in focus

The two faces of the Integrated Stress Response in cancer progression and therapeutic strategies

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ABSTRACT

In recent years considerable progress has been made in identifying the impact of mRNA translation in tumour progression. Cancer cells hijack the pre-existing translation machinery to thrive under the adverse conditions originating from intrinsic oncogenic programs, that increase their energetic demand, and from the hostile microenvironment. A key translation program frequently dysregulated in cancer is the Integrated Stress Response, that reprograms translation by attenuating global protein synthesis to decrease metabolic demand while increasing translation of specific mRNAs that support survival, migration, immune escape. In this review we provide an overview of the Integrated Stress Response, emphasise its dual role during tumorigenesis and cancer progression, and highlight the therapeutic strategies available to target it.

1. Introduction

Protein synthesis is the final step in the central dogma of cell biology (Crick, 1970). Its regulation, in concert with the modulation of gene transcription, dictates tissue identity and sustains specific functional and energetic requirements (Buszczak et al., 2014).

Structural expansion of the translation machinery at the earliest stages of evolution defines a high biological complexity amenable to tuning and regulation (Goldman et al., 2010; Kazana and Von Der Haar, 2014). Indeed, short term adaptation to physiological and pathological challenges relies on the fast and precise mechanisms governing translation regulation (Li et al., 2014; Liu and Aebersold, 2016; Schwanhüusser et al., 2011).

Cancer cells, which energetic and biosynthetic requirements are dictated by intrinsic (oncogenic signals) and extrinsic (microenvironmental cues) challenges, take advantage of the pre-existing translation machinery to survive and metastasize.

A clinically detectable metastasis results from a complex multi-step process starting in the primary tumour, where one or few cancer cells acquire the potential to invade and survive the dissemination process, and finishes with the colonisation of distant organs (Seyfried and Huysentruyt, 2013). The pioneer cell(s) of a metastatic lesion faces a variety of microenvironmental challenges of different origins in the primary tumour (nutrients deprivation, hypoxia, inflammatory signalling, therapeutic targeting), as well as dissemination-associated stresses (including anoikis, ROS).

By hijacking the translation machinery, the metastatic cell is therefore equipped to survive a combination of widely diverse stresses while undertaking phenotypic changes, such as epithelial-to-mesenchymal transition (EMT) and metabolic rewiring, to be able to colonise a foreign microenvironment (Anastasiou, 2017; Sciacovelli and Frezza, 2017).

One of the principal nodes that regulate translation by sensing and integrating intra- and extra-cellular signalling in cancer progression is the Integrated Stress Response (ISR) (Costa-Mattioli and Walter, 2020; El-Naggar and Sorensen, 2018). Either inhibition or activation of the ISR disrupt the homeostatic equilibrium of the cancer cells. As a consequence, protein synthesis represents a potential targetable vulnerability for the treatment of cancer. In recent years, research into the mechanisms defining translational rewiring have attracted increasing interest leading to the development, pre-clinical and clinical use of drugs aimed at targeting the translation machinery.

2. The Integrated Stress Response

In eukaryotes, protein synthesis consists of 4 steps: initiation,

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elongation, termination and ribosome recycling (Pisarev et al., 2007). As a rate-limiting step, mRNA translation initiation is the most highly regulated.

Briefly, the canonical translation initiation pathway consists of the recruitment of the 43S ribosomal pre-initiation complex (PIC) to the mRNA 5′ untranslated regions (5′-UTR) in a cap-dependent manner, downstream scanning and start codon recognition (Pestova et al., 1998). The PIC is formed by the ternary complex, composed by the eIF2 trimeric protein (eIF2α, eIF2β and eIF2γ), GTP and a methionine-charged tRNA, assembled with the 40S ribosomal subunit and associated to many other regulatory eIFs. The dynamics of PIC formation and disassembly are dictated by eIF2γ -driven GTP hydrolysis and by the guanine-nucleotide exchange factor eIF2B-driven eIF2 recycling, respectively. Concomitantly, the eIF4F complex binds to the mRNA to unwind its 5′-UTR secondary structures and recruits the 43S PIC through the bridging of the multi-subunit eIF3 complex. Finally, the 60S ribosomal subunit is recruited to form an 80S initiation complex, which will proceed to the elongation phase. For a more detailed description of the translation initiation pathway we refer the reader to Jackson et al., 2010 and Smith et al., 2021.

Overall, more than 25 proteins forming more than 12 initiation factors are involved in the initiation process (Gebauer and Hentze, 2004). Among these proteins, eIF2 is regulated in the context of cancer progression and provides a timely adaptive response to disruption of homeostasis. Upon stress, phosphorylation of the eIF2α subunit at Serine 51 promotes the formation of an eIF2-eIF2B inhibitory complex that negatively regulates global cap-dependent translation while driving translation of a specific subset of mRNAs in a cap-independent manner (Adomavicius et al., 2019; Pavitt et al., 1998).

eIF2 phosphorylation is mediated by four kinases: PERK, that is one of the four arms of the UPR (unfolded protein response), Protein kinase R (PKR), Heme regulated kinase (HRI), and general control non-derepressible 2 (GCN2), that are activated under different stress stimuli like viral infections, heme depletion and amino acids deficiency, respectively (Chen, 2007; Deval et al., 2009; Galluzzi et al., 2008; Kaufman, 1999; Nakamura et al., 2010).

Collectively, these alternative mechanisms of eIF2 activation allow cells to integrate different stress stimuli with a single translation control machinery in a process defined as the “Integrated Stress Response” (Harding et al., 2003) (Fig. 1).

Selective translation is an intrinsic property of the mRNA and is mediated by cis-regulatory elements present in their 5′-UTRs which dictate accessibility to the eIFs. Among these, structural elements such as internal ribosome entry sites (IRES) and upstream open reading frame (uORF) are the most characterized structures (Johnstone et al., 2016; Weingarten-Gabbay et al., 2016).

An IRES consists of internal RNA structures capable of binding ribosomes to initiate translation though a cap-independent mechanism (Pelletier and Sonenberg, 1988). IRES-mediated translation supports the expression of several oncogenes such as BCL2, MYC, HIF1A, and VEGFA upon stress (Bastide et al., 2008; Cobbold et al., 2008; Lang et al., 2002; Sherrill et al., 2004).

uORFs are short sequences localized along the 5′-leader portion of mRNAs that work by inhibiting the translation of downstream ORFs including the canonical start site under normal conditions, but quickly mobilize their expression in response to stress. The mRNA of the transcription factor ATF4, a master regulator of the cellular response to stress, contains uORFs allowing its selective translation upon eIF2α phosphorylation (Harding et al., 2000).

ATF4 is a member of the activating transcription factor/cAMP responsive element binding protein family, it mainly acts as a transcriptional activator, but it has firstly been described as as repressor of transcription (Karpinski et al., 1992).

The timely increase in ATF4 levels leads to transcription of pro-survival factors involved in the antioxidative response, amino acid transport and biosynthesis, and autophagy, as well as pro-apoptotic factors that may be activated if the stresses cannot be resolved.

In the process of adaptation to amino acid starvation or ER stress, ATF4 directs an autophagy gene transcriptional program implicated in the formation and function of the autophagosome by regulating multiple

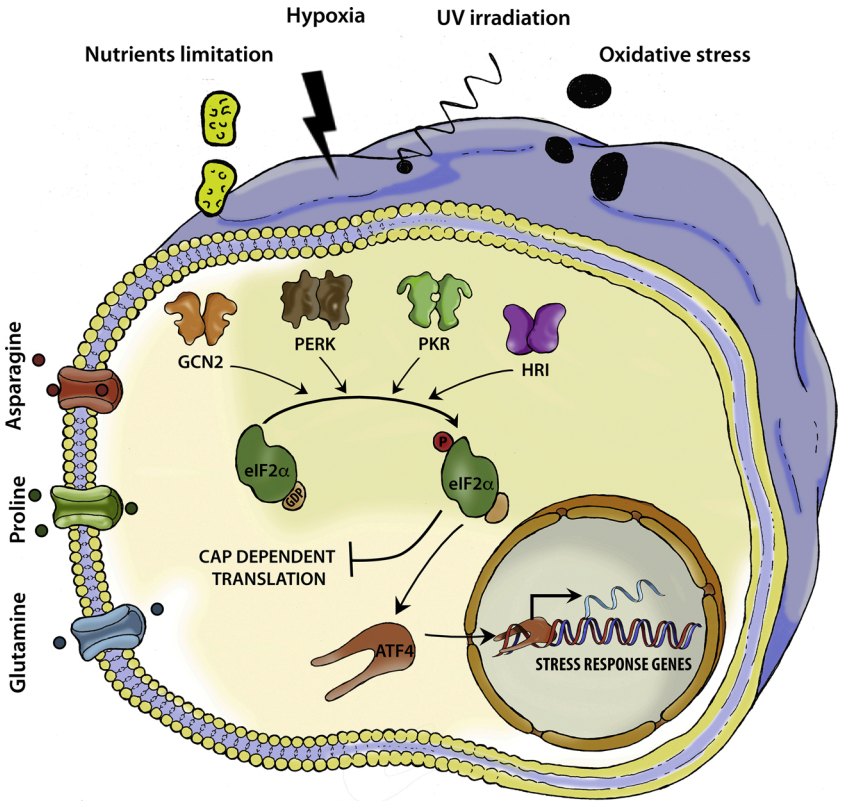

Fig. 1. The Integrated Stress Response. Schematic representation of the signalling cascade activated in response to stress signals. A wide range of stressors, such as hypoxia, nutrient limitation, UV irradiation and oxidative stress activate GCN2, PERK, PKR and HRI kinases. The activity of these kinases converges on eIF2α phosphorylation, that negatively regulates global cap-dependent translation while driving translation of a specific subset of mRNAs in a cap-independent manner. The ATF4 transcription factor, the main effector of the ISR, translocates to the nucleous and binds to target genes involved in cellular adaptation to stress. The global protein synthesis attenuation concomitant to the adaptive gene expression restores cell homeostasis. However, when the stress can not be resolved, the induction of the ISR contributes to a maladaptive response, triggering cell death.

ATG genes and autophagy regulatory factors (B'Chir et al., 2013). More indirectly, ATF4 mediates the transcription of REDD1, which in turn sustains repression of mTORC1 signalling, promoting autophagy in nutrient deprivation conditions (Whitney et al., 2009).

Furthermore, ATF4 can promote resistance to metabolic stress and cancer therapy by inhibiting cell death pathways. An interesting example is the ATF4 driven upregulation of the antiapoptotic member of the BCL-2 family MCL-1, which confers resistance to bortezomib (Hu et al., 2012). Moreover, ATF4 activates the transcription of NUPR1, which in turn drives the transcription of genes involved in metabolic stress response, DNA repair and cell cycle regulation (Jin et al., 2009).

Among the ATF4 target genes is GADD34, a component of the protein phosphatase 1 complex that dephosphorylates eIF2α providing a negative feedback mechanism that reduces the ISR and restores global protein synthesis (Ma and Hendershot, 2003; Novoa et al., 2001).

However, if the stress is not resolved, ATF4 can activate molecular pathways promoting cell death.

ATF4 promotes apoptosis by either directly driving transcription of the BCL2 family members like *PMAIP1* (Armstrong et al., 2010) or through activation of apoptotic genes-targeting transcription factors like CHOP and ATF3. CHOP can induce cell death by inducing overexpression of BCL2L11 and BBC3 of BCL2 family (Puthalakath et al., 2007) and by upregulating DR5 (Zou et al., 2008) or the oxidase ERO1α (Marciniak et al., 2004). Additionally, ATF4 can form heterodimers with CHOP and ATF3 promoting the expression of proapoptotic genes such as ATF5 (Teske et al., 2013) and TRB3 (Ohoka et al., 2005). Finally, ATF4 can also induce necrosis, as described in response to glucose deprivation (Leõn-Annicchiarico et al., 2015).

3. Dual role of the Integrated Stress Response in cancer

The ISR is an evolutionarily conserved adaptive program activated in response to microenvironmental cues, such as hypoxia and nutrient limitation, as well as cell-intrinsic factors, including ER-stress and oncogene activation, and evolved to restore cell homeostasis. However, perturbations in the induction of the ISR can contribute to a maladaptive response, triggering apoptosis-mediated cell death. Increasing evidence demonstrating that ISR activation is advantageous for tumour cells contrast with the tumour-suppressive anti-proliferative effects that have been also linked to its function. In some cases, the activation of an ISR has shown anti-tumour effect, and the inability to activate ISR has been linked to malignant transformation. For instance, abrogation of eIF2α phosphorylation activates the proliferative capacity of NIH 3T3 cells and mutations which render PKR either catalytically inactive or insensitive to stress, thereby impairing the activation of the ISR, can induce malignant transformation (Barber et al., 1995; Donzé et al., 1995; Koromilas et al., 1992). Moreover, in a mouse model of HER2+ breast cancer the PKR-eIF2α arm displays anti-tumour function, and in combination with targeted therapy suppresses tumour growth (Darini et al., 2019).

This suggests that elevated eIF2α phosphorylation can reduce tumour burden by decreasing proliferation through attenuation of global protein synthesis and by activating pro-apoptotic pathways. However, it has recently been shown that overexpression of HER2 in human non-transformed mammary epithelial cells leads to ATF4 expression and drives cell migration (Zeng et al., 2019).

Although apparently contradictory, these two lines of evidence highlight two faces of the ISR in cancer. Concomitant to a decreased proliferative rate, cancer cells benefit from ISR pathway activation that leads to angiogenesis, metastasis, immune escape and stemness (García-Jiménez and Goding, 2019). One example is metastatic dissemination induced by activating the ISR in response to "get me out of here" signals that trigger escape from a stressful tumour microenvironment (Falletta et al., 2017). For instance, PERK-dependent activation of the ISR by hypoxia increases the invasive potential of breast cancer cells (Nagelkerke et al., 2013). The same axis activated by glucose deprivation also promotes endothelial cell survival and angiogenesis (Wang et al., 2012), while in melanoma, glutamine limitation, TNFα and TGFβ stimulate eIF2α phosphorylation-dependent metastatic potential (Falletta et al., 2017; Feng et al., 2014). Notably, ISR-driven translation of ATF4 reduces oxidative stress and prevents anoikis (Avivar-Valderas et al., 2011; Dey et al., 2015), a pre-requisite for successful metastatic dissemination, and in melanoma is involved in targeted and immunotherapy resistance (Falletta et al., 2017; Nagasawa et al., 2020). Furthermore, recent work demonstrated that hypoxia, through activation of the ISR in concert with the mTORC1 pathway, stimulates translation of stemness factors determining breast cancer cells plasticity (Jewer et al., 2020).

Cell intrinsic signals, including oncogene activation or tumour suppressor inhibition can also trigger the ISR to increase the cancer cell fitness. For instance, in spontaneous mouse and human lymphoma MYC overexpression activates the PERK-eIF2α arm, leading to increased cell survival via the induction of cytoprotective autophagy (Hart et al., 2012). In Esophageal Squamous Cell Carcinoma ATF4 overexpression promotes invasion and metastasis (Zhu et al., 2014), while in Skin Squamous Cell Carcinoma eIF2α phosphorylation increases translation of oncogenic transcripts (Sendoel et al., 2017). Finally, in highly regulated bi-directional crosstalk between the tumour milieu and the immune system whereby the tumour shapes the microenvironment and immune infiltration enhances metastasis and drug resistance, a role for translational reprograming is emerging (Grivennikov et al., 2010; Wellenstein and de Visser, 2018). Indeed, recent studies have linked eIF2α phosphorylation to the increase in translation of PD-L1 in liver cancer (Xu et al., 2019), and in human lung cancer cells a CRISPR-based screen revealed a strong induction of PD-L1 through the ISR activated by impairment of heme production (Suresh et al., 2020).

4. Targeting the Integrated Stress Response as a therapeutic strategy in oncology

Our current view of cancer progression suggests that cancer cells exploit a dynamic equilibrium by taking advantage of the adaptive and avoiding the maladaptive programs activated by the ISR. Clinically, this dualism has offered an interesting therapeutic opportunity whereby either activation or inhibition of ISR potentially inhibits cancer progression.

4.1. Activation of the Integrated Stress Response

Different strategies to chemically activate the ISR have been adopted in clinical or pre-clinical settings. Mechanistically, ISR activation can be achieved by activating the kinases that phosphorylate eIF2α or by inhibiting eIF2α de-phosphorylation.

ONC201 is a first-in-class imipridone molecule in phase II clinical trial for the treatment of refractory solid tumours and haematological malignancies (Prabhu et al., 2020; Stein et al., 2017). It activates a PERK-independent, HRI and PKR-dependent phosphorylation of eIF2α that, in concert with inhibition of AKT/ERK signalling, activates the transcription of several pro-apoptotic genes (Kline et al., 2016). In vitro it bears preferential cytotoxicity in tumours over normal cells (Amoroso et al., 2021). Interestingly, ONC201 is capable to elicit an immune response by promoting intra-tumour NK cell recruitment (Wagner et al., 2018), while cancer stem cells appear to be sensitive to ONC201 treatment (Prabhu et al., 2015). CYT997 (Lexibulin), a microtubule-disrupting agent investigated in phase I clinical trial for the treatment of advanced cancers (Burge et al., 2013), has been recently shown to inhibit the growth of osteosarcoma in vivo by ISR-induced apoptosis (Wang et al., 2019). The same mechanism of action has been demonstrated for Nelfinavir, an FDA-approved antiretroviral agent recently repurposed as anticancer drug (Brüning et al., 2009).

The use of amino acid-degrading enzymes has been proposed for the treatment of cancer addicted to specific amino acids. For instance, the

insufficient expression of asparagine synthetase (ASNS) in immature lymphocytes, the leukemic cells of origin, renders them auxotrophic for asparagine (Al-Baghdadi et al., 2017; Bunpo et al., 2010; Reinert et al., 2006). In this context, the chemotherapeutic agent asparaginase reduces plasma asparagine concentration by converting it into aspartic acid and ammonia and triggers eIF2α phosphorylation in leukemic cells by activating GCN2, which in turn induces the ISR to drive apoptosis (Müller and Boos, 1998; Szymanska et al., 2012; Williams et al., 2020). CB-839, a Glutamine Synthase inhibitor in clinical trial for haematological malignancies and solid tumours, depletes intracellular glutamine levels triggering the GCN2-dependent ISR with cytostatic and cytotoxic effects (Gregory et al., 2018). Halofuginone (HF), a synthetic analogue of a febrifugine alkaloid derived from the plant Dichroa febrifuga, reduces the cellular pool of proline by competing with it for the prolyl-tRNA synthetase active site (Follo et al., 2019; Keller et al., 2012; Sundrud et al., 2009). The therapeutic potential of HF in breast, ovarian and thyroid cancer cell lines is associated to its ability to induce an ISR and activate autophagy, and it is in clinical trial for the treatment of progressive solid tumour and Kaposi sarcoma (clinicaltrials.gov: NCT00064142) (Young et al., 2016). However, the effect of amino acid starvation is strictly context dependent, and cancer metabolic dependencies need to be carefully considered. For example, amino acid depletion represses anti-tumour immunity, impairing metabolic cross-talk with the immune microenvironment and sublethal depletion of the amino acid pool could give resistance or increase cancer progression (Crump et al., 2021).

Salubrinal, an inhibitor of the eIF2α phosphatase GADD34, has been investigated in pre-clinical settings: its antiproliferative capacity has been exploited in melanoma in combination with drugs targeting eIF4F (Kardos et al., 2020), in cholangiocarcinoma in synergy with mTOR inhibitors (Zhao et al., 2016) and in hepatocellular carcinoma in combination with a resveratrol analogue (Yu et al., 2019). Recently CoSAL, Salubrinal in complex with copper, was revealed to have high cytotoxic activity in in-vitro models of ovarian cancer (Masuri et al., 2020). Guanabenz Acetate (GA), an antihypertensive drug that inhibits GADD34 leading to p-eIF2α accumulation, was repositioned as a potential anti-cancer therapy (Haggag et al., 2021; Wang et al., 2014). In patient-derived hepatocellular carcinoma cells, and in triple-negative breast cancer cells GA induces ER-stress-mediated apoptosis and autophagy (Hamamura et al., 2014; Kang et al., 2019).

In these scenarios, the cytotoxic effect of ISR activation have been exploited in combination with a variety of different therapies to push cancer cells towards a maladaptive response, leading to apoptosis.

4.2. Inhibition of the Integrated Stress Response

ISR attenuation in cancer cells has been achieved either through the inhibition of the four kinases that phosphorylate eIF2 or by keeping the cap-dependent translation machinery active even in presence of phosphorylated eIF2.

The importance of the PERK-eIF2 axis in tumorigenesis and cell proliferation has promoted the development of inhibitors to target this molecular pathway. The first PERK inhibitors were the ATP mimetics GSK2606414 and GSK2656157 (Axten et al., 2013, 2012), which target the active site of the kinase thereby inhibiting PERK auto-phosphorylation and phosphorylation of eIF2α. Assays in human xenograft models showed tumor suppression in different types of cancer. Still, despite their good therapeutic efficiency, toxicity problems in the pancreas, together with off-target effects on other kinases like RIPK1, has led to clinical development of these compounds being halted (Rojas-Rivera et al., 2017) . AMG44 and AMG52 were generated as potent and highly selective PERK inhibitors with excellent pharmacokinetic properties, allowing their use in vivo without pancreatic toxicity, and inducing antitumor immunity in different preclinical models of cancer (Mohamed et al., 2020). Another potent PERK inhibitor, LY-4, has a high efficiency in vivo against BRAF V600E mutant melanoma (Pytel et al., 2016) and MYC-driven lymphoma (Tameire et al., 2019).

The guanine and adenine analogue 2-aminopurine inhibits PKR (EIF2AK2) by competing for the ATP binding site but lacks potency and specificity. The compound C16 showed function in a similar fashion and in a recent study exhibited anti-neogenesis activity in vitro and in vivo in HCC cells, however it retains some specificity problems targeting some cyclin dependent kinases (Chen et al., 2008; Watanabe et al., 2020).

A series of indeno[1,2-c]pyrazoles such as Aminopyrazolindane can inhibit HRI, but these compounds have a very poor bioavailability and are quickly eliminated (Rosen et al., 2009). To date, no specific HRI inhibitors have been developed.

The development of potent and selective GCN2 inhibitors is also very limited and their application in oncology is poorly explored. Some ATP analogs like indirubin-30-monoxime, SP600125 and a SyK inhibitor have been described but are not specific (Robert et al., 2009). GZD824 can inhibit the GCN2 pathway under conditions of amino acid starvation but it has yet to be tested in vivo (Kato et al., 2020). By contrast, compounds 6D and 6E, which can strongly inhibit the GCN2 pathway by targeting the ATP binding site on the kinase domain, are very specific and showed high activity in vitro and in vivo in xenograft models (Fujimoto et al., 2019).

An alternative strategy to block the ISR is provided by the Integrated Stress Response Inhibitor (ISRIB) and its derivatives ISRIB A1 to ISRIB A17. These compounds bind to the regulatory site of eIF2B increasing its dimerization and activation, keeping eIF2B active even in presence of phosphorylated eIF2 (Zyryanova et al., 2021). In patient-derived xenograft models of advanced and castration-resistant prostate cancer, ISRIB selectively triggers cytotoxicity and decreases metastatic progression (Nguyen et al., 2018). Moreover, in breast cancer setting, ISRIB can prevent the expression of plasticity factors such as NANOG, SNAIL and NODAL in hypoxic tumours or in response to mTOR inhibition and chemotherapy (Jewer et al., 2020).

5. Concluding remarks

Cancer cells hijack the translation machinery to create a dynamic homeostatic balance allowing them to proliferate in response to oncogenic activation and survive microenvironmental adverse conditions. The Integrated Stress Response is an evolutionarily conserved mechanism that, in concert with other translation reprograming machineries, plays a central role in regulating this equilibrium allowing cancer cell to survive, metastasize and escape immunity.

In this review we highlight the role of eIF2 phosphorylation-dependent translation reprogramming in cancer and the therapeutic strategies directed towards this central node. In the recent years, many pre-clinical and clinical studies have been dedicated to targeting the ISR machinery, and two opposite approaches have been developed to treat cancer (Fig. 2). On one side, the cytotoxic effects of ISR activation have been successfully exploited in highly proliferating cancer settings, such as HER2+ breast cancers and haematological malignancies (Darini et al., 2019; Kline et al., 2016). However, while the efficacy of eIF2 phosphorylation has been widely demonstrated in decreasing the tumour burden, especially when used in combinatorial therapies, further analysis of the pleiotropic effects of ISR activation are necessary to prevent pro-survival mechanisms such as migration, drug resistance and immune escape. On the other side, ISR inhibition through direct targeting or eIF2 kinase inhibition has been proven fruitful for both its cytostatic effects as well as its anti-angiogenic, anti-metastatic properties (Jewer et al., 2020; Nguyen et al., 2018).

Whilst at first sight this may appear a paradox, the efficacy of the two opposite approaches reveals that the activation of ISR is strictly context dependent and very likely associated to tumour location and stage of progression. Therefore, extreme care is needed in considering the efficacy of this therapeutic targeting. For instance, if sublethal doses are employed, or if tumour heterogeneity confers resistance to a subpopulation, ISR activation could trigger ‘get out of here’ signals that might

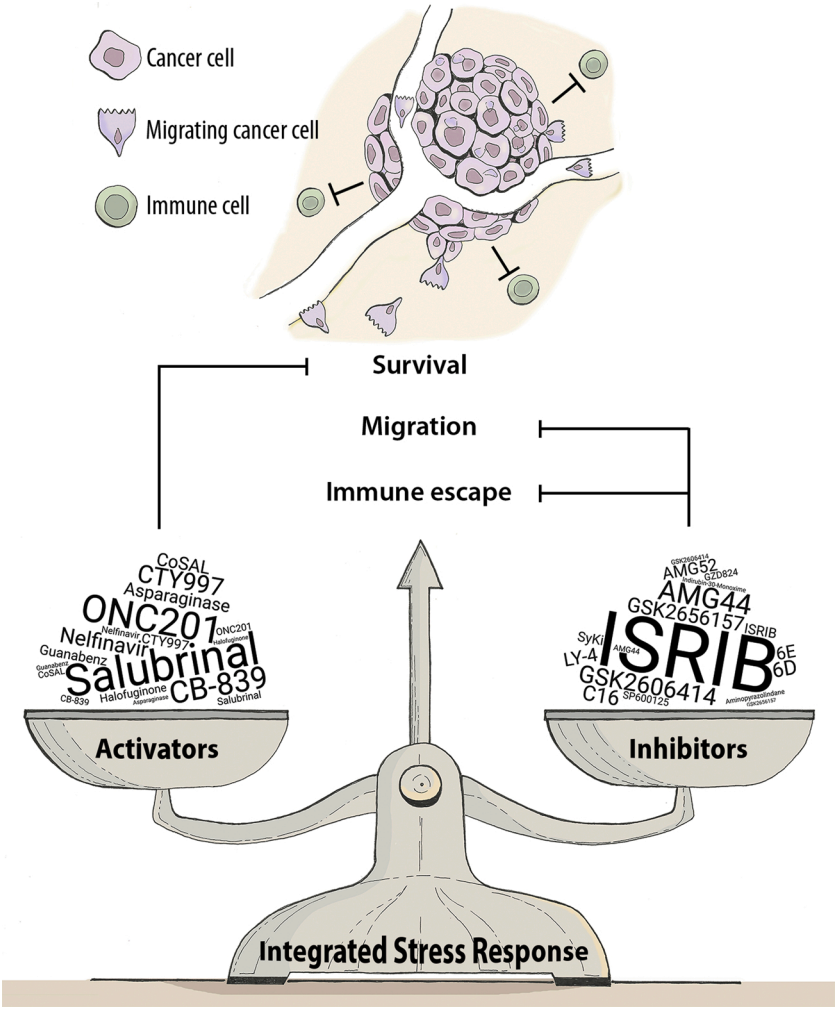

Fig. 2. Targeting the Integrated Stress Response in cancer. Simplified representation of the main effects of Integrated Stress Response (ISR) pathway activation on the tumour and its therapeutic targeting. The cells of a growing tumour mass face a plethora of stresses determined by intrinsic cues, such as the increasing metabolic demand imposed by the activation of oncogenic signals, and by extrinsic signals, such as hypoxia and nutrient demand. Growth and survival are supported by the activation of the ISR pathway that restores the cancer cells homeostatic balance, imposes metastatic traits and immune evasion. Clinically, inhibition of cancer progression has been achieved with direct or indirect targeting of the ISR. Either inhibition or activation of the ISR disrupt the homeostatic equilibrium of the cancer cells. Current evidence suggests that targeting the translation machinery is a promising strategy for cancer treatment. This simplified model does not include other tumour-associated cell types and tissues and other cancer cell phenotypes.

enhance disease progression.

Finally, a role of translation reprogramming in the immune compartment is now emerging. For instance, activation and polarisation of macrophages strictly relies on translation regulation (Tabatabaei et al., 2020). Moreover, nutritional stress creates a tumour microenvironment restrictive to T cell activation, determining pathological immune evasion in pancreatic adenocarcinoma (Crump et al., 2021). Increasing efforts are now dedicated to achieving a better understanding of the ISR role in defining the immune landscape, the crosstalk with cancer cells and the effects of therapeutic targeting.

The development of advanced technology allowing single cell approaches such as the pioneering advent of single-cell measure of transcriptome-wide ribosome association and cell-type resolved quantitative proteomics analysis (Brannan et al., 2021; Dyring-Andersen et al., 2020) will provide a deeper understanding of these processes and create new opportunities for therapeutic intervention in oncology.

Declaration of Competing Interest

The authors report no competing interest.

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