important results from this study is the identification of ADRB2 downstream signaling as a potential predictive factor for patients likely to gain benefit from adjuvant beta blocker therapy while receiving androgen ablation therapy.

Conclusions
Although the current study provides a new mechanistic understanding of the effects of stress on cancer progression, there remain many unanswered questions with regard to such effects. Among these is the identification of specific patient subsets that are most likely to benefit from interventions targeted against stress-related pathways. Whether such subsets should be identified based on behavioral and/or molecular features is currently unknown. Moreover, identifying reliable downstream markers to test the efficacy of stress-based interventions may allow a more rational selection of therapies. Much like cancer, stress pathways are extremely complex, and it is unclear whether SNS-targeted interventions will be sufficient or whether blocking other pathways, such as HPA mediators or inflammation, will also be required. Addressing these and other questions will be an important component of realizing the full translational potential of the preclinical findings presented in this and other research. Nevertheless, the field continues to rapidly evolve, and novel signaling mechanisms are being discovered that provide a deeper understanding of the effects of behavioral stress on tumor biology. The present study moves the field forward by demonstrating that behavioral stress enables prostate cancer cells to evade apoptosis, an important characteristic in the process of tumor growth and metastasis. In addition, the authors provide a new understanding of mechanisms by which prostate cancer cells could acquire resistance to androgen therapy.

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iPad, iPod, iPhone — iRHOM sounds like the latest gadget you must have. There are even two iRHOM versions. iRHOM1 (also known as RHBD/F1) appears to have broad functionality, whereas iRHOM2 (also known as RHBD/F2) has more restricted and exclusive functions. iRHOMs are proteolytically inactive homologs of rhomboid proteases. They localize to the membrane of the ER and were initially shown to be part of the ER protein quality control machinery both in Drosophila and mammalian cells (1). Three recent studies demonstrated that an additional function, at least for iRHOM2, is mediating the release of TNF-α from macrophages (2–4). iRHOM2 acts as a cargo receptor

The cytokine TNF-α is a major drug target for rheumatoid arthritis, an inflammatory joint disorder. An alternative approach is to target the protease TNF-α convertase (TACE), which releases TNF-α from cells. However, because TACE cleaves other proteins involved in development and cancer, a tissue-specific inhibition of TACE in immune cells appears mandatory. In this issue of the JCI, Issuree et al. report that iRHOM2 is a TACE activator in immune cells. Loss of iRHOM2 largely protects mice from inflammatory arthritis, making iRHOM2 a potential drug target for this condition.

iRHOM2 takes control of rheumatoid arthritis

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Likewise, the clinical scores, which indicate erosion in wild-type mice, but this effect was ameliorated with iRHOM2 deficiency. Serum transfer from the K/BxN mouse induced joint swelling and cartilage degradation of TNF-\(\alpha\). Serum transfer from the K/BxN mouse model mimics human RA (6), even though it is not fully dependent on the production of TNF-\(\alpha\). 

Inflammatory arthritis can be induced in mice by the transfer of serum from K/BxN mice, but this requires that the recipients express complement C5a receptor (C5aR) and Fc\(\gamma\) receptor (Fc\(\gamma\)R) activate iRHOM2 expression and TACE maturation in the immune system. Immune cells lack significant iRHOM1 expression. Upon knockout of iRHOM2, TACE inhibition, clearly implicating both proteins in the increased TNF-\(\alpha\) production. Receptor activation strongly increased iRHOM2 expression, which is a mechanism to activate TACE and increase TNF-\(\alpha\) release (3). Surprisingly, however, not only mature, but also immature, TACE levels were increased. This indicates that receptor activation also regulates TACE expression levels, which may be an additional mechanism besides increased iRHOM2 expression to increase TNF-\(\alpha\) release. Whether these mechanisms are additive or redundant for TNF-\(\alpha\) production remains to be tested.

**Propagating the signal**

Inflammatory arthritis can be induced in mice by the transfer of serum from K/BxN mice, but this requires that the recipients express complement C5a receptor and Fc\(\gamma\) receptor (8). However, the molecular mechanisms linking receptor activation and TNF-\(\alpha\) production are not understood in detail. Issuree et al. now demonstrate a role for iRHOM2 and TACE in this process (5). In murine macrophages or human monocytes, the activation of C5a receptor and Fc\(\gamma\) receptor increased TNF-\(\alpha\) production, which was blocked by iRHOM2 knockdown or TACE inhibition, clearly implicating both proteins in the increased TNF-\(\alpha\) production. Receptor activation strongly increased iRHOM2 expression, which is a mechanism to activate TACE and increase TNF-\(\alpha\) release (3). Surprisingly, however, not only mature, but also immature, TACE levels were increased. This indicates that receptor activation also regulates TACE expression levels, which may be an additional mechanism besides increased iRHOM2 expression to increase TNF-\(\alpha\) release. Whether these mechanisms are additive or redundant for TNF-\(\alpha\) production remains to be tested.

**Location, location, location**

TACE is ubiquitously expressed and has major substrates and functions besides TNF-\(\alpha\) cleavage (9, 10). In fact, mice with global TACE deletion die perinatally as a result of reduced EGFR signaling during development (11), and study of a TACE-deficient patient demonstrated essential roles for TACE in skin and intestine (12). Thus, it is surprising that iRHOM2-deficient mice show a myeloid cell–specific — and not a general — block of TACE activity. The explanation comes from the expression profiles of iRHOM2 and its homolog iRHOM1 and the new finding that iRHOM1 can have a...
similar function as iRHM2 in promoting TACE activity and TACE substrate cleavage (5). In other words, iRHM1 can functionally compensate for the loss of iRHM2 and vice versa, at least in tissues in which both proteins are expressed. As shown by Issuree et al. in this issue of the JCI (5) and by others previously (2, 3), iRHM2 expression is high in myeloid cells, in which iRHM1 is expressed at low levels and cannot functionally compensate for iRHM2, leading to the observed loss of TACE function in iRHM2-deficient macrophages as well as in lymph nodes and bone marrow (Figure 1B). In contrast, in mouse embryonic fibroblasts, in which both iRHM1 and iRHM2 are expressed, the single loss of either iRHM1 or iRHM2 did not affect TACE maturation (Figure 1C), which is a frequently used readout for TACE activity. However, loss of both proteins prevented TACE maturation, demonstrating functional redundancy of iRHM1 and iRHM2 in mouse embryonic fibroblasts. Additionally, several organs from iRHM2-deficient mice were analyzed for TACE maturation. No change in the ER-mediated proteolysis (patho)physiological functions, its client spectrum, and its potential cross-talk with iRHM1. Is iRHM2 a druggable target? At first glance, the answer may be no, because the membrane protein iRHM2 is not an enzyme, and it is largely buried in the ER membrane. However, this is also true for presenilin 1 and 2, which are the catalytic subunits of the protease γ-secretase and are major targets in the development of Alzheimer’s disease therapeutics; small-molecule presenilin inhibitors have been developed successfully. Some of them even appear to preferentially block presenilin 1 over its homolog presenilin 2 (17). Likewise, specificity to iRHM2 over iRHM1 would be needed for the TNF-α-dependent diseases.

In summary, the new study in this issue by Issuree et al. provides three major advances in our understanding of the biology and medical importance of iRHM2. First, this work demonstrates that iRHM2 is relevant for another TNF-α-dependent disease, RA. Second, the study provides insights into the regulation of iRHM2 expression and the molecular mechanisms of RA. Third, it provides evidence that the homolog iRHM1 has a similar function as iRHM2 in controlling TACE activity. This is relevant for evaluating iRHM2 as a potential drug target in RA and other TACE-dependent diseases. The new discoveries about iRHM2, but also the many remaining open questions, show that this is an exciting time for iRHM research. The new work by Issuree et al. brings us back to the initial question: are iRHM1 and iRHM2 gadgets that you must have? The data presented here suggest that, as is often the case with iGadgets, selection of the appropriate version may be personal and context dependent.

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