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REPLY

Targeting notch in prostate cancer—combination is the key

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On behalf of my co-authors, I would like to thank Shigeo Masuda and Juan Carlos Izpisua Belmonte, as well as Weranja K. B. Ranasinghe, Graham S. Baldwin, Arthur Shulkes, Damien Bolton and Oneel Patel for their constructive comments on our Review (Marignol, L., Rivera-Figueroa, K., Lynch, T. & Hollywood, D. Hypoxia, notch signalling and prostate cancer. *Nat. Rev. Urol.* **10**, 405–413; 2013),[1] which highlight important issues regarding targeted therapy (Masuda, S. & Izpisua Belmonte, J. C. A recipe for targeted therapy. *Nat. Rev. Urol.* doi:10.1038/nrurol.2013.110-c1)[2] and the importance of normoxia (Ranasinghe, W. K. B., Baldwin, G. S., Shulkes, A., Bolton, D. & Patel, O. Normoxic regulation of HIF-1α in prostate cancer. *Nat. Rev. Urol.* doi:10.1038/nrurol.2013.110-c2).[3] Our Review has highlighted a number of unexplored cross-talk pathways between notch and hypoxic signalling in prostate tumours, which we proposed could underlie disease progression and treatment resistance and possibly be regulated by hypoxia-inducible factor 1α (HIF-1α). The importance of this cross-talk is strengthened by the recognized stabilization of HIF-1α under normoxic conditions, as highlighted by Ranasinghe *et al.*[3] in their correspondence.

The increasing number of recognized hallmarks of cancer continues to add layers of complexity to the development of novel therapies. Targeting one hallmark inevitably leads to compensatory mechanisms that rescue tumour survival. This concept, elegantly addressed in the field of radiation oncology with the development of synthetic lethality approaches,[4] will inevitably need to be applied to other fields. The combination of targeted therapies is likely to carry a high risk for enhanced toxicity. Given the multifunctional properties of the notch pathway, its inhibition might enable the simultaneous targeting of several cancer properties, with manageable gastrointestinal toxicity.[5]

The potential double-edged sword of notch inhibition by γ-secretase inhibitors (GSIs) highlighted by Shigeo Masuda *et al.*[2] must be considered alongside the assessment of these agents in the management of prostate cancer. The balance between the oncogenic and tumour suppressor actions of the notch pathway in prostate tumours remains to be fully elucidated, and in this regard dissection of the specific effect of each notch receptor on cellular fate is of utmost importance. Despite the advantage that GSIs are FDA approved and their toxicity is well documented and manageable with steroids, one major drawback of these agents is their lack of specificity.[6] The development of more selective compounds could assist the pharmacological shift of notch signalling towards its tumour suppressing properties.

Targeting the tumour microenvironment and tumour angiogenesis is extensively being examined in combination with docetaxel in metastatic castration-resistant prostate cancer.[7] As mentioned by Shigeo Masuda *et al.*,[2] antiangiogenic agents have been tested in patients with metastatic castration-resistant prostate cancer, including bevacizumab, which failed to improve overall survival when combined with docetaxel in the CALGB 90401 phase III clinical trial[8] and aflibercept,[9] which also failed to demonstrate convincing efficacy. Nonetheless, the outcome of pending phase III trials must be awaited before any conclusions can be made regarding the lack of efficacy of these strategies. Considering the central mediating role of HIF-1α in prostate tumours, the addition of anti-HIF1α therapies might also be warranted. A number of these agents (NSC-134754, Digoxin, P3155, PX-478) have demonstrated preclinical efficacy in prostate tumours but their clinical potential remains to be examined. As elegantly demonstrated by Kioi *et al.*[10] in irradiated glioblastomas, it is possible that targeting angiogenesis is not sufficient to achieve long-term tumour eradication.

The concept of treatment-resistant tumour stem cells at the heart of tumour progression is attractive and is supported by an increasing body of evidence. Aside from the notch-mediated responses highlighted in our Review, notch has also been implicated in: cancer immunosurveillance in both circulating tumour cells[11] and the bone marrow;[12] epigenetics;[13] and proteomic modifications.[14] Thus, the effects of the notch pathway on the development of prostate tumours, their response to treatment and cancer stem cells require extensive examination, which is further warranted by the great promise of combined anti-angiogenic and antitumorigenic inhibition of the notch pathway.[15] We believe that these agents have potential for preventing the progression of prostate cancer throughout the disease course in combination with current therapies.

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Competing interests
The author declares no competing interests.

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