HHS Public Access

Author manuscript

Transplantation. Author manuscript; available in PMC 2017 August 01.

Published in final edited form as:

Transplantation. 2016 August ; 100(8): 1597–1598. doi:10.1097/TP.0000000000001209.

Isoform-Selective HDAC Inhibitor Therapy for Transplantation: Are We Ready for HDAC6?

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The 18 known mammalian histone/protein deacetylases (HDACs) are divided into 4 groups, termed class I (HDAC1, HDAC2, HDAC3, HDAC8), class IIa (HDAC4, HDAC5, HDAC7, HDAC9), class IIb (HDAC6, HDAC10), class III (SIRT1-7) and class IV (HDAC11) enzymes[1]. While these enzymes were initially defined by their ability to deacetylate histones and dampen histone-DNA and histone-protein interactions, they are now recognized as regulating the functions of thousands of nonhistone proteins[2]. A large number of broadly active pharmacologic HDAC inhibitors (pan-HDACi) have been developed and are in clinical trials as anti-cancer agents due to their abilities to promote tumor cell-cycle arrest, differentiation and apoptosis[3]. There is also interest in the potential use of HDACi therapy for autoimmunity and transplantation, but there are concerns that the various pan-HDACi compounds may be too broadly acting and/or toxic for clinical use beyond oncology.

In ongoing studies of the biochemical and pharmacologic regulation of Foxp3+ T regulatory (Treg) cells in transplantation and autoimmunity, my lab has shown that the exposure of Foxp3+ Treg cells to pan-HDACi, but not class I-specific HDACi, promoted Foxp3 acetylation and increased Treg suppressive functions, with therapeutic efficacy in experimental autoimmune and transplant models[4, 5]. Pan-HDACi are thought to primarily block the functions of classical, Zn^{2+}-dependent class I and class IIb HDACs, since class IIa HDACs appear to lack significant deacetylase activity, at least against canonical substrates. Hence, our pharmacologic and other data suggested the potential relevance of HDAC6, the main class IIb HDAC, as a therapeutic target in transplantation and autoimmunity, and we subsequently confirmed this using both HDAC6-deficient mice and highly selective HDAC6i[6].

Even in the strange world of HDAC biology, HDAC6 is unusual, as it localized primarily in the cytoplasm, and has 2 catalytic domains and a C-terminal zinc finger domain (ZnF-UBP) binding with very high affinity for free ubiquitin and mono- and polyubiquitinated proteins. HDAC6 regulates the acetylation of many proteins, including α-tubulin, cortactin and

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Specific contributions

WWH wrote the entire article.

Disclosures

The author declares no funding or conflicts of interest.

HSP90, and also has multiple deacetylase-independent functions. Even the significance of its 2 catalytic domains is unclear, given conflicting data that each domain functions independently, that both domains are required for catalytic activity, or that the catalytic activity resides primarily within the C-terminal second domain. Beyond its deacetylase activity, HDAC6 has a critical role in the handling of ubiquitinated proteins via its C-terminal ZnF-UBP domain. This domain serves to control levels of misfolded proteins and their turnover via the proteasome, or in the case of large proteins, by promoting their accumulation in aggresomes. In the presence of high levels of ubiquitinated protein aggregates, or upon exposure to HDAC6i, HDAC6 is dissociated from heat shock protein 90 (HSP90) and the latter's client proteins, are released. While many such client proteins are degraded, HSF1 activates a heat-shock response. Indeed, many of the effects of HDAC6 targeting are often mimicked by pharmacologic inhibitors of HSP90 (HSP90i). However, while the effects of HDAC6i on Foxp3+ Treg cells require an intact heat-shock response, additional HDAC6-selective effects are apparent, including the ability of HDAC6, upon TCR activation, to translocate to the nucleus and directly regulate the levels of Foxp3 acetylation in Treg cells[7]. Lastly, HDAC6 is required for formation of cytoplasmic stress granules that reversibly isolate and prevent mRNAs from undergoing translation, and for ubiquitin-dependent basal autophagy.

In this issue, Ellis et al[8] present an in vitro comparison of the effects of a pan-HDACi (SAHA) versus a moderately HDAC6-selective compound on human T cell proliferation and cytokine production, as well as evidence that the HDAC6i, at high dose, can prolong murine skin allograft survival in vivo. The authors argue that their particular HDAC6i, known as KA1010, is more potent than SAHA at regulating T cell activation and IFN-γ production, but the data really show that it is no worse than SAHA when one compares each compound at its optimal concentration. The data on increases in Treg function are of uncertain significance, since no efforts were made to assess whether the Treg were functionally competent, whether key epigenetic features of Foxp3 were present and were promoted by HDAC6i therapy, including increased Foxp3 intronic (CNS2) demethylation and increased Foxp3 acetylation, or that Treg-dependent tolerance could be achieved. However, the findings that a moderately selective HDAC6i can have salutary effects on human T cell activation, proliferation and cytokine production, and display efficacy in a stringent murine skin allograft model, even if continued high dosing (160 mg/kg/d) was necessary for efficacy, are notable in the context of ongoing efforts by various groups to develop selective HDACi for use in nononcologic settings.

Lastly, it is not clear whether investigators at Karus, maker of KA1010, are truly intent on developing their compound for transplant applications, in the same way that companies interested in autoimmunity often begin their clinical trials in patients with psoriasis and if successful, quickly move to other disease indications. The comparisons in the current paper included use of cyclosporine-A, though that compound is now largely being replaced in clinical use by the more potent FK506 (Tacrolimus), and maintenance therapy rather than a tolerogenic strategy was employed. Given the excellent 1-year survival data in many types of clinical transplantation, the prospects of expensive drug trials extending over many years to show efficacy against chronic rejection or other long-term sequelae posttransplantation are usually regarded with disinterest by Pharma. Likewise, HDACi compounds like KA1010 are

classed as hydroxymates and typically have genotoxic (Ames-positive) effects[9], though nonhydroxymate HDAC6i compounds with positive effects on Treg biology have recently been identified[10]. Whether interest in such approaches will be continue to develop or will be abandoned will likely be affected by the results of ongoing trials of Treg cell therapy in transplant recipients[11]. If and as the limitations of such approaches are delineated, broad interest in the pharmacologic regulation of Treg cells in transplant recipients may well emerge. If that scenario were to eventuate, work by the current group appears well placed to proceed with clinical development of HDAC6-selective agents for clinical transplantation.

Acknowledgments

Funding

Supported in part by grants from the National Institutes of Health (1R01CA158941, 1R01HL114468, and 1R01AI123241).

Abbreviations

(HDACs)	histone/protein deacetylases
(pan-HDACi)	pharmacologic HDAC inhibitors
(Treg)	T-regulatory

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