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Polyketide Synthases Don't Determine Enediyne Ring Size

Enzyme systems all generate the same simple linear heptaene intermediate

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Enediyne

Enediynes like calicheamicin are among the most potent antitumor agents ever found, but the way polyketide synthase-thioesterase (PKS-TE) enzyme systems initiate the biosynthesis of their nine- or 10-membered macrocyclic core structures (shown) has long been a mystery. PKS-TEs from different microorganisms are specific for one ring size or the other, but it wasn't known whether ring size is determined by the PKS-TE itself or by accessory enzymes that follow it in the biosynthetic pathway. Now, Ben Shen and coworkers at the University of Wisconsin, Madison, have compared three nine-membered and two 10-membered PKS-TE systems under highly controlled conditions and found that they all generate the same simple linear heptaene intermediate (*Proc. Natl. Acad. Sci. USA,* DOI: 10.1073/pnas.1003442107). The work suggests that accessory enzymes are likely of key importance in modifying common PKS-TE intermediates to produce enediynes of both sizes. Liang Zhao-Xun of Nanyang Technological University comments that the results "clear up nagging doubts" about the biosynthetic role of PKS-TEs and "will certainly help the field move forward" toward a better understanding of enediyne biosynthetic divergence.

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