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Structures and Biosynthesis of Enediyne Natural Products

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Abstract

Enediyne natural products are important member of natural product family with strong DNA cleavage activity. This biological activity makes them excellent candidates for developing novel antibiotics and antitumor drugs. Highly unsaturated enediyne cores, sugar moieties and aromatic moieties are basic components of structures of enediyne natural products. Genes encoding enzymes responsible for enediyne natural product biosynthesis are clustered in enediyne gene clusters. Each gene cluster consists of dozens of genes that encode enzymes for biosynthesis of enediyne core, sugar moieties and aromatic moieties as well as tailing enzymes.

Review

Natural products produced by many plants, bacteria and fungi as secondary metabolites have been the major drug source for pharmaceutical industry for the last several decades [1]. Enediyne natural products discovered in 1980s are unique member among natural product family with potent DNA cleavage activity [2-4]. A typical enediyne natural product is structurally characterized by a highly unsaturated enediyne core containing two acetylenic groups conjugated to a double bond in nine- or ten- membered carbocycle [5]. Thus the enediyne natural products are conveniently categorized into two subfamilies, nine-membered enediynes and ten-membered enediynes. Figure 1 shows several examples of nine-membered enediynes (C-1027 from Streptomyces globisporus [6] and neocarzinostatin from *Streptomyces macromomyceticus* [7]) and ten-membered enediynes (calicheamicin from *Micromonospora echinospora* [8] and esperamicin from *Actinomadura verrucosopora* [9].

Although total synthesis of almost all enediyne natural products has been achieved by organic synthesis [10-13], the blue print of their biosynthesis in cells is still not quite clear to us. Before discovery and sequencing of enediyne gene clusters, researchers speculated biosynthesis pathways of enediyne natural products by biomimetic synthesis [14] and feeding of isotope labeled starting material to enediyne producing bacteria strains [15].

Discovery and sequencing of gene clusters for C-1027 and calichaemicin biosynthesis announced the genomic era of enediyne biosynthesis study [16-18]. Sequencing of gene clusters for neocarzinostatin, naduropeptin and dynemicin [19-22] quickly followed the above two pioneer reports. All enediyne gene clusters encode a conserved iterative enediyne type I polyketide synthase (PKSE). Although we are convinced that the role of PKSE is to provide a carbon skeleton for synthesis of enediyne cores, the genuine structure of the carbon skeleton is not confirmed and whether 9-membered and 10-membered enediyne cores share the same intermediate carbon skeleton is still under debate. Several polyketide products were isolated from expression of 9-membered PKSE SgcE and 10-membered PKSE CalE8 in *E. coli* and also from *in vitro* assays of their activities. The isolated polyketides include heptaene [23], methylhexaenone [24] and nonaketide [25], and other truncated polyketides [26-29]. These polyketides are potential precursors towards enediyne core biosynthesis, as claimed by their discoverers. However, some people argue that none of these polyketides is true precursor and PKSE needs a trans-acting enzyme for function regulation [26,27,30,31]. Moreover, what enzymes are involved in maturation of the carbon skeletons to enediyne cores is still a mystery to us.

While the enediyne cores serve as active sites of DNA cleavage activity, peripheral moieties such as sugar moieties and aromatic moieties are responsible for DNA binding specificity and stabilization of enediyne cores. Structures of enediyne cores are rather conserved among enediyne natural products, and diversity of enediyne natural product family is achieved by variations of peripheral moieties. As a result, biosynthesis pathways for peripheral moieties are less conserved among enediynes. Due to limit of space, detailed discussion on various biosynthesis pathways of enediyne peripheral moieties is not provided in this paper. Interested readers are encouraged to read reports on biosynthesis of C-1027 [17] and calichaemicin [16] and Liang's review paper [32].

In summary, enediyne natural possess exquisite structures and valuable biological activities. Biosynthesis of enediynes is a complicate and highly regulated process involving 70~80 gene products from enediyne gene clusters. Synthesis of enediyne cores starts with function of iterative type I polyketide synthases, whose role is yet to be established by further research. Synthesis of peripheral sugar and aromatic moieties are much more diverse among enediynes. Most enzymes responsible for synthesis of these moieties and covalent attachment to enediyne cores have already been assigned with related functions.

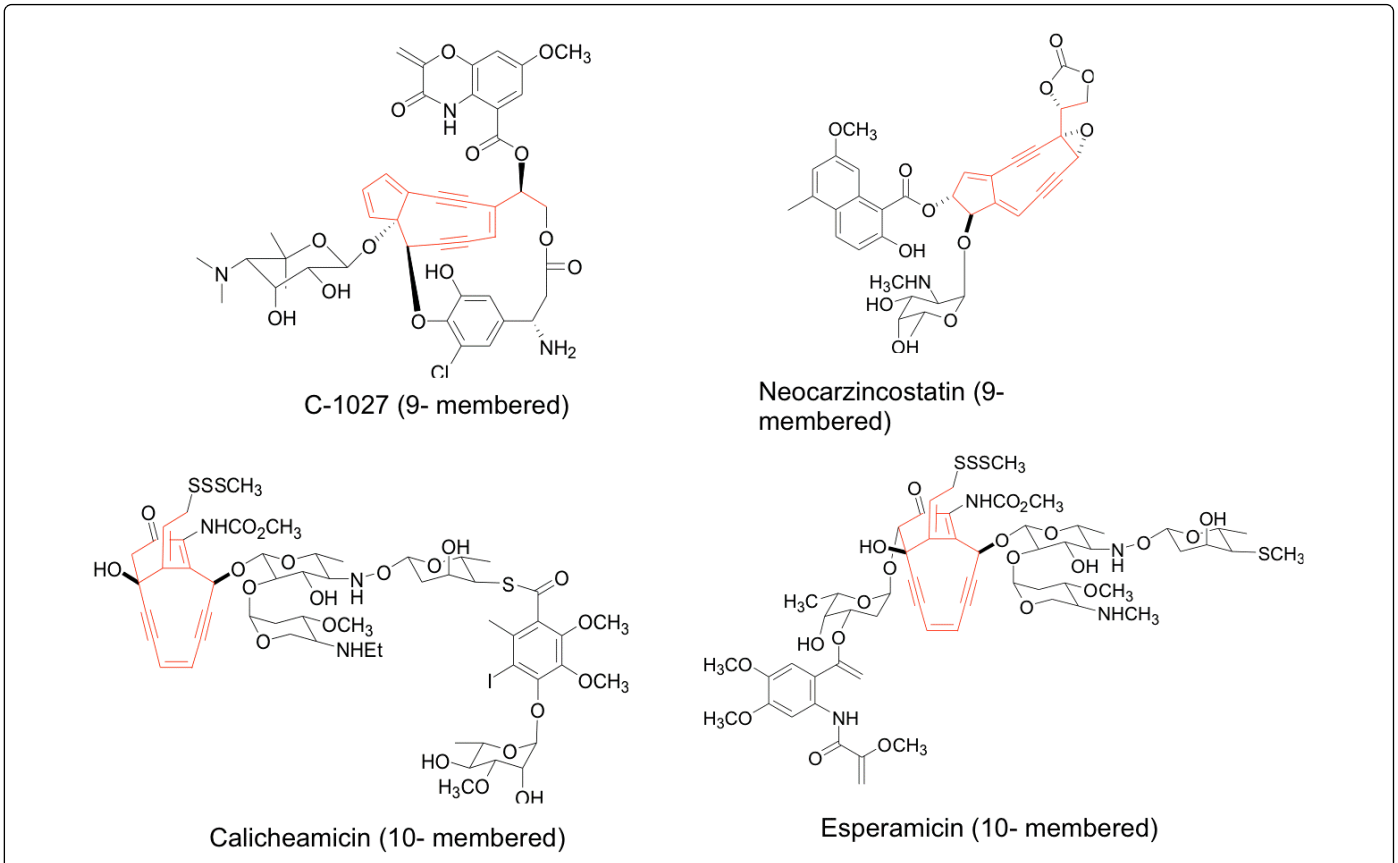

Figure 1: Structures of several enediyne natural products. All enediyne natural products contain highly unsaturated enediyne cores shown in red.

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