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Abstract	:	The World Health Organization reports that one of the top global causes of illness and mortality is cancer, with nearly 10 million deaths in 2020. Changes in cellular metabolism are common characteristics of a wide variety of malignancies. Enzymatic deficits cause many tumors to lose the ability to synthesize amino acids required for their growth, survival, or proliferation. Thus, some tumors depend on the extra-cellular supply of specific amino acids to meet their needs, allowing them to survive. Amino acid depletion as a targeted therapy takes advantage of these tumor traits by depleting certain amino acids in the body that is required for the tumor to survive. This review aims to discuss the potential and challenges of arginine-depleting enzymes as a means in treating arginine auxotrophic cancers. Previously, arginine deiminase (ADI) of bacterial origin has been studied for the in vivo arginine auxotrophic tumour therapy. However, it has been hampered by drawbacks, including immunogenicity and toxicity issues. Thus, human arginase I (hARGI) has been considered a better candidate due to its low immunogenicity and toxicity effects. However, hARGI's application as an anti-cancer drug is hindered by its low activity towards arginine owing to its high Km values indicating the enzyme's low substrate affinity. Thus, it is necessary to improve the enzyme catalytic capability and stability for more practical application in therapeutic cancer treatment. With the advancement of bioinformatics tools, more studies are anticipated to rationally engineer the enzyme for more practical clinical application in the treatment of arginine auxotrophic cancers.