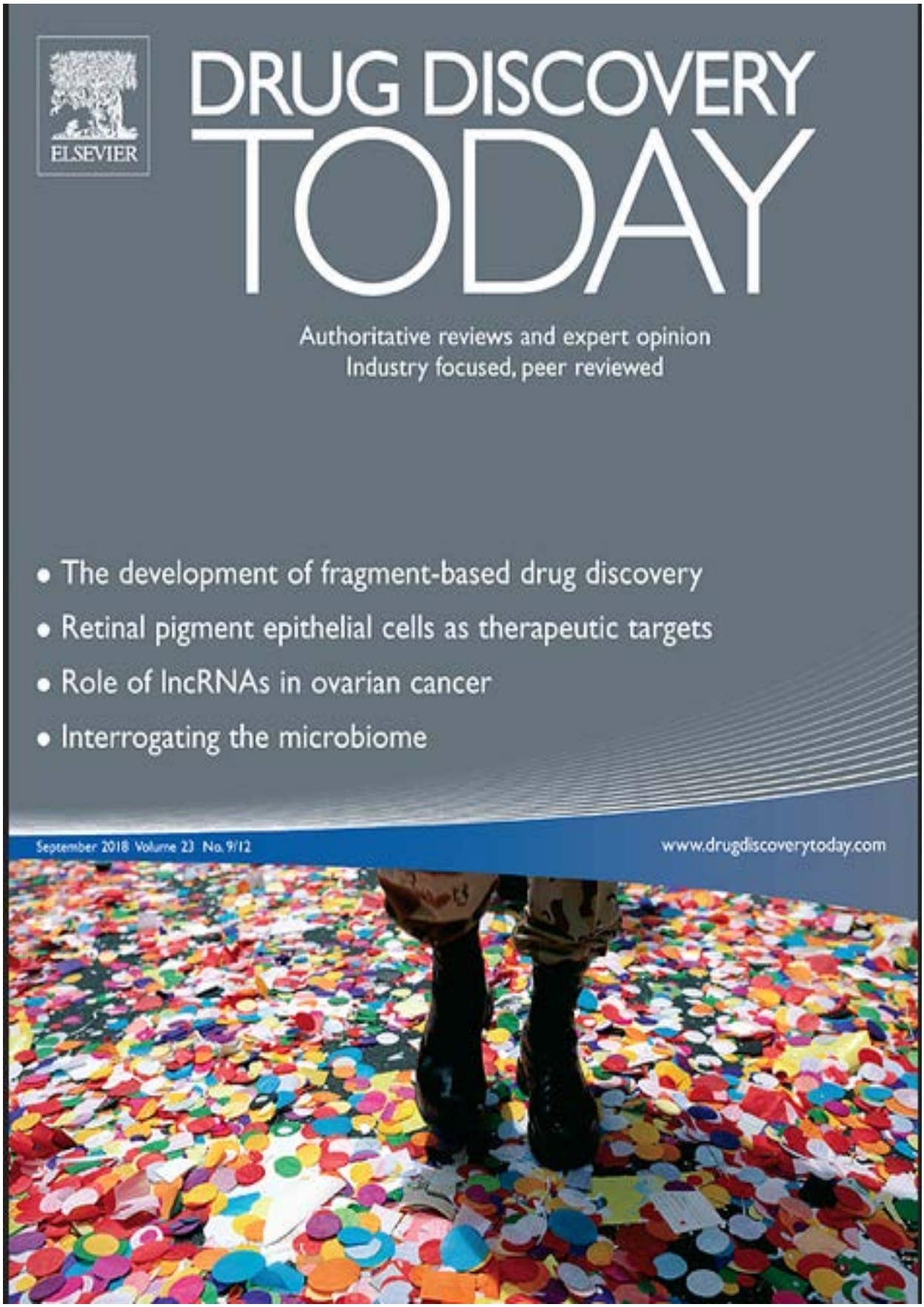

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Small-molecule inhibitors of macrophage migration inhibitory factor (MIF) as an emerging class of therapeutics for immune disorders

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Macrophage migration inhibitory factor (MIF) is an important cytokine for which an increasing number of functions is being described in the pathogenesis of inflammation and cancer. Nevertheless, the availability of potent and druglike MIF inhibitors that are well-characterized in relevant disease models remains limited. Development of highly potent and selective small-molecule MIF inhibitors and validation of their use in relevant disease models will advance drug discovery. In this review, we provide an overview of recent advances in the identification of MIF as a pharmacological target in the pathogenesis of inflammatory diseases and cancer. We also give an overview of the current developments in the discovery and design of small-molecule MIF inhibitors and define future aims in this field.

Introduction

Despite its discovery over 50 years ago in 1966 [1,2], the functions of the cytokine macrophage migration inhibitory factor (MIF) have still not been fully elucidated. Initially, MIF was identified as a T-cell-derived mediator that inhibits random movement of macrophages. Its activity was found to correlate with delayed-type hypersensitivity reactions, a prominent feature of several chronic diseases in humans [2]. In addition, MIF is released at sites of infection, causing macrophages to concentrate and carry out antigen processing and phagocytosis [3]. Today, MIF is recognized as a crucial player in innate immune responses and has a role in multiple diseases [4,5]. Therefore, the development of small-molecule MIF inhibitors that inferfere with its functions is quickly gaining importance.

The human MIF gene was cloned and expressed for the first time in 1989 [6]. MIF is a relatively small protein that consists of 114 amino acids and has a molecular mass of 12 345 Da. Structural analysis of MIF revealed its striking similarities to bacterial enzymes from the tautomerase superfamily. Searching the human genome indicated that D-dopachrome tautomerase (D-DT) is another gene with marked homology to MIF. Owing to this similarity, D-DT is also referred to as MIF2 and an overlapping functional spectrum for MIF and D-DT has been suggested [7]. This should be considered in the evaluation of MIF cytokine activities and in the development of small-molecule MIF modulators.

MIF, a member of the tautomerase superfamily [8], is found across various organisms including bacteria, mice, plants, protozoa, helminths, molluscs, arthropods and fish [9–11]. These tautomerase superfamily members have similar enzyme activity involving an amino-acid-terminal proline that acts as a general base in keto-enol tautomerisation reactions of α-keto-carboxylates. In addition to its cytokine activity, MIF harbors keto-enol tautomerase and low-level dehalogenase activity, providing a functional link to other members of the tautomerase superfamily [10]. MIF is a homotrimeric protein in which three monomers associate to form a symmetrical trimer (Fig. 1a). Each MIF trimer has three tautomerase active sites at the interfaces of the monomer subunits. Characteristic for this family, MIF has an N-terminal

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