Available online at www.sciencedirect.com

SCIENCE DIRECT®

Cellular Signalling 17 (2005) 535–547

CELLULAR SIGNALLING

www.elsevier.com/locate/cellsig

Review

Unraveling signalling cascades for the Snail family of transcription factors

Bram De Craene[a], Frans van Roy[b], Geert Berx[a,*]

[a]*Unit of Molecular and Cellular Oncology, Department for Molecular Biomedical Research, VIB-Ghent University, Technologiepark 927, B-9052 Ghent (Zwijnaarde), Belgium*

[b]*Molecular Cell Biology Unit, Department for Molecular Biomedical Research, VIB-Ghent University, B-9052 Ghent (Zwijnaarde), Belgium*

Received 17 September 2004; accepted 8 October 2004
Available online 24 November 2004

Abstract

During development and carcinogenesis, the gradient of different molecular factors, the availability of corresponding receptors and the interplay between different signalling cascades combine to orchestrate the different stages. A good understanding of both developmental processes and oncogenesis leads to new insights into normal and aberrant regulation, processes that share some mutual key players. In this review, we will focus on the Snail family of transcription factors. These proteins, which share an evolutionarily conserved role in invertebrates and vertebrates, are implicated in several developmental processes, but are involved in carcinogenesis as well. We will highlight the different signalling cascades leading to the expression of Snail and Slug and how these factors are regulated on the transcriptional level. Then we will focus on how these factors execute their functions by repression of the numerous target genes that have been described to date.

Keywords: Snail; Slug; Signalling; Development; Cancer; EMT

Contents

Abbreviations: AER, apical ectodermal ridge; bZIP, basic region-leucine zipper; BMP, bone morphogenetic protein; EGF, epidermal growth factor; EGF-CFC, EGF (-like motif)-cripto, FRL-1, and cryptic (motif); EMT, epithelial mesenchymal transition; ER, estrogen receptor; FGF(R), fibroblast growth factor (receptor); HGF/SF, hepatocyte growth factor/scatter factor; ILK, integrin linked kinase; NES, nuclear export sequence; PTHrP, parathyroid hormone related peptide; RA, retinoic acid; SCF, stem cell factor; TBP, TATA box binding protein.

* Corresponding author. Tel.: +32 9 331 37 40; fax: +32 9 331 36 09.
E-mail address: Geert.Berx@dmbr.UGent.be (G. Berx).

0898-6568/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.cellsig.2004.10.011

1. Introduction

Tightly regulated developmental processes eventually result in an organism in which all cellular components have well-defined functions. Oncogenesis, on the other hand, is a deregulated process characterised by mutations or amplifications in critical pathways. For many carcinoma types, different progression stages have been described starting from destabilised cells to metastasis. Cancer progression and its final outcome are not easy to predict, as it is difficult to take into account many unknown variables. Epithelial mesenchymal transition (EMT) is one of the highly controlled key processes that occur in development. In general, EMT can be induced by a diverse set of molecules, and aberrations of this process drive carcinoma cell invasion and metastasis [1]. Members of the Snail family have been described as playing an important role in both development and cancer [2,3]. They have been shown to act as transcriptional repressors that bind DNA with their carboxyterminal zinc fingers. Snail proteins share an evolutionarily conserved role in invertebrates and vertebrates. They are implicated in the generation and migration of mesoderm and neural crest cells in several vertebrate species. The intimate relationship between epithelial-mesenchymal transitions and cell migration in these developmental processes supports the evidence for the important role of these factors in carcinogenesis. This review focuses on the different signalling cascades leading to the expression of the Snail family of transcription factors and the mechanisms controlling downstream pathways and the repression of target genes.

2. Signalling cascades leading to Snail or Slug expression in development and cancer

2.1. Receptor tyrosine kinase signalling leads to Snail or Slug expression in development and cancer

Fibroblast growth factor (FGF) signalling via FGFR1 is required for the expression of *mSnail* during gastrulation in mice (see Fig. 1 for an overview). FGF thereby controls E-cadherin expression in the mesoderm and regulates morphogenetic cell movements during gastrulation. Besides its morphoregulatory role during gastrulation, FGFR1 also functions in the specification of mesoderm cell fate, as this receptor is required for the expression of the T box genes *Brachyury* and *Tbx6* at the primitive streak [4]. T box genes in turn may also regulate cell adhesion and EMT at gastrulation. In zebrafish, the *Brachyury* homolog *no tail*, and the T box gene *spadetail* have both been implicated as positive regulators of *Snail* expression [5,6].

In chicken limb development, *cSnail* can be induced irreversibly in the flank by brief exposure to FGF-2 and FGF-8. Both *cSnail* and *cTwist* are co-expressed during the early stages in chick limb development. When chick flank is reprogrammed to form a limb, *cSnail* is induced more rapidly than *cTwist*, and therefore Twist expression is not necessary for activation of *cSnail* in the flank. As is seen during gastrulation, T-box genes are expressed rapidly in response to FGF signalling. The expression of *Tbx-4* and *Tbx-5* is likely to be connected to patterning along the head–tail axis, while cSnail appears to be linked to setting up a new outgrowth [7]. *cSlug* expression can be progressively detected from stage 21 in the progress zone. The progress zone is an area of undifferentiated, rapidly proliferating mesenchymal cells; the maintenance of which depends on the presence of the apical ectodermal ridge (AER), one of the major signalling centres in the developing limb. Beads soaked in FGF-2 or FGF-4 maintain *cSlug* expression after AER removal. FGF-2 is unable to induce *cSlug* expression in non-expressing mid-proximal mesenchyme [8]. Retinoic acid (RA) bead implants lead to downregulation of *cSlug* expression, accompanied by abolition of limb outgrowth. Dual bead implants demonstrate antagonism between RA and FGF-4, suggesting that a localised antagonistic effect underlies the molecular mechanism controlling the transition between the undifferentiated and differentiated states during normal limb development [9]. Later on, the cooperative action of FGF and bone morphogenetic protein (BMP) signalling leads to the regulation of genes implicated in the molecular cascade responsible for apoptosis. From stage 27, *cSnail* is induced in interdigital areas in limb outgrowth in chick/duck development, as was demonstrated by soaked beads experiments with BMPs and FGFs. The expression was lost if beads were added with inhibitors for these growth factors [10]. These observations point to a positive regulatory role for Snail in apoptosis, despite the fact that the Snail family of transcription factors has extensively been described as having an anti-apoptotic role, both in *C. elegans* [11] and vertebrates [12]. A possible explanation for the expression of Snail in the interdigital zone is the regulation of changes in adhesion, which must necessarily occur during involution of the interdigital tissue [10].

The effect of growth factors on the expression of members of the Snail family was also demonstrated in cell culture. NBT-II rat carcinoma epithelial cells transfected with antisense Slug cDNA were able to resist EMT induction by FGF-1 or hepatocyte growth factor/scatter factor (HGF/SF) [13]. In the same cell system, epidermal growth factor (EGF)