Foxk1 regulates cancer progression

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Provenance and Peer Review: This article was commissioned by the editorial office, Annals of Translational Medicine. The article did not undergo external peer review.


doi: 10.21037/atm-2020-94

View this article at: http://dx.doi.org/10.21037/atm-2020-94

Cancer remains a major cause of morbidity and mortality. The lifetime risk for developing cancer is one in three and approximately 1.7 million new cases of cancer were diagnosed in the U.S. in 2019 according to the American Cancer Society (1). Worldwide, gastric carcinoma (GC) is the fourth most common malignancy and is the second leading cause of death (1,2). GC is a malignant disease and is associated with a poor long-term prognosis (1,2). Therefore, new therapies are warranted, which require an enhanced understanding of the mechanisms that govern gastric cancer progression. Previous in vitro studies have defined pathways (sonic hedgehog, stem cell signaling, cell cycle, DNA damage, Notch, PI3K/AKT, Tgfb, Wnt, etc.) and transcription factors (TP53, EGR1, GATA, GLI, STAT, MYC/MAX, SMAD2/SMAD3/SMAD4) that are expressed in gastric cancer cell lines (3). One pathway that has received intense interest is the forkhead/winged helix transcription factor family.

Forkhead was initially discovered in the fly and disruption of the gene resulted in a forked head phenotype (4). More than 100 members have been assigned to the family based on the homology of the 100 amino acid containing DNA binding domain (the forkhead/winged helix or Fox domain) (5-7). These family members function as transcription factors to regulate cell and lineage specification during development, metabolism, aging or survival, stem cell populations, tissue repair, diseases and others (5-7). For example, Foxd3 (Genesis) has been shown to be expressed in embryonic stem cells (8) whereas Foxb1 has been shown to be a regulator of neural progenitors (9) and Foxm1 has been shown to be expressed in regenerating hepatocytes (10). In addition, Foxo factors have been shown to inhibit apoptosis, regulate PI3K signaling and serve as an anti-aging factor (7). More recently, members of this family have been shown to function as pioneer factors as they have the ability to bind nucleosomal DNA and unwrap the chromatin thereby exposing DNA binding motifs for the binding of other transcription factors and subsequent regulation of gene expression (8,9). In addition to this array of molecular and cellular functional roles, this family also regulates cell cycle kinetics. Foxk1 has been shown to be an essential regulator of cell proliferation.

Foxk1 was initially termed MNF (Myocyte Nuclear Factor) based on the restricted expression pattern in the myogenic lineages during murine embryogenesis and was discovered in the Williams’ laboratory (10,11). Structurally, Foxk1 harbors motifs that have important functional roles including: the leucine zipper motif, the Sin3 interacting motif (SIM) domain, and the Forkhead-associated (FHA) domain, which increase the complexity regarding its functional role(s), the winged helix DNA binding domain (WHD) and the transcriptional activation domain (TAD) (Figure 1A) (12,13). For example, Foxk1 is the prototype for the FHA domain, which is a phosphopeptide-binding motif that functions to recruit interacting proteins and regulate cell cycle kinetics (14). Previous studies have demonstrated that Foxk1 and its interacting partners (Fhl2, Sds3 and others) function to repress the p21 gene thereby promoting...
cell proliferation and repressing lineage differentiation \((\text{Figure 1B})\) (14-17). Using gene disruption technology, \textit{Foxk1} null mice have been shown to be partially lethal and the limited null mice that survived were growth retarded and had impairments in tissue regeneration (18). Studies have also shown an increase of Foxk1 expression associated with a number of malignancies including: melanoma, breast, pancreatic, osteosarcoma, glioblastoma, ovarian, esophageal, prostate and gastric cancers (19-24).

The role of Foxk1 and GC was further examined in the recent study by Wang \textit{et al.} (25). These investigators used computational biology, western blot analysis and tissue microarrays to define FoxK1 expression in GC cell lines and human gastric cancer specimens. Not only did they verify an induction of Foxk1 expression associated with GC (compared to controls) but they also observed a correlation between those having increased Foxk1 expression and malignant progression of GC (25). Next, using \textit{in vitro} assays, overexpression or siRNA knockdown strategies and EdU incorporation Wang \textit{et al.}, demonstrated that Foxk1 increased GC cell proliferation, migration and invasion \((\text{Figure 1B})\) (25). Importantly, they further demonstrated that increased Foxk1 expression portended a poor prognosis for patients with GC. Wang \textit{et al.}, then established the mechanistic role for increased Foxk1 expression and GC as Foxk1 was shown to suppress autophagy in GC via the PI3K/AKT/mTOR pathway \((\text{Figure 1B})\) (25).

The study by Wang \textit{et al.}, has a number of important findings. First, they used human \textit{in vitro} (GC cell lines) and \textit{in vivo} (GC samples) specimens. Second, they used a large number of GC samples (43 pairs of GC and control or non-GC specimens). Third, their results supported the notion that Foxk1 functioned in the context of GC as a repressor of autophagy via the PI3K/AKT/mTOR pathway (25). This study provides the rationale for using Foxk1 as a molecular marker for progression of GC and response to treatment. Moreover, based on this study, Foxk1 may be an important target for GC treatment. Therefore, small molecule or chemical genetics strategies may be employed, in the future, to identify Foxk1 specific inhibitors that may be used in combination with surgical debulking or chemotherapies in patients with GC. In some respects, the findings by Wang \textit{et al.}, are somewhat predictable. This is, in part, due to the previous studies that have conclusively shown that Foxk1 directly interacts with Fhl2 (12), promotes cell proliferation (12-18), has increased expression in other human cancers including GC and functions to regulate autophagy (19-24). Nevertheless, if these studies further establish a role for Foxk1 as a regulator of GC malignant progression and ultimately lead to effective therapeutics then the medical impact will be significant.

In summary, Foxk1 is an important regulator of cell proliferation, quiescence and differentiation in stem cell populations and cancer. The studies by Wang \textit{et al.}, provide an important platform to decipher putative inhibitors of Foxk1 with the goal of bending the malignancy outcome curve for GC.

\textbf{Acknowledgments}

The authors acknowledge the laboratory of R. Sanders Williams and their initial studies and contributions focused on MNF (Foxk1). The authors further acknowledge all the graduate students, technicians and postdoctoral fellows that

\textbf{Figure 1} Foxk1 is an important regulator in stem cell and cancer cell populations. (A) Schematic highlighting the domains of the FOXXK1 protein. The Sin3 interacting domain (SID) physically interacts with Sin3 and its associated complex. The Forkhead-Associated Domain (FHD) interacts with phosphothreonine proteins (such as SDS3) and is important in the regulation of cell cycle kinetics. The winged helix domain (WHD) binds to DNA and allows FOXK1 to function as a transcriptional regulator. The transcriptional activation domain (TAD) is located in the carboxy terminal region of the protein. (B) FOXK1 has been shown to have a number of permissive roles and repressive roles in stem cell and cancer cell populations.
have contributed to our knowledge of Foxk1 biology in the Garry laboratory. We also want to recognize all those investigators and their laboratories that have contributed to the field of study focused on Fox transcription factors and were not referenced in this manuscript due to page limitations.

**Funding:** None.

**Footnote**

**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-2020-94). DJG and MGG report other from NorthStar Genomics, outside the submitted work. GM has no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Garry DJ, Maeng G, Garry MG. Foxk1 regulates cancer progression. Ann Transl Med 2020. doi: 10.21037/atm-2020-94