

## Review

## Predictive Value of Schlafen 5 (SLFN5) for Intestinal Metaplasia (IM) to Gastric Cancer Progression

Fanayan S

Department of Biomedical Sciences, Macquarie University, North Ryde, NSW 2109, Australia.

Received May 05, 2016; Accepted May 11, 2016; Published May 13, 2016

Copyright: © 2016 Fanayan S

\*Corresponding Author: Fanayan S Department of Biomedical Sciences, Macquarie University, North Ryde, NSW 2109, Australia, E-mail: susan.fanayan@mq.edu.au

### Introduction

Gastric cancer (GC) is one of the most common cancers and a leading cause of cancer-related death worldwide. The development of intestinal gastric adenocarcinoma occurs through a complex, multi-step process, which represents the culmination of an inflammation-metaplasia-dysplasia-carcinoma sequence. The sequence, known as the Correa cascade of multistep gastric carcinogenesis, involves progression from normal mucosa through chronic non-atrophic gastritis, atrophic gastritis (AG) and intestinal metaplasia (IM) to dysplasia and carcinoma [1].

Intestinal metaplasia (IM), the background from which dysplasia and, ultimately, carcinoma develop, confers an increased risk of progression to gastric cancer. IM is quite heterogeneous, with several subgroups currently recognized [2,3], including incomplete (Type I) and complete types (Types II and III), based on morphological features as well as mucin content [4].

The risk of developing gastric IM and cancer is high in those with family history of gastric cancer and patients from ethnic backgrounds in which gastric cancer is prevalent [5]. Risk factors for IM include *Helicobacter pylori* infection (major cause of gastric cancer, responsible for approximately 60% of cases), high salt intake, smoking, alcohol consumption, and chronic bile reflux.

If detected early, while tumors are still localized, the 5-year survival rate is > 90%. Unfortunately, patients with gastric cancer are typically asymptomatic until advanced disease is present, when 5-year survival drastically reduces to less than 20% [6]. Identification and surveillance of patients with precursor conditions and lesions may lead to early diagnosis, and ultimately, reduction of gastric cancer. Improved methods of detection, based on new biomarker panels, to detect GC at an early stage, when treatment is effective, will improve survival. However, protein biomarkers capable of predicting which patients will progress from IM to gastric cancer are currently lacking.

In a recent issue of *Journal of Gastroenterology*, Companioni Nápoles et al. [7] observed higher levels of Schlafen 5 (SLFN5) expression in human immune cells (Jurkat T-lymphoid and HL-60 myeloid cell lines), following treatment with interferon-alpha (IFN). They then evaluated SLFN5 expression, by immunohistochemistry, in paraffin-embedded samples from individuals with non-atrophic gastritis, atrophic gastritis, complete IM, incomplete IM, and GC, and shown that SLFN5 expression was higher in IM samples that progressed to GC than in the same lesions that did not progress to GC.

SLFN5 is a member of the Schlafen family, involved in important functions, such as regulation of cell proliferation and induction of immune responses [8, 9]. Members of the SLFN family are highly conserved, inter-

feron (IFN-)-inducible proteins [10], which when overexpressed, impairs T-cell proliferation and activation [8]. However, the precise functions and mechanisms of action of SLFN proteins remain to be established.

Several studies have reported anti-tumor activity of SLFN5 in different cancers. In a recent study, Sassano et al. [10] have shown that SLFN5 regulates motility and invasiveness of renal cell carcinoma (RCC) cells, with higher SLFN5 expression correlated with an overall better survival in RCC patients, implying a tumor suppressor activity for SLFN5, through negative regulation of the expression of matrix metalloproteinase (MMP) genes, such as MMP-1 and MMP-13 [10]. Anti-neoplastic effect of SLFN5 has also been shown in malignant melanoma, in which its induction by IFN- was accompanied by suppression of cell growth and invasion [9]. Induction of SLFN5 expression, by IFN- signaling, is believed to play a role in maintaining T cells in a non-activated or quiescent state, inhibiting their response to environmental cues and creating a permissive environment for malignant transformation [11].

The observed correlation between SLFN5 expressions in gastric IM with histological progression to GC is significant and will be of value for future efforts in discovery and development of specific and sensitive markers with utility to identify IM patients with increased probability of progression to GC.

### References

1. Kapadia CR (2003) Gastric atrophy, metaplasia and dysplasia. A clinical perspective. *J Clin Gastroenterol* 36:29-36.
2. Filipe MI, Muñoz N, Matko I, Kato I, Pompe-Kirn V, et al (1994) Intestinal metaplasia types and the risk of gastric cancer: a cohort study in Slovenia. *Int J Cancer*. 57:324-329.
3. Matsukura N, Suzuki K, Kawachi T, Aoyagi M, Sugimura T, (1980) Distribution of marker enzymes and mucin in intestinal metaplasia in human stomach and relation to complete and incomplete types of intestinal metaplasia to minute gastric carcinomas. *J Natl Cancer Inst* 65:231-240.
4. Gonza'lez CA, Sanz-Anquela JM, Gisbert JP, Correa P (2013) Utility of subtyping intestinal metaplasia as marker of gastric cancer risk: a review of the evidence. *Int J Cancer* 133:1023-1032.
5. Gomez JM, Frye JW, Patrie JT, Sauer BG, Shami VM, et al. (2013) The presence of gastric intestinal metaplasia in patients undergoing EGD with biopsy is associated with a family history of gastric cancer in the United States. *J Gastroenterol Hepatol Res* 2:479-482.
6. Park JM, Ryu WS, Kim JH, Park SS, Kim SJ, et al. (2006) Prognostic factors for advanced gastric cancer: stage-stratified analysis of patients who underwent curative resection. *Cancer Res Treat* 38:13-18.
7. Companioni Nápoles O, Tsao AC, Sanz-Anquela JM, Sala N, Bonet C, et al. (2016) 5 expression correlates with intestinal metaplasia that progresses to gastric cancer. *J Gastroenterol*

- 
8. Mavrommatis E, Fish EN, Platanias LC (2013) The schlafen family of proteins and their regulation by interferons. *J Interferon Cytokine Res* 33:206-210.
  9. Katsoulidis E, Mavrommatis E, Woodard J, Shields MA, Sassano A, et al. (2010) Role of interferon  $\gamma$  (IFN $\gamma$ )-inducible schlafen-5 in regulation of anchorage-independent growth and invasion of malignant melanoma cells. *J Biol Chem* 285:40333-341.
  10. Sassano A, Mavrommatis E, Arslan AD, Kroczyńska B, Beauchamp EM, et al. (2015) 5 (SLFN5) is a regulator of motility and invasiveness of renal cell carcinoma cells. *Mol Cell Biol* 35:2684-2698.
  11. Puck A, Aigner R, Modak M (2015) Expression and regulation of Schlafen (SLFN) family members in primary human monocytes, monocyte-derived dendritic cells and T cells. *Results Immunol* 5:23-32.